Laser Phototherapy

Clinical Practice and Scientific Background

Lars Hode / Jan Tunér

Prima Books

Laser Phototherapy
Clinical practice and scientific background

A guide for researchers, doctors, dentists, veterinarians and other interested parties within the medical field

By

Lars Hode and Jan Tunér

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Preface

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Where to start? Fourth century B.C.E. Greece would be appropriate when the father of medicine Hippocrates practiced Heliotherapy at his centre in Kos using the wonderful Greek sunlight for therapy. The god of Light was of course Apollo and it was no accident that his son was Asclepius, the god of medicine. The great philosopher of this era was Aristotle who was not afraid to look for a meaning or "telos" in the natural phenomena that he so tirelessly observed. We now know that photic radiation has a general anti-inflammatory and pain relieving effect by suppression of inflammatory interleukins, bradykinin and prostanoid activity. It behooves us all to ponder, in the spirit of Aristotle, why light is so potent. It truly is the flux of life and we have the given power to amplify and modulate it with the laser.

Where should I start in my own "enlightenment"? As an academic Maxillofacial Surgeon, I had come to use high intensity lasers more and more in my surgical practice with tumors and vascular anomalies, particularly. For example, I could resect half the tongue for a carcinoma with minimal after pain, beautiful soft mucosal healing and a lack of the need for suturing. It was only later that I came to realize that the first two effects were low intensity manifestations of the carbon dioxide wavelength on C and A delta pain fibers and also a bio-modulation of the tissue bed reducing scarring by modifying myo-fibroblastic action.

A seminal event then occurred when I attended the Second Congress of the international Laser Therapy Association (later to be the World Association) in 1992 at Guy's Hospital in London. This changed my professional life as I listened to the President, Dr Mary Dyson's presentations on the cellular response to LPT wavelengths. It obeyed the Arndt- Schulz law, whereby low energies stimulate and high energies inhibit in a bi-phasic manner. Then there were the lectures of the Estonian photo biologist, Professor Tina Karu, identifying the specific photo-acceptors in tissue, particularly cytochrome-c-oxidase in the mitochondria. She intoned: "we can talk to the cells with light but we must learn the language". I had always wanted the cells to obey me, but now I saw a new and exciting pathway to accomplish this! The Japanese pioneer Toshio Oshiro's classification of the three categories of LPT (or LLLT as he preferred to call it) identified the first type as "Simultaneous", whereby a high intensity wavelength would have a low intensity bio-modulatory effect on the tissue bed: this was what I was seeing as a surgeon. Oshiro's other two categories were "Pure" (low intensity laser alone) or "Combined" (using high and low intensities in combinations): everything began to make sense. In addition, I realized how many of my patients had pain and healing difficulties, but that there was now a ready means to help them with the LPT. However, I must "learn the language" in terms of wavelengths, energies and pulsing characteristics - but that was an exciting new field for me. The other brilliant lecturers in the conference gave me inspiration to make a start. I realized as a surgeon that operation might not be necessary in some cases with this new option. The first edition of this book came out later in 2002 providing a much needed dictionary of effects to help me further.

It was an example of Jungian "synchronicity" that I was at that time a professor at The Royal London Hospital where there was a monument in the grounds commemorating the gift by Niels Finsen of a Finsen Lamp to Queen Alexandra, the Danish patron of the hospital. This was used to treat Lupus Vulgaris, tuberculosis of the skin, for which there was no current therapy. The hospital governors initially turned down the offer in true conservative style, but the queen was very persistent! The wavelength was produced by a Xenon Arc to provide a non-laser light beam comprising blue light of around 400 nanometres and UVA 1. Finsen published his ground breaking results on 800 patients with 56 per cent "complete cure", 26 per cent "good" and 12 per cent "minimal", for which he was awarded a Nobel Prize for Medicine and Physiology in 1903. So it was a little daunting to follow on in that tradition of light therapy myself, although using different wavelengths. Einstein, of course, was awarded his Nobel Prize for physics in 1921: his work predicted the entity of "stimulated emission" which led to Theodore Mailman producing the first laser in 1960. Finsen's light could now be amplified by the stimulated emission of radiation to lead to high intensity and eventually LPTs in surgery and medicine. For the initiation of the latter, it required the inspired observation by Professor Endre Mester in Budapest in 1967, when evaluating the effect of a low powered red ruby laser light on skin cancer in mice, that showed an effect which he had not anticipated in that shaved hair grew back more quickly in his treated group than in the untreated group: so laser biostimulation was discovered. In the future a wide range of wavelengths were investigated for this effect, when it was found that near infrared was particularly efficacious with deep penetration.

The F.D.A gave clearance for Class 3B lasers (lasers with an upper limit of incident power of 500 milli-watts: 0.5 of a watt) in February 2002 after a study on carpal tunnel syndrome. I was lucky to have heard many of the pioneers in this field, which has expanded exponentially, at my London Conference. This book records & interprets faithfully the clinical and research work since then, that has laid the basis for this exciting and fascinating method of treatment, so welcome in an era when it is realized that no drug is without possible adverse reactions. I recommend the book and its celebrated authors unreservedly.

What are future directions that this book may track? Let me put on my thinking cap to suggest a few:

1. The exploration of enhancing the effect of LPT by combining it with other forms of Energy Medicine. For example the number of treatment sessions can be significantly reduced for myogenous pain, in my experience of several hundred cases, by combining it with trigger point acupuncture.
2. Evaluation of Trans Cranial Use: already there are promising preliminary results in closed head injuries, attention deficit conditions and post stroke.
3. Consideration of the effect of resonant frequencies that may entrain predictable tissue photo-acceptors. One must bear in mind developments in string theory in quantum physics.
4. Careful evaluation of the claims for the use of Class 4 Lasers, which extend the range of incident powers from the conventional upper limit of a 3B laser of 0.5 watts to as high as 15 watts, avoiding excess thermal effects by using large diametre lenses to spread the spot: this enables deep penetration and very high energy dosing, it is claimed. This is a very controversial field but it does require examination.

But there are so many exciting possibilities and I know that future editions of this book will continue to catalogue and evaluate them with an Aristotelian search for "telos" or meaning.

Terminology in this book

The therapeutic lasers used today are mainly below 500 mW. However, many lasers used for surgery can be defocused and arranged to give energy densities of the same values as the former. Thus, a therapeutic laser could be defined as a laser using energy densities below the threshold where irreversible changes in cells occur.

We now favour the term *Laser phototherapy (LPT*) which is an emerging terminology. An advantage of this term is that it offers a good description of the therapy and an option to define various phototherapies by using “LED phototherapy”, “Broadband polarised light phototherapy” etc. And they are all part of *Photomedicine*.

The term "soft laser" was originally used to differentiate therapeutic lasers from "hard lasers", i.e. surgical lasers. Several different designations then emerged, such as "MID laser" and "Medical laser". "Biostimulating laser" is another term, with the disadvantage that one can also give inhibiting doses. The term "bioregulating laser" has thus been proposed. One of the most frequent terms, "low-power laser", is misleading, since high-power lasers, too, are used for laser therapy.

An unsuitable name is "low-energy laser". The energy transferred to tissue is the product of laser output power and treatment time, which is why a "low-energy laser", over a long period of time, can actually emit a large amount of energy.

Regarding the laser instrument itself, we have chosen to use the term *therapeutic laser* rather than "Low-Level Laser", since high-level lasers are also used for laser therapy. Another reason is that many of the traditional laser types today are not really Low Level anymore and the commercial trend, at least, is towards higher output power. The MeSH definition is as follows:

- *Treatment using irradiation with light at low power intensities and with wavelengths in the range 540nm-830nm. The effects are thought to be mediated by a photochemical reaction that alters CELL MEMBRANE PERMEABILITY, leading to increased mRNA synthesis and CELL PROLIFERATION. The effects are not due to heat, as in LASER SURGERY.*

Low-level laser therapy has been used in general medicine, veterinary medicine, and dentistry for a wide variety of conditions, but most frequently for wound healing and pain control.
- Year introduced: 2002.

It is obvious that the nanometre range used by MeSH in inappropriate and should be changed, at least to 540-1064 nm. LPT effects have been observed for much higher ranges such as Er:YAG and even CO_2, but the photobiology of these wavelengths is less explored.

The question of nomenclature is far from solved. This is because there is a lack of full agreement internationally, and the names proposed thus far have been rather unwieldy. The degree of confusion is illustrated in scientific journals, even the specialised ones, where different terms are sometimes used in the same issue and, indeed, even in one and the same paper. Although we are using the term LPT in this book, we are aware of the fact that this term is not yet accepted by MeSH. As key words in scientific papers we will still have to adhere to the accepted MeSH terms.

MeSH key words in PubMed search: LLLT, Laser Biostimulation, Laser Irradiation, Low-Power Laser Therapy, Low-Level Laser Therapy, Low-Power Laser Irradiation, Low-Power Laser Therapy. Best search result is achieved for "LLLT".

A message from the authors.
Our first modest book in English appeared in 1996. In those days the scientific documentation was poor and there was no PubMed for convenient access to literature search. Documentation was obtained by buying papers from libraries, scanning lists of references, buying new papers and so forth. From that year we have constantly been upgrading the collected knowledge by adding new references. In the early years we included whatever there was; abstracts from congresses and articles from national or regional journals. These are still there, although having less scientific relevance today, remaining partly out of editorial convenience and partly because they can serve as historic references of an emerging medical method.

"Modern medicine without lasers is not modern"

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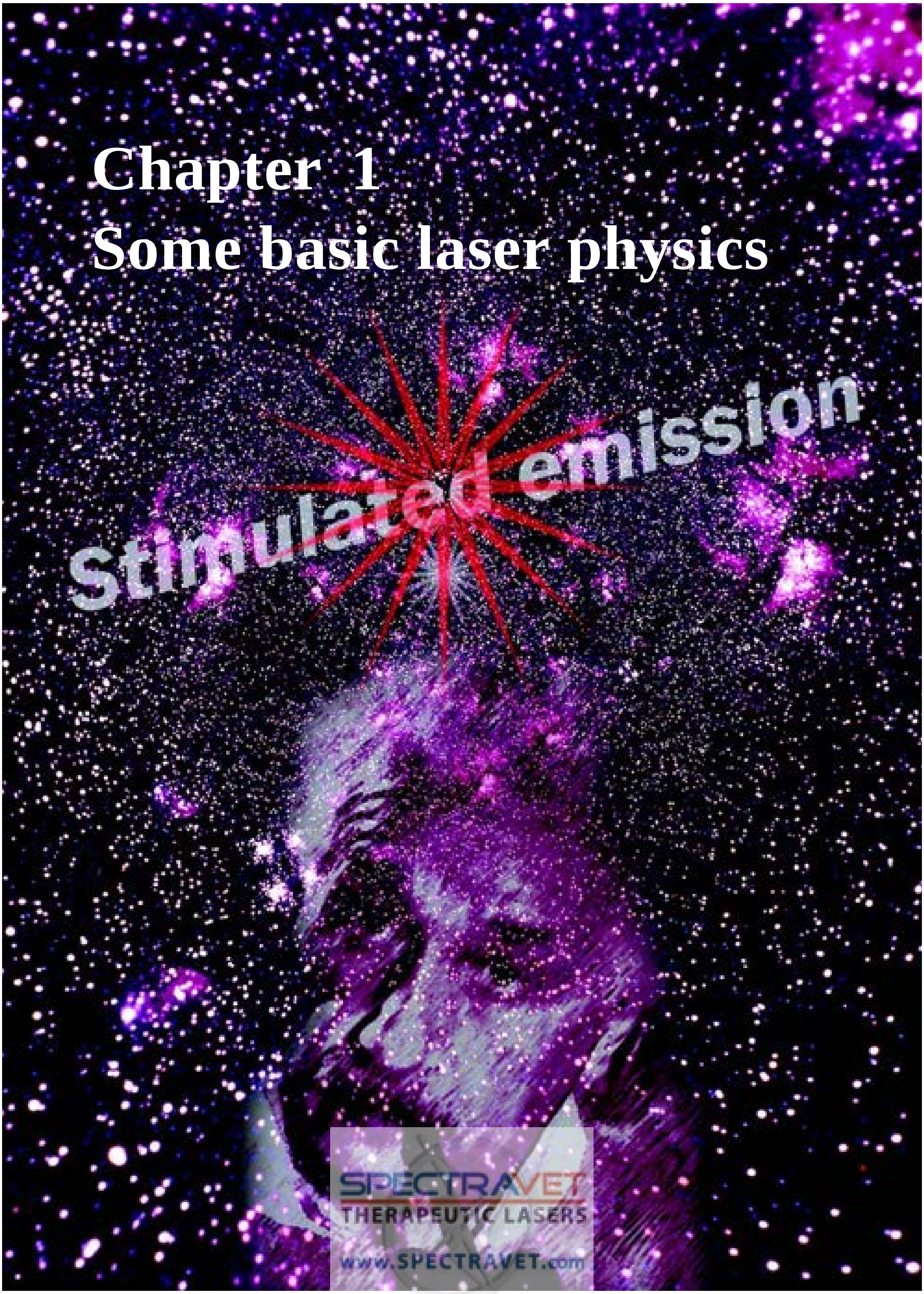
Table of contents

Chapter 1
Some basic laser physics



1.1 Introduction

This book is not intended to be a textbook in physics. With the title "Laser phototherapy" we need to explain something about light. The aim of this chapter is also to explain for the reader why some lasers and other light sources can be harmful to the eyes. We will also describe various types of lasers and other light sources which are used within medicine, and some of their characteristics.

1.2 Physics

For some people, just the word physics may cause cold shivers running down their back. But physics can be made interesting - even fun. We hope that this will be the case when you read this chapter.

Physics can be seen as the most fundamental of the natural sciences. Chemistry, for example, can be viewed as a complex application of physics, as it focuses on the interaction of energy and matter in chemical systems. We also know that biology is, at its heart, an application of chemical properties in living cells and tissue, which means that it is also, ultimately, ruled by the physical laws.

Physics also is important to all applied science and engineering that has taken us from the candle to the laser. Since physics covers such a wide area, it is divided into several specific fields, such as electronics, quantum physics, astronomy and biophysics etc. Here we will concentrate on photo medicine.

However, we will start by looking on a very essential part of physics, namely ENERGY. We want to point out though, that this is not meant to be a textbook in physics, but some little

1.3 Energy

As light is a form of energy, we need to know something about energy in general. The word energy is widely used in different connections, and various meanings are often ascribed to it. Here, however, we have limited ourselves to energy in the context of natural sciences, like physics.

Energy is the most fundamental concept in our universe. Everything is energy - stored or moving. Matter is a form of energy, solid, floating or gaseous. Heat is energy. Light is energy. Movement is energy. Sound is energy. Electricity is energy - everything is energy. Energy lights our cities. Energy powers our vehicles, trains, planes and rockets. Energy warms our homes, prepares our food, plays our music and gives us pictures on television. We use energy to do work.

If we run or walk, energy is converted from stored chemical energy to kinetic energy. Energy from the sun gives us light, rain and wind and it helps plants grow. Energy stored in plants is eaten by animals, giving them energy to keep them warm and to move. Everything we do is connected to energy in one form or another. Even cooling needs energy - it takes energy to move heat from one place to another.

One of the most fundamental laws of the universe is called "The principle of energy". According to this law, energy can neither be created nor destroyed. It can only be transformed from one form to another. This law is a fundamental principle of physics.

There is also another fundamental law that you may have heard of - the first law of thermodynamics. It says that "the total inflow of energy into a system must equal the total outflow of energy from the system, plus the change in the energy contained within the system". This law is used in all branches of physics.

Energy is usually written E. The most important unit for energy is the joule [J]. This name comes from the English physicist James Joule. One joule is a fairly small amount of energy.

When you buy a pack of sugar, it is usually written on the label that it the energy content is a certain amount of joules. An older unit is the calorie where 1 calorie is the amount of energy that needs to raise the temperature of 1 gram water (= 1 cm^2) one degree Celsius. Though being an older unit, it is still much used because it is practical.

The joule is important because it is the metric unit: 1 joule = 1 watt-second. Turning that around it will tell us that one watt is the energy amount of one joule delivered once per second.

Power is usually written P, and is the same as strength. A strong lamp has a higher power than a weak one. Power is measured in watts [W]. The relation between energy and power is simply the time. $E = P \times t$

At home you have probably a metre for electricity. It counts how much electric energy you use. This is measured in kilowatt hours (kWh). 1 kilowatt is 1000 watts and one hour is 3600 seconds, so 1 kWh is 1000 × 3600 = 3.600.000 watt-seconds, i.e. 3.600.000 joules. It is about the same as if you have an electric heater and switches it on the highest power (let us say 1000 watts) and leaves it on for one hour. Correspondingly, a 40 watt lamp can run for 25 hours on 1 kWh.

Our most important source of energy is the sun. The solar energy is radiation energy and it is called electromagnetic radiation. To every square metre at right angel to the sun rays, 1400 watts is coming in. Part of this energy will be reflected and approximately the remaining will be absorbed by the matter it hits and converted from radiation energy to heat (thermal energy). A white stone reflects more than a black stone, which in turn absorbs more and hence will become warmer.

1.4 Radiation

Radiation means energy that is moving. There are different forms of radiation. Sound is one type - mechanical energy, transported through a medium, such as air, water, metal. The speed of sound in air is 340 metre per second and about 5000 metre per second in metal. Mechanical energy needs a medium - no sound can be transported through vacuum.

Particle radiation means that physical particles (a physical particle, such as an electron has a mass in rest - i.e. with the speed = 0 metre/second) is emitted from a source. Example is alpha and beta radiation and cosmic radiation. The speed of such radiation is always less than the speed of light in vacuum (about 300.000.000 m/s). Principally, even a hale storm or rain is an example of particle radiation.

The third type of radiation is the electromagnetic radiation. This will be explained further later, but in short we can say that the energy here consists of photons, a form of particles with 0 mass in rest, moving with the speed of light. The speed of light (in vacuum) can never be reached when matter is mooving

1.4.1 Electromagnetic radiation

The radiation emitted by the sun, light-bulbs, fires, radio transmitters, etc. is called electromagnetic radiation. This form of energy travels with the speed of light, i.e. 300.000 kilometres per second (to be more exact: c = 299.792.456.2 ± 1.1 m/sec).

Isac Newton showed that light is a form of waves, with a measurable wavelength and a certain frequency related to that wavelength.

On the other hand, Albert Einstein showed, 200 years later, that light appears as particles, like pouring sand. This is most obvious if the intensity is very low. These particles are called photons. The photon is the smallest amount of electromagnetic radiation and can not be divided.

So this form of energy is appearing in a dualistic way, so the photons can both be seen as waves and particles, so we can call them "wave particles" or wave packets. Each photon has a defined wavelength and a frequency related to that wavelength.

1.5 Wavelength and frequency

All waves have a wavelength and a frequency. The wavelength is the length of one wave cycle, which can be measured as the distance between successive wave crests. Wavelength is usually represented by the Greek letter lambda (λ). Wavelength is measured in metres [m] or some factor of metres (e.g. nanometres [nm] 10-^{9} m = 0.000000001 m).

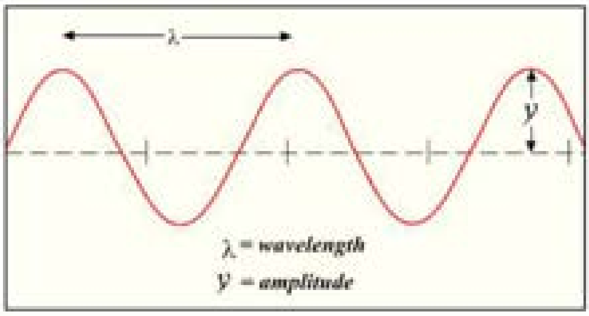


Figure 1.1 Wavelength and amplitude

Frequency refers to the number of cycles of a wave passing a fixed point per unit of time. Frequency is normally measured in hertz [Hz], equivalent to one cycle per second, and various multiples of hertz.

In general, for all form of waves (sound waves, water waves) there is a relationship between the wavelength and the frequency (usually in physics denominated the Greek letter pronounced new). This relation is then written:

$$\lambda \times \nu = v$$

where v = the speed of the wave measured in metres per second. For the electro-magnetic radiation, the speed v is the speed of light, usually written c. In a medium (i.e. other than in vacuum) the formula will be:

$$\lambda \times \nu = c/n$$

where n is the index of refraction.

The electromagnetic radiation has a very wide spectrum and to specify what part of it we mean, we can use either wavelength or frequency. In this book, we will consequently use wavelength in all but a few cases. One reason not to use frequency is that "frequency" often arises in discussions of pulsed radiation, and is then used to denote pulse frequency (number of pulses per second).

1.6 Photon energy

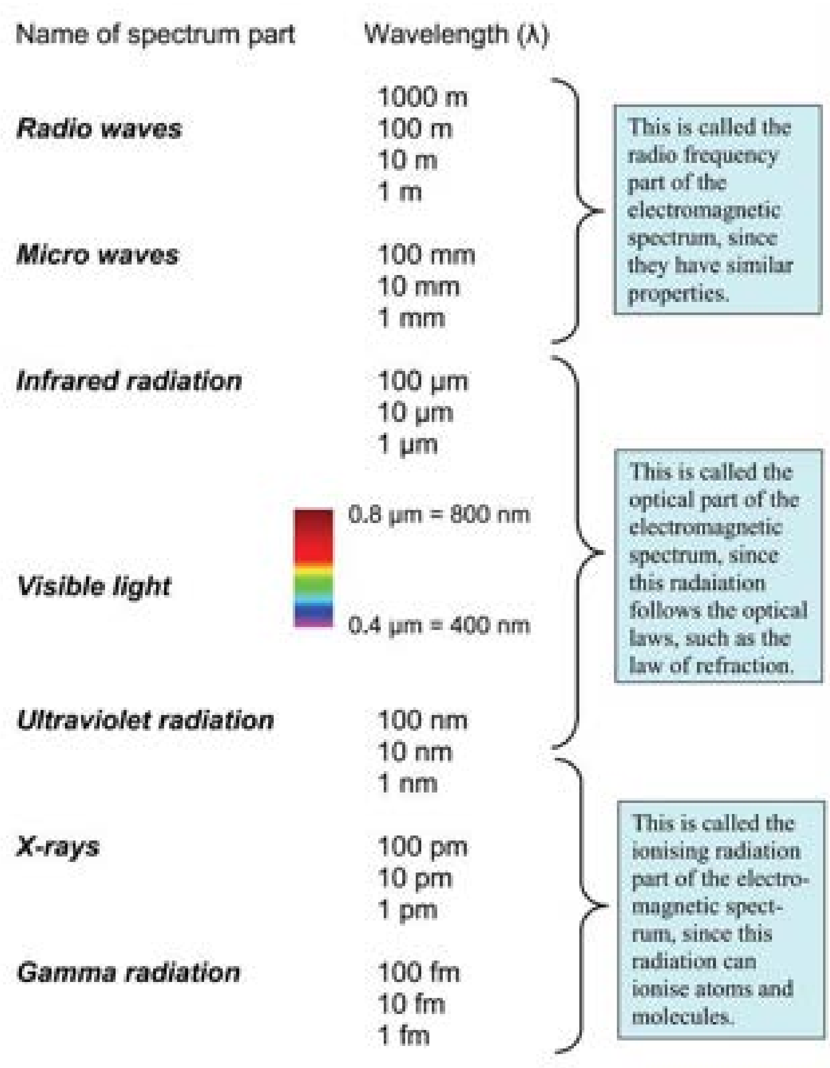
Photons of different wavelengths have different energy levels. Photon energy (E) is proportional to frequency (λ) and can be expressed as

$$E = h \times \nu = h \times c / \lambda$$

where h is equal to Planck's constant. If we use wavelength instead of frequency, photon energy would be inversely proportional to the photon's wavelength. Photons with a long wavelength therefore have a low energy, while photons with a short wavelength have a high energy.

1.7 The electromagnetic spectrum

Electromagnetic radiation spans over an enormous range of wavelengths, often referred to as the wavelength spectrum, and the different parts of this spectrum have been given different names. Very long waves, metres to kilometres, are named radio waves. Shorter waves, down to a millimetre, the waves are named micro waves. Further, wavelengths down to about one (to be more specific - 0.8) micro metre, they are called infrared radiation or heat radiation. The unit micro means millionth and micro metre is hence a millionth of a metre, written 0.000001 metre. Micro metre is usually written µm where µ is a greec letter. The visible part of the electromagnetic spectrum spans between 0.4 and 0.8 µm. Often, the unit nanometre is used instead of µm and we will consequently use nanometre (nm) in this book. 1 µm equals 1000 nm. With this unit, the visible spectrum lies between 400 and 800 nm. With shorter wavelengths than 400 nm we enter the ultra violet radiation, invisible like the infrared. After ultra violet comes x-rays and then gamma rays.


Name of spectrum part
Wavelength (λ)
Radio waves
1000 m
100 m
10 m
1 m
Micro waves
100 mm
10 mm
1 mm
This is called the radio frequency part of the electromagnetic spectrum, since they have similar properties.
Infrared radiation
100 µm
10 µm
1 µm
0.8 µm = 800 nm
Visible light
0.4 µm = 400 nm
This is called the optical part of the electromagnetic spectrum, since this radaiation follows the optical laws, such as the law of refraction.
Ultraviolet radiation
100 nm
10 nm
1 nm
X-rays
100 pm
10 pm
1 pm
Gamma radiation
100 fm
10 fm
1 fm
This is called the ionising radiation part of the electro-magnetic spect-rum, since this radiation can ionise atoms and molecules.

Name	Wavelengths	Used for	Source
Radio waves	1000 - 1 m	Radio, TV, telecommunications, cellular telephones	Radio transmitters, electric cables
Microwaves	1000 - 1 mm	Radar, telecom, microwave ovens, speed measuring	Klystrons, magnetrons, masers
Infrared (IR)	1000 - 0.8 μm	Radiation heaters, infrared heating, remote control	Hot objects, IR lamps, fires, LEDs, lasers
Visible light	800 - 400 nm	Illumination, photography, imaging, holography	Light-bulbs, flash lamps, candles, LEDs, lasers
Ultraviolet (UV)	400 - 1 nm	Solarium, curing of plastics, sterilisation	UV lamps, lasers, accelerators
X-rays	1000 - 1 pm	X-raying, radiation treatment of tumours	X-ray tubes, accelerators
Gamma Rays	1000 - 1 fm	Radiation treatment of cancer, sterilisation of food	Radioactive isotopes, particle accelerators

Table 1.1 The electromagnetic spectrum

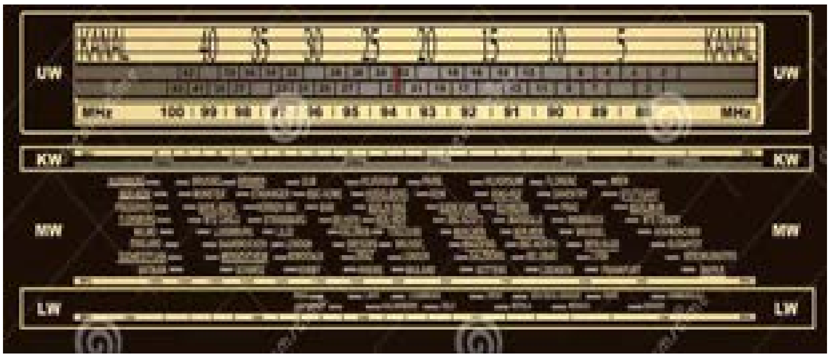


Figure 1.2 Classic radio dial

1.7.1 The optical region

Part of the spectrum of electromagnetic radiation follows the laws of optics. It includes wavelengths between approximately 10 and 100.000 nm, and is usually referred to as "optical radiation", even though most of it lies outside the visible spectrum (i.e. wavelengths of about 400-800 nm). Both infrared (IR) and ultra-violet (UV) radiation exhibit many similarities with visible light, and are therefore regarded as part of the optical region.

In the following, when we use the word "light" we usually also incluce radiation outside the visible part, i.e. from about 200 nm in the ultraviolet region, and up to about 10.000 nm in the infrared region. This includes also the spectrum that concerns phototherapy.

1.7.2 Radiation risks

Although most lasers are harmless, some lasers certainly can cause eye injury. The most dangerous types combine high power (> 100 mW) with a collimated beam and have a wavelength in the interval 700 nm - 1400 nm. So called laser pointers are harmless. A divergent beam can be quite strong and still carry a low risk; the more divergent, the less risk.

Because different wavelengths have different photon energy, the risks of exposure to various kinds of electromagnetic radiation are also of varying magnitude. High-energy photons (gamma rays, X-rays and ultra-violet light) can "break" (ionise) atoms and break up chemical bonds in molecules which they encounter, while low-energy photons (radio waves and microwaves, infrared and visible light) do not cause ionisation, but only excitation and heating. Photons in the optical field, either as visible light, ultraviolet or infrared, can be reflected, transmitted (that is, go right through) or absorbed when they hit matter. Tissue is generally more transparent to wavelengths near infrared (750 - 850 nm) than to visible light. When a photon is absorbed, it sheds all of its energy into the matter and is annihilated. The energy shed is transformed to another type of energy, mostly thermal. Consequently, if high-power radiation (many watts = many photons per second) hits an object, a great deal of heat can result (for example, a stone in the sun becomes hot). By concentrating a beam on a small area, e.g. by focusing it, a high power density is achieved in that small area and the heat built up during the absorption of the radiation can be so great that the beam burns, melts or vapourises the material in the area encountered. This technique is used in surgical lasers. In this way, all radiation (if sufficiently intense) can injure an individual or burn an object.

1.7.3 Can electromagnetic radiation cause cancer?

Electromagnetic radiation can injure living organisms if it

1) is of sufficient intensity to burn (many watts) and/or
2) contains high-energy photons (short wavelength).

N.B. Whether the photons come from a “natural” or from an artificial light source is of no significance - one photon with a certain energy is exactly the same as another one with the same energy! However, those types of radiation involving photons in which the energy level is so high that they can ionise are dangerous even in small doses, because ionisation is by nature damaging. This type of radiation is usually called ionising radiation.

In principle, all ionising radiation is carcinogenic, since cell damage may result from exposure to it. All electromagnetic radiation with a wavelength shorter than 320 nm (UVB radiation, UVC radiation, X-rays, and gamma radiation) is ionising, and thus in principle dangerous to us even in relatively low quantities. In the range from 320 nm to 400 nm (the UVA band), long-term exposure - to sunlight or in a solarium, has been shown to cause damage, though only rarely cancer.

There is a fairly clear wavelength limit at which photon energy becomes so high that the photons can ionise matter which they hit. This limit is 320 nm (for physicists: this corresponds to 3.91 eV) so that photons with a shorter wavelength than this are capable of ionising molecules or atoms in tissue and hence can cause cancer (they are carcinogenic).

An example of a source of radiation which produces carcinogenic ultraviolet radiation is the old quartz lamp. The casing of such a lamp is not made of glass but of quartz. This material, unlike glass, allows ultraviolet radiation to pass through it, and tolerates much higher temperatures. Quartz lamps produce much of their radiation in the wavelength field around 250 nm. Ultraviolet radiation with such a short wavelength is very aggressive and is used, for example, to kill bacteria and other micro-organisms. Because the radiation from quartz lamps is carcinogenic, these lamps were banned in most countries about 40 years ago. A laser with the same wavelength and the same strength is just as dangerous - neither more nor less. (See chapter 1.18 “Risk of eye injury” on page 33). The risk factor depends on both the dose and the power density of the radiation.

1.7.4 Protective mechanisms

Human beings have always been subjected to solar radiation. The sun emits all of the types of radiation shown in the table on the previous page, though only radio waves, microwaves, infrared radiation (thermal radiation), visible light, and the longwave part of ultraviolet radiation are not absorbed by the atmosphere and therefore reach the surface of the earth. Of those types of radiation that reach the ground, only a small part of the ultraviolet radiation (known as UVB) is dangerous to human beings. We have as a consequence developed protective mechanisms against it. Special cells (melanocytes) in the outer skin produce melanin, which absorbs UV radiation and prevents it from reaching the deeper and more sensitive tissues.

1.8 Light

Light is the part of the electromagnetic spectrum where we have sensitive detectors - eyes. Most of us experience light of different wavelength as different colours.

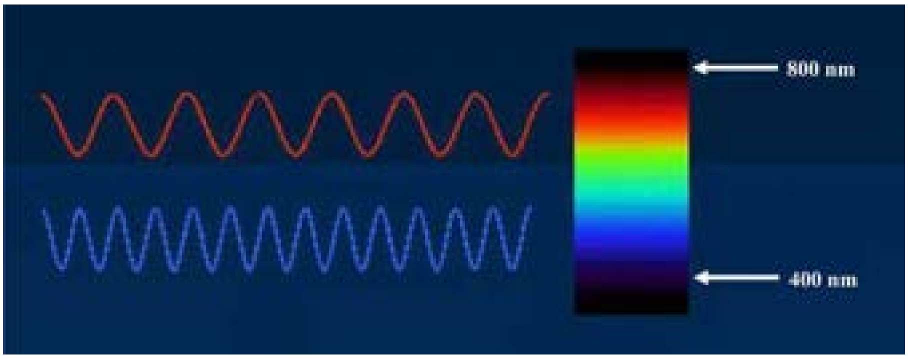


Figure 1.3 The long wavelengths are experienced as red light, short as blue or purple and medium as yellow-green. Our eyes are not equally sensitive to the different light wavelengths and the diagram below will illustrate this.

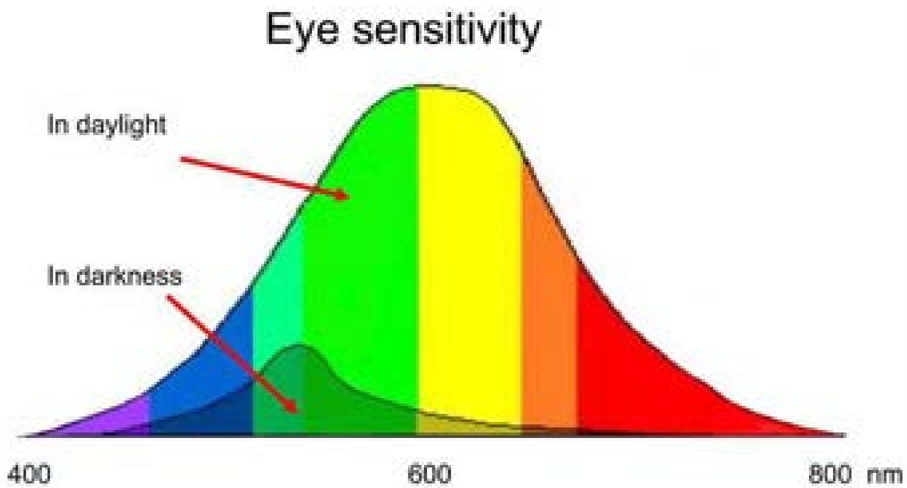
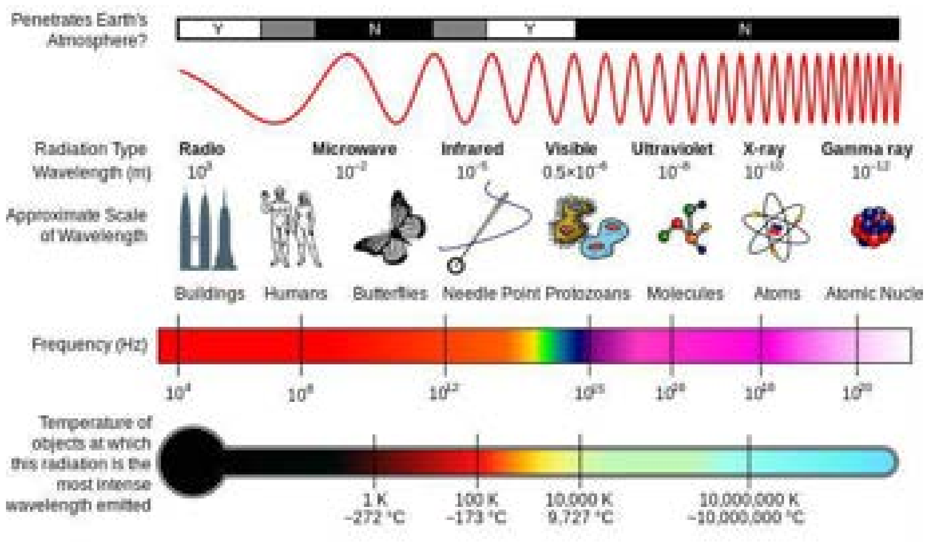


Figure 1.4 Eye sensitivity

For our eyes, infrared radiation is invisible, but some cameras may "see" it. This lady directs a laser probe with four laser diodes emitting infrared light against the camera. For the camera, it looks white due to its high intensity. (The four "glowing" spots in her forhead appear due to internal reflections in the camera's lens system.)

1.9 The optical spectrum

All electromagnetic radiation has a spectrum - a wavelength distribution. Light from ordinary light sources (sun, filament lamps, light tubes) are very wide banded, contrary to the laser.



Courtesy Wikipedia

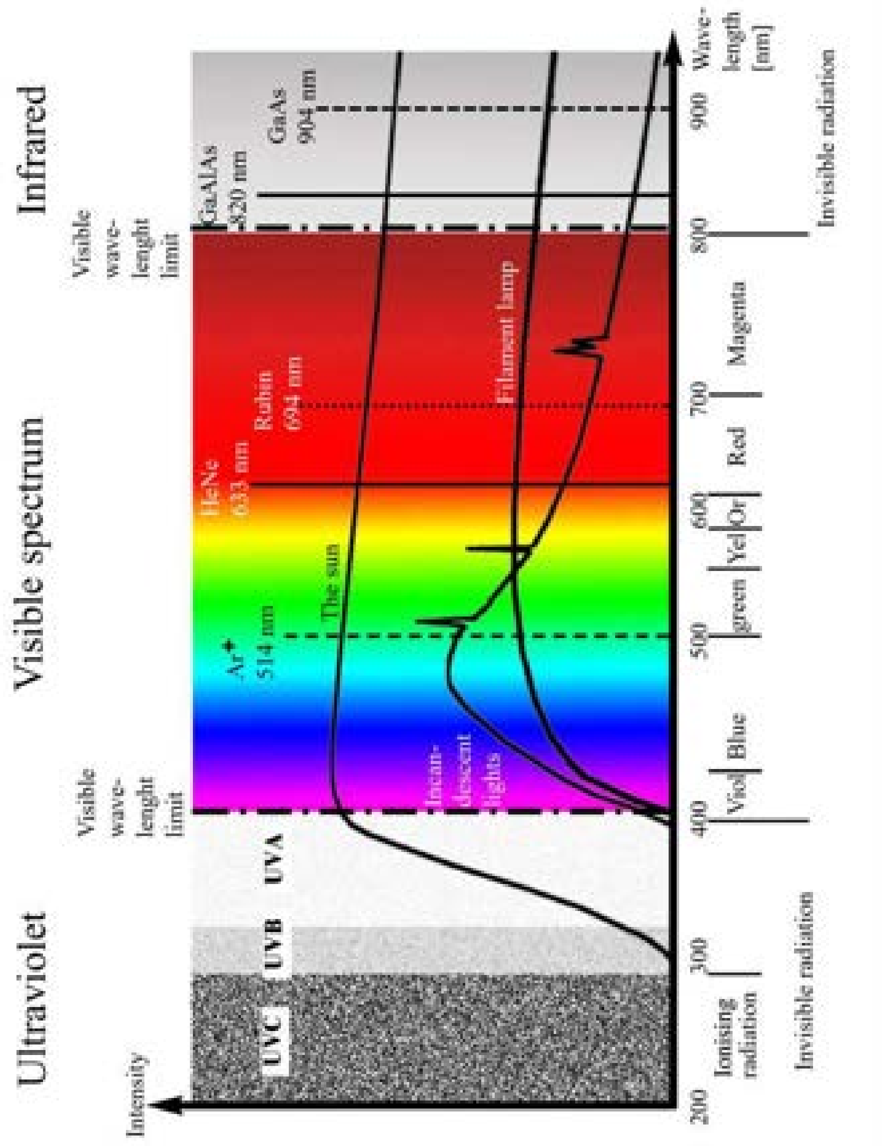


Figure 1.5 This diagramme shows the wavelength distribution of light from various sources, including sunlight, filament lamps, fluorescent lamps, and several different lasers. Note that the spectrum of a laser is shown as a narrow vertical line; the laser emits light of only "one" wavelength. N.B. This line has nothing to do with the fact that laser light is sometimes collimated to a narrow beam!

1.10 Light sources

In comparison to the very wide electromagnetic spectrum, the visble spectrum is very, very narrow. All light is creatid in matter. The properties of the light depends very much of the properties of that matter. The matter is usually solid or in gas form. Often a high temperature is needed.

When we supply energy to matter, part of it can be converted to light. If we heat a piece of iron enough, it will start emitting light when the temperature is around 500 °C. The temperature of the tungsten filament in a filament lamp can be 1200 °C or more. The higher the temperature, the more bluish is the emitted light.

The colour of light

If we are not colour blind, we experience different wavelengths of light differently. Long wavelengths we see as red. Short wavelengths we wee as blue. By mixing different wavelengths, we can create thousands of colours. In a colour television there are only three colours: red, blue and green.

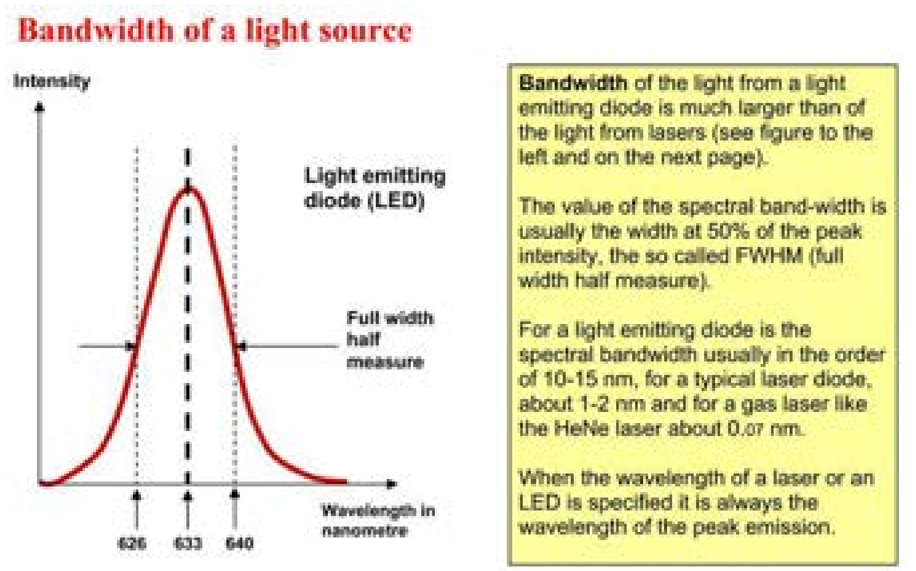


Figure 1.6 Bandwith of a ligth source

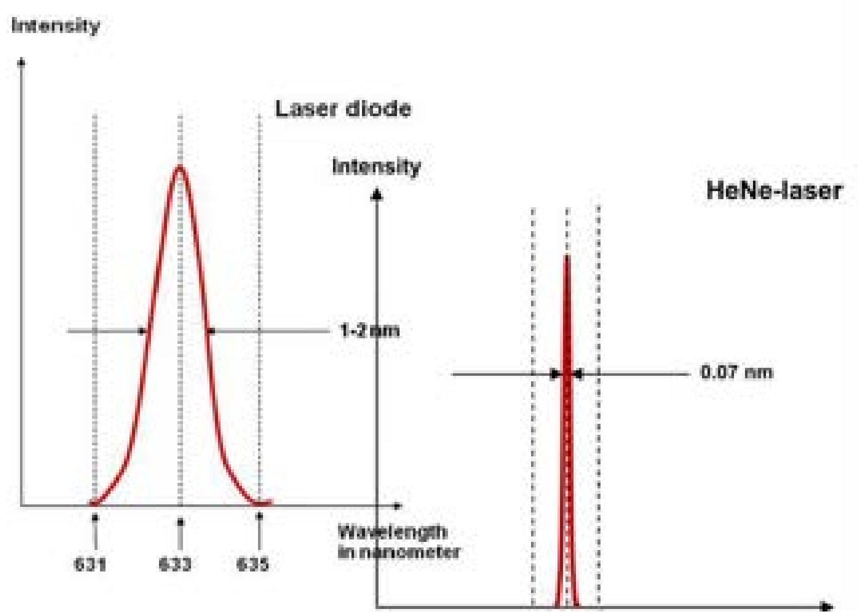


Figure 1.7 Different bandwidths

1.11 Various sources of radiation

1.11.1 Natural sources of radiation

The sun is our main natural source of radiation and energy. Like the lights used for general illumination, it has a very wide spectrum (i.e. composed of photons with considerably varying wavelengths). Outside the atmosphere the solar spectrum is different from what it is on ground level due to the atmospheres filtering effect. Our atmosphere contains different gases (like nitrogen, oxygen, water vapour, carbon dioxide, ozone and other) with different absorption of different light wavelengths. The atmosphere also contain different particles that absorps and scatters light.

On the earth's surface, solar spectral radiation has its highest intensity at 440 nm, blue light, over and under which it decreases. The sun, then, is actually blue, though any self-respecting child will draw it in yellow. It looks yellow to us because our eyes are most sensitive to yellow - 550 nm (see chapter 1.18 “Risk of eye injury” on page 33). Under 440 nm, the intensity of solar radiation drops, falling to zero at 290 nm (with the ozone layer in its present state). The carcinogenic part of solar radiation lies between 290 and 320 nm, and is known as UVB radiation. There is no upper limit to the sun's long-wave radiation, but at very long wavelengths - radio waves - the intensity is very low.

1.11.2 Man-made light sources

All conventional light sources are more or less broadband. The most narrow-banded are low-pressure gas discharge lights, such as neon lights (red) or sodium lights (yellow). These often feature a dominant wavelength, meaning that most photons have this wavelength or a wavelength close to it. These light sources have a function in some ways reminiscent of a laser's.

Of all the hundreds of types of lamps, we have chosen to study only two types in more detail: the light emitting diode and the laser. They are both used in therapeutic instruments and it is important to know the difference between them.

1.11.3 The light-emitting diode (LED)

Another light source, which is relatively narrow-banded, is the light-emitting diode. This is a small, inexpensive semiconductor lamp, which should not be confused with a laser. Typical LEDs produce red, yellow, green, blue or even white light (three LEDs in one case). There are LEDs which emit infrared radiation, generally with wavelengths around 950 nm (entirely invisible). These are often used in television remote control units.

According to the European Standard IEC 601, an LED is: "*Any semiconductor p-n junction device which can be made to produce electromagnetic radiation by radiative recombination in the semiconductor in the wavelength range from 180 nm to 1 mm, produced primarily by the process of spontaneous emission*."

1.12 Flash lamps

Certains lamps, such as gas discharge lamps - often xenon - powered with strong current pulses, can produce flashes of light. Small such flash lamps can be found in cameras. Stronger lamps, such as those used in solid state lasers are made thousandfold stronger. This is also the case in a type of instrument, named IPL (Intense Pulsed Light) devices. They are mainly used for permanent hair reduction, skin rejuvenation and acne treatment.

Figure 1.8 IPL wounds

This picture shows the result of hair removal with an IPL device with too high pulse energy. From the rectangular shape of the burn marks, we can see that it is done with an IPL instrument and not a ruby or alexandrite laser.

This picture shows a relatively small IPL instrument. The handpiece contains the water cooled flash lamp with a reflector and interchangeable optical band pass filters

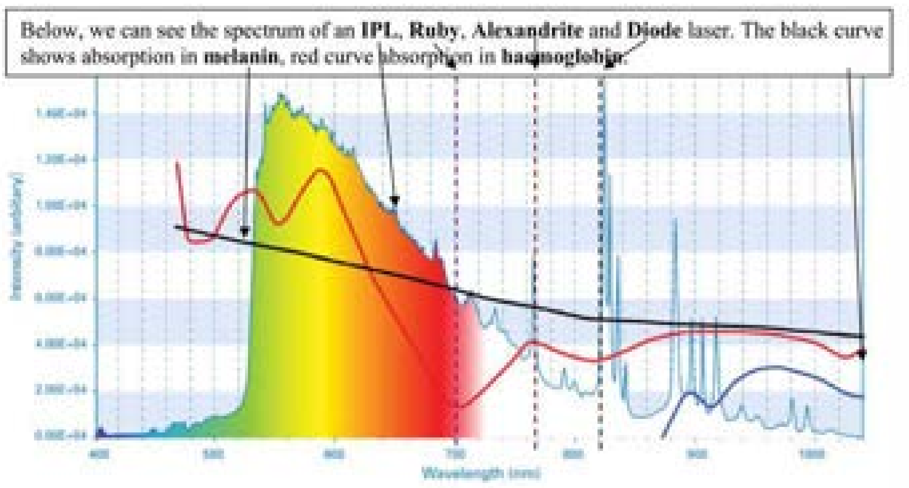


Figure 1.9 Absorption of melanin and haemoglobin

1.13 The laser

The laser is the latest and most advanced of our light sources. The word LASER is an acronym for Light Amplification by Stimulated Emission of Radiation.

Some credit for the development of the laser theory is given to Albert Einstein. In his theory "Zur Quantum Theories der Strahlung", published 1916, he first used the name stimulated emission. Other important steps have been taken by Arthur Shawlow, Charles Townes and Theodor Maiman. Maiman presented the first working laser, a ruby laser, at a press conference on 7th July 1960.

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According to the European Standard IEC 601, the definition of a laser is: “*Any device which can be made to produce or amplify electromagnetic radiation in the wavelength range from 180 nm to 1 mm primarily by the process of controlled stimulated emission*”.

A laser is a device that emits electromagnetic radiation in the optical region. If this radiation is visible, a laser is a lamp. If the radiation is infrared, the laser is source of infrared radiation (correspondingly if the radiation is ultra violet).

When you put the question above, you often get the answer: a beam! The correct answer is, though, a device that produces a beam (of visible or invisible light). You can also say that a laser is a tool - it can be small or large and look like just anything.

Another correct answer is that a laser is a light amplifier. A predecessor of the laser was the MASER (Microwave Amplification by Stimulated Emission of Radiation). It works on the same principle as the laser, but within the microwave range.

1.13.1 Laser design

A laser, whether large or small, always includes the following parts:

Energy source	(power supply)
Lasing (amplifying) medium	(solid, liquid or gas)
Resonating cavity	(mirrors)

How energy is supplied to the lasing medium depends on the structure of the medium. The energy source may be an electrical current, optical radiation from a flash lamp or another (pumping) laser, radio waves or microwaves, or a chemical reaction. The lasing medium must be able to store the energy supplied, by a process called population inversion. This stored energy can then be emitted in an organised fashion, known as stimulated emission of radiation. When a photon with the right photon energy enters the electromagnetic field of the excited atom with energy stored in this way, some of the energy is emitted by means of an identical photon being created. The first photon is not absorbed. Hence, both the new and the old photon can then travel along and stimulate other atoms in the lasing medium to emit their stored energy. An "avalanche" of light, with all the photons of exact same photon energy, thus occurs.

In the figure below, the lasing principle for a CO_2 laser in an atomic energy diagram is shown. When energy is fed into the gas mixture in a CO_2-laser, we can make electrons increase their energy from energy level 000 to 1. This is often called pumping. From level 1 (that is a non stable level) the electron energy goes to level 001 that is a so called meta-stable level. In this energy level, electrons can stay for a "long" time. If, during this time, a photon with the wavelength 10.6 µm will pass this energised CO_2 molecule closely enough, the electron on energy level 001 will be stimulated to fall down to energy level 100 with lower energy. The difference in energy between these two levels will go out in the form of a photon with 10.6 µm wavelength. From level 100, the electron will pass lower energy levels (020 and 010) quickly (pico seconds) and its remaining energy will be released in the form of molecule vibration (heat) or rotation or photons with longer wavelengths. It is also possible for a CO_2-laser to emit 9.6 µm light (see the diagram) but then the output power usually is lower that what is possible with 10.6 µm wavelength.

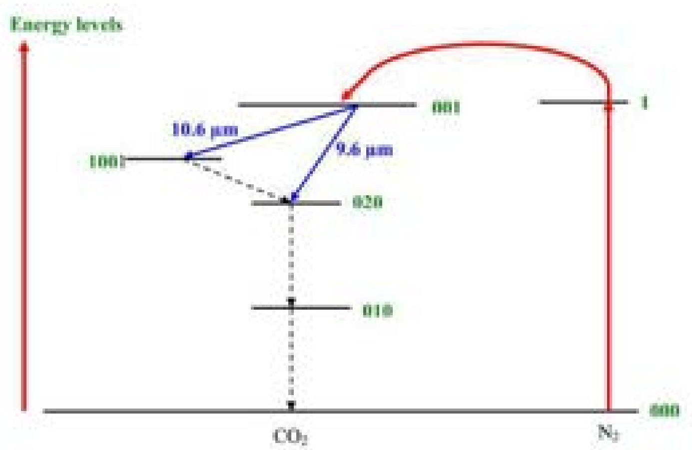


Figure 1.10 Energy diagramme for CO_2 lasers

Due to the fixed energy leves of the laser medium, the radiation from a laser always has a certain fixed wavelength unlike the radiation from other light sources consist of a whole range of wavelengths. There are currently thousands of different types of laser, and these produce visible light, UV, or IR radiation of various wavelengths. As can be seen from the example above, a laser has one characteristic wavelength, though it is sometimes possible to choose one or several other wavelengths. There are a few lasers designed such that the wavelength can be changed, even during operation - tunable lasers.

Further, the lasing medium is generally elongated in shape, often in the form of a channel (gas lasers) or a narrow rod (solid state lasers) or doped channel in a semiconductor crystal. There is also fibre lasers, where the lasing medium is part of the optic fibre, also used to conduct the laser light produced.

Summing up: Stimulated emission only occurs when the incident photon has exactly the right energy as the released photon; the first photon causes release of the second photon simultaneously, i.e. the second photon must follow the oscillations of the first photon, so that the two photons oscillate together in phase. This phase-locked, wavelength specific, photon chain reaction results in the monochromatic (one wavelength), coherent (fixed phase relation) characteristics of laser light.

1.14 Practical lasers

Generally in any laser, we have three different units: Power supply, lasing medium and a resonator. See figure on next page. The power supply is adjusted to the laser type and can use electric energy, radiation energy (e.g. flash lamps or light from other lasers) or even chemical energy. The lasing medium can be a gas mixture, a crystal or a liquid (dye laser). The resonator consists of two mirrors reflecting light back anf forth, making photons pass the energised lasing medium many times, building up an avalanche of light between the mirrors

The mirrors form the resonating cavity, (typically a Fabry-Perot resonator). This makes the light produced in the lasing medium, reflected back into the lasing medium several times and stimulates new light production. The resonating cavity is of two-fold importance: it increases the lasing medium's amplification and makes the light more coherent (See chapter 9.1 “The role of coherence in laser phototherapy” on page 662).

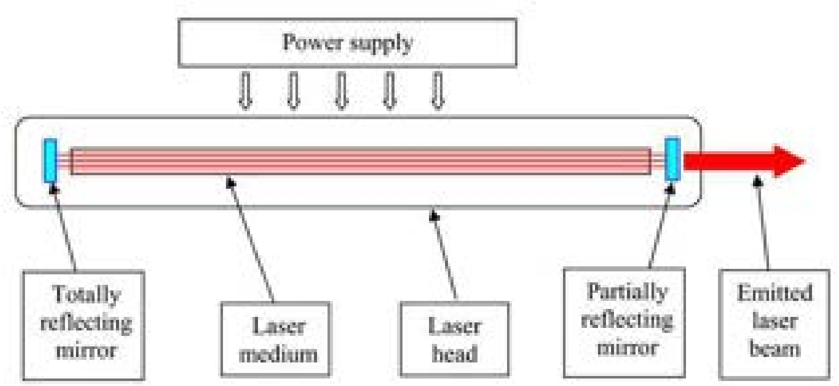
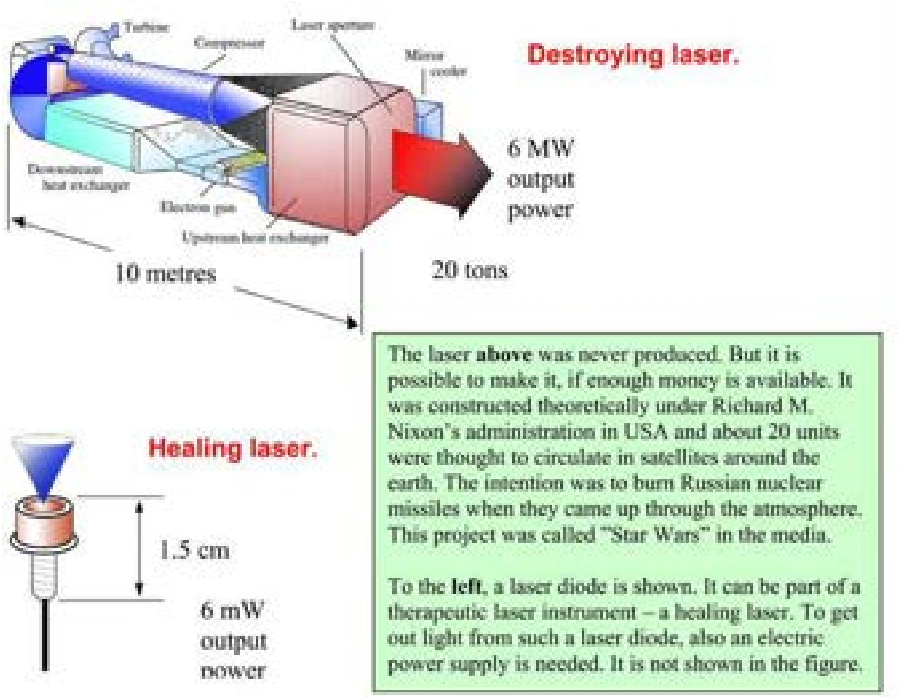


Figure 1.11 Principle design of a laser

Sometimes, such as in most semiconductor lasers, the mirrors are fitted at the ends of the crystal. The elongation and mirror arrangement also make it possible for the light to emerge as a more or less parallel beam (that may be focused to an extremely small point). How parallel depends on the elongation and on diffraction in the aperture. To extract the light from the laser, one mirror (and sometimes both) is made somewhat transparent - most often with 1 to 20% transparency, so that between 99% and 80% of the light is reflected back. Hence, the power inside a laser is always higher than the output power.

Other optical components may be arranged between the mirrors, permitting wavelength selection, polarisation of the laser light, or Q-switching (a pulsing method making it possible to achieve very intense and very short pulses). By inserting a non linear crystal, optical overtones (e.g. double frequency) can be generated - one example of this is the KTP laser (frequency-doubled Nd:YAG laser with 532 nm wavelength).

The emitted laser beam is often rather parallel, especially in gas lasers and solid state lasers. In semiconductor lasers the beam is usually fanshaped. However, by using a collimator we can make the beam rather parallel.



1.14.1 The properties of laser light

Laser light has two essential characteristics which differentiate it from "normal" light:

(1) its very narrow bandwidth
(2) its high level of coherence

Coherence means that the photons are well ordered - they are connected and build light waves that remain synchronised with one another over long distances. A narrow bandwidth is necessary for a high degree of coherence. These two characteristics are typical of all laser light and are important with regard to laser therapy. Neither of them, however, has any major significance in the use of lasers as surgical instruments. Two other characteristics that many people believe are typical of lasers are:

(3) parallel beams
(4) high intensity

These characteristics can often be brought about in a laser by chosing the size and geometric design of the lasing medium and resonating cavity as mentioned above, **but laser light does not need to be parallel or particularly strong**. These two characteristics are, however, most important with respect to lasers as surgical instruments. They are also the properties of laser light that make it harmful to the eye under certain circumstances. Narrow and parallel beams can allow the entire volume of light to pass through the pupil of an unprotected eye - it is thus not difficult to imagine how an intense laser light source can be dangerous to our light-sensitive eyes. (See 1.18 “Risk of eye injury” on page 33.)

1.14.2 Coherence

Coherence generally means order, or synchronicity. When a troop of soldiers is marching, it moves coherently, but if the soldiers are free to leave, they start to move incoherently. The same is true of the sound emanating from a flute (a flute is a typical “sound laser” - it has a resonance cavity, and its sound is monochromatic and coherent).

Coherent movement.
Soldiers, marching (moving coherently) over a bridge, will influence the mechanical structure differrently than they would if they were walking or running (moving incoherently) over the same bridge

Non-coherent movement
The tone of a flute may cause a crystal glass to break due to interference and resonance, but a wide-band, incoherent sound of the same intensity cannot break the glass. Interference is the effect of adding two or more waves. This addition may result in either amplification (constructive interference) or attenuation (destructive interference) of the resulting amplitude. Amplification is what makes extra high peaks when water waves meet, or what makes one pitch sound particularly strong when we sing at various pitches in the bathroom.

When a rough surface is illuminated with visible laser light, a kind of grainy quality can be observed in the light. These grainy elements, or granules, are called laser speckles and occur as a result of interference between different light beams. This is because light with a sufficiently high coherence length can be "combined" in the same way that waves of water combine when they meet. (More about speckles and their medical importance in chapter 9.1 “The role of coherence in laser phototherapy” on page 662)

Waves of coherent light stay in phase in long trains of waves. The length of these trains of waves, the coherence length, may vary from one light source to another. An ordinary light bulb has a low coherence length, a matter of thousandths of a millimetre. A HeNe laser, on the other hand, may have a very high coherence length - decimetres or even several metres. A semiconductor laser usually has a coherence length of no more than a millimetre or so.

N.B. In a laser beam, the different parts of the wave field can have a fixed phase relation but are normally not "in phase".

The concept of coherence consists of both spatial and temporal coherence and it is mainly the former that is of interest here. However, the two are related to each other through the relation: $\Delta\omega \times \Delta t \geq 2\pi$ where $\Delta\omega$ represents the frequency interval within which the radiation is emitted and where Δt is close to the coherence time - higher Δt means a higher degree of temporal coherence. In short: Coherence means "order" or synchronicity and may be defined as a property of wavelike states that enables it to exhibit ***interference***.

1.15 Interference

In the left figure below, two waves in phase are added and through interference (constructive) the resulting wave has high amplitude.
In the left figure below, two waves in phase are added and through interference (constructive) the resulting wave has high amplitude.

In the right figure below, two waves in counter phase are added and interfering (destructive) resulting in a wave with low or zero amplitude (cancel out each other).

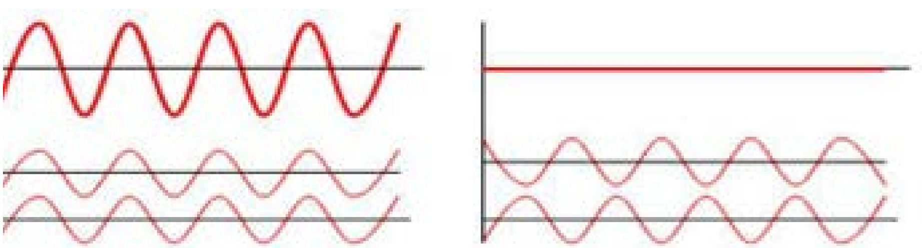


Figure 1.12 Waves in counterface

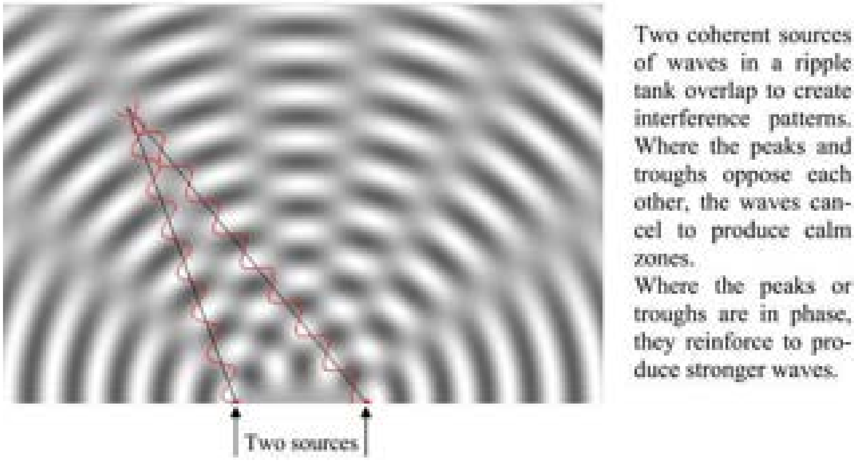


Figure 1.13 Interference pattern

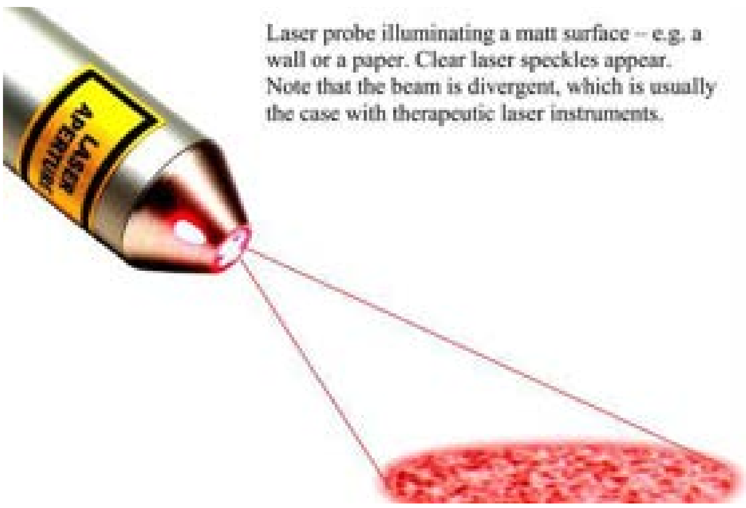


Figure 1.14 Laser speckles

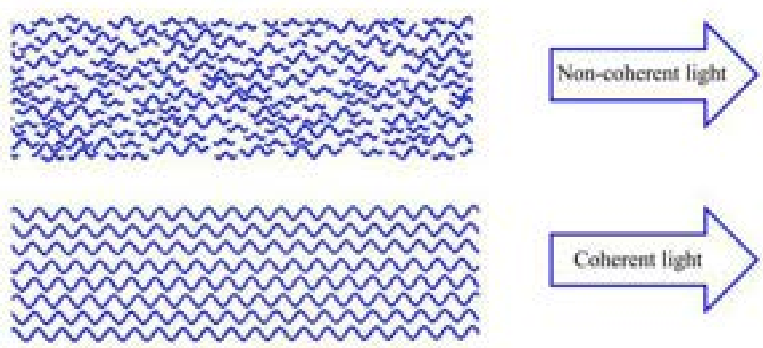


Figure 1.15 Coherent and non-coherent light. Two beams of light, moving from left to right. Same intensity, same wavelength and both parallel. The top figure shows light with short coherence length (ordinary light) and the bottom figure, light with long coherence length - laser light.

Here we describe an experiment that you can perform yourself (if you have a laser emitting visible light): Three dimensional laser speckles are formed. The further away from the source (milk-glass plate), the larger they are.

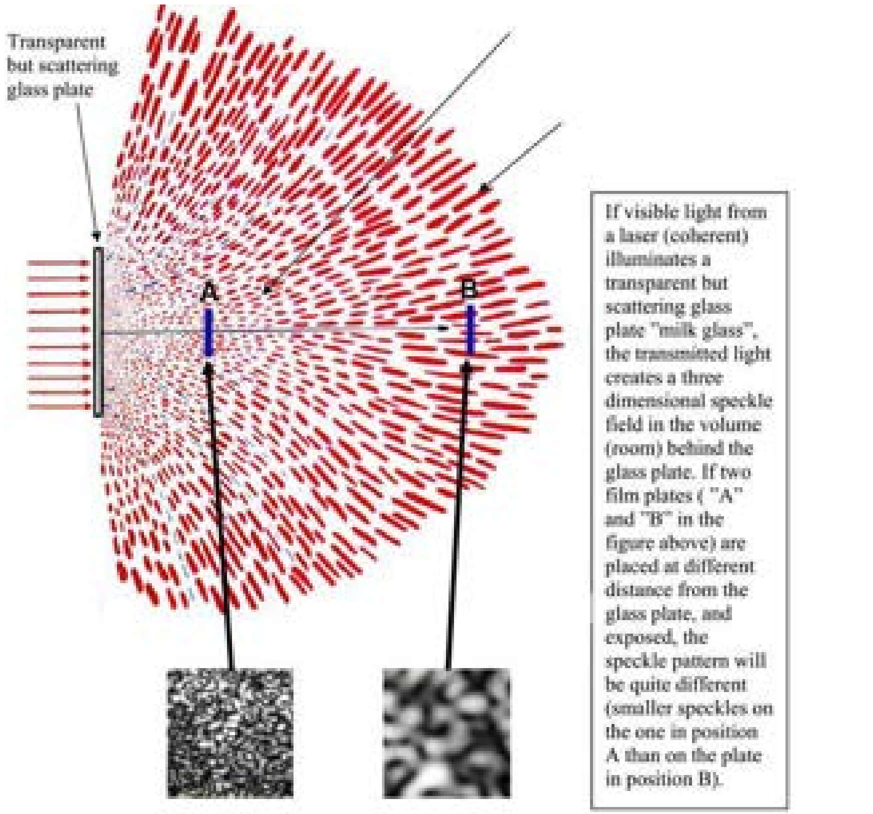


Figure 1.16 Speckle pattern

1.16 Laser beam characteristics

1.16.1 Polarisation

Light - whether from a laser or another source - can be non-polarised or polarised. It can also be more or less polarised (partially polarised). There are two types of polarisation: linear and circular, which can be described using the following analogy. We can take a long rope and tie one end round a tree, then stretch the rope so that it does not touch the ground. We then create wave motion by moving the rope up and down - the waves move vertically in accordance with the up and down movement. The wave is vertically linearly polarised. If we instead move the rope from side to side, the wave is horizontally linearly polarised. Finally, if we rotate the rope, a corkscrew-like wave motion results. This is circular polarisation, and we can differentiate between right and left rotational circular polarisation.

Polarised light can be achieved by filtering with "polarisation" filters. Special prisms or other optical components (e.g. Brewster window) can also be used. Most lasers and other light sources are not equipped with polarising means and consequently emit non-polarised light.

1.16.2 Output power

There are weak and strong laser as is the situation with all lamps. A strong laser has a high output power. Power is measured in watts (W). The strength or power output of a laser is thus measured in watts or milliwatts (mW = a thousandth of a watt). Higher output power is of some consequence, in that at a higher power output, one achieves a higher power density, which is often desirable. Also, a higher output power means that a certain desired dose (the amount of energy fed into the tissue) is more quickly reached because energy is the same as power multiplied by time. What we mean by dose is described in the next chapter.

When you buy an ordinary lamp, it is always its power consumption that is specified, and almost never its output power (radiance). Hence a 60 W lamp consumes 60 watts and yields, typically, 1 - 2 watts of visible light power. The remaining part of the input power is converted to heat in the glass casing and metal socket, and to directly emitted, invisible infrared radiation. The power specified for a laser is always its output power. Hence a 60 watt laser consumes considerably more than 60 watt but yields 60 watts of radiation power (visible or invisible).

1.16.3 Continuous and pulsed lasers

Most light sources emit light at a constant intensity. This is known as continuous wave emission (cw). However, it is also possible to make lasers and other lamps with varying intensity, known as amplitude modulated emission. The variability of modulated light may be small (low degree of modulation) or large (high degree of modulation). In the extreme case (100% modulation), the intensity periodically reaches zero. If the light intensity only varies between a maximum and zero, the modulation is known as square-wave amplitude modulation, and the light source is said to be pulsed. See figure 1.18.

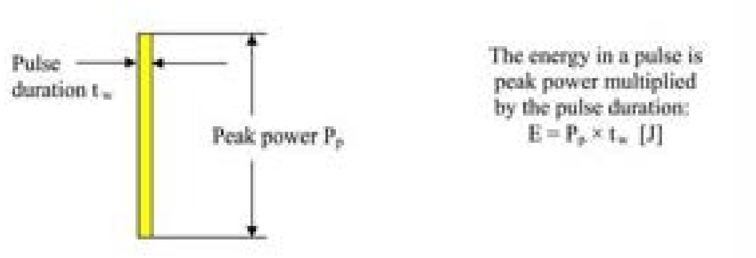


Figure 1.17 Peak power

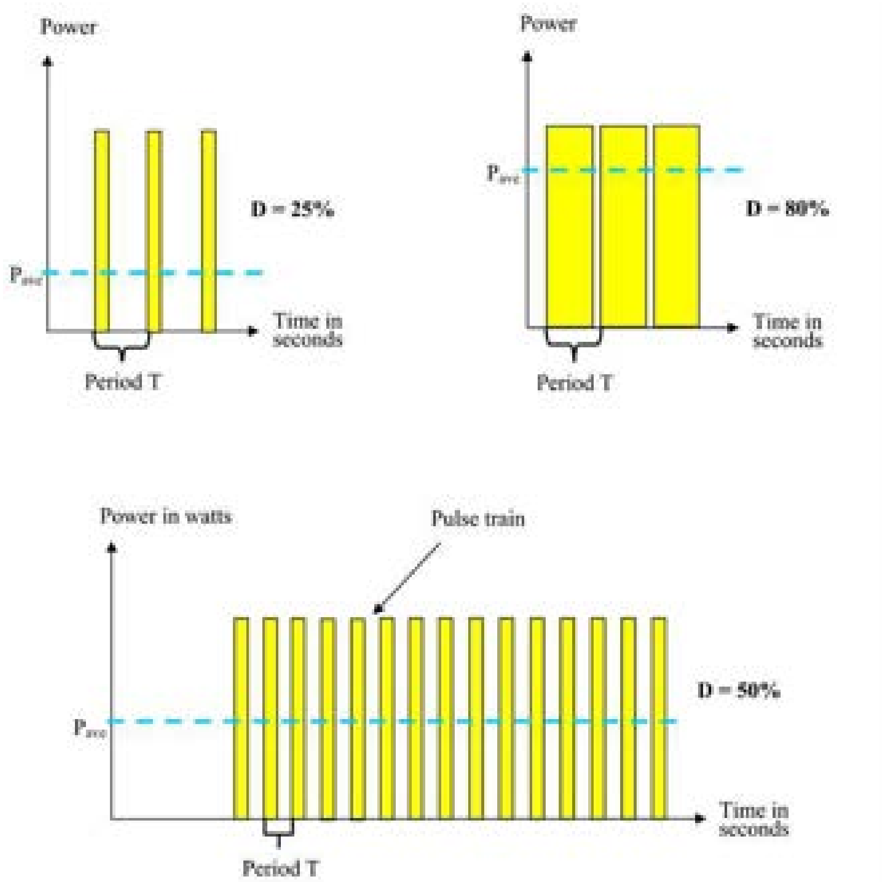


Figure 1.18 Different types of pulsing

A light source can be pulsed either electrically, by switching its power on and off or by using a chopper (mechanical shutter, Kerr cell, Pockels cell, etc.). It may be pulsed at a high or a low frequency, meaning many or few pulses per second. Pulse frequency is measured in hertz [Hz] or kilohertz [kHz] etc. If a lamp (or laser) emits visible light and is pulsed at a low frequency (up to about 30 pulses per second), we can see that the light is blinking/flickering.

If the length of the periods of light are equal to the length of the periods of zero intensity, the "duty cycle" is 50%, as light is emitted during 50% of the period time.

Some lasers and lamps can be pulsed like flash bulbs, i.e. with extremely short and very intense light pulses and rather long intermission times (very low duty cycle). This kind of rather extreme pulsing is usually named super-pulsing. Examples of lasers that can be super-pulsed are YAG lasers, CO_2 lasers and GaAs lasers.

Note 1. Pulse frequency, often called pulse repetition rate, has nothing to do with the frequency of the light itself - the carrier wave.

Note 2. "Frequency modulation" has nothing to do with this. It refers to variation of the frequency of the carrier wave. This is often the case in radio transmission and is named FM.

1.16.4 The peak power value

When a laser is pulsed, the laser light power varies between the pulse peak output power and zero. It is possible to design a laser to achieve extremely high peak pulse output power - even trillions of watts. However, the pulse duration is then correspondingly low. The pulse peak power value is of importance for the penetration of light into tissue. The power density during these very high power pulses is of course also very high, yielding and extremely high photon flux with an increased probability of both multi-photon and bleaching effects (see chapter 11.2.13 “Multi-photon effects” on page 725)

1.16.5 Average power output

When a laser is super pulsed, the laser light power varies between the peak pulse output power and zero. In such cases, the laser's average power output is of importance, especially in dosage calculation, see chapter 3.4.2 “Calculation of doses” on page 100. The peak pulse power value is of some relevance for the maximum penetration depth of the light.

For pulsed lasers, the output power value to be used for dose calculation is the laser's average power. When a laser is chopped, the pulsing can have different duty cycles. If the light is "on" for 30% of the time and "off" for 70% of the time, the duty cycle is 30%. Then the average power is 30% of the peak power (if the switching is momentary, i.e. a true square wave). The duty cycle of the GaAs-laser is extremely low - in the order of 0.001.

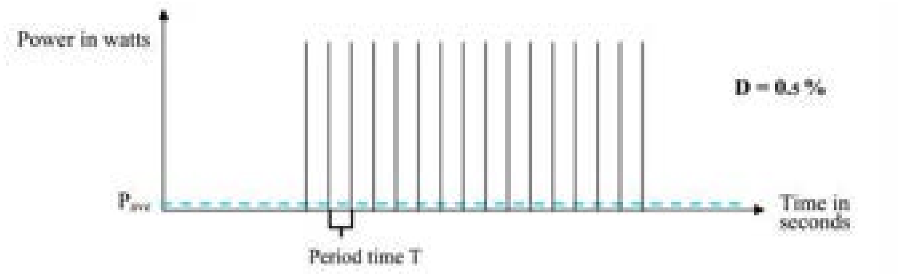


Figure 1.19 Super pulsing

1.16.6 Power density

Power density is another way of saying "light intensity" or "light concentration", and is the light output power per unit area of the tissue being illuminated by the laser light. This is usually measured in watts per square centimetre (W/cm^2). High power density is achieved, for instance, in the focus of a magnifying glass. If the magnifying glass is moved closer to the objective point, so that the light spot grows, the light is spread over a wider area and the power density is correspondingly lower. Spreading the light over a larger area leads to a directly proportional reduction of power density.

For example, a 10 mW therapeutic laser with the light focused on an area of 1 mm2 gives a power density of 1 W/cm^2. A surgical laser with 10 W output power focused on a spot with a diametre of 0.1 mm, gives a power density of more than 100.000 W/cm^2. Power density is of significance both in laser surgery and laser therapy.

1.17 Light distribution

Lasers can be used in many different applications. If we want to use it as a pointer we need other beam properties than if we want to have an even light distribution over a certain surface.

1.17.1 Beam divergence

It is a common misconception that light from a laser is always in the form of a parallel beam. The light from a gas laser is usually rather parallel, while the light from a diode laser normally is more divergent, with an angle of "spread" of around 10-90 degrees. This is due to diffraction when the light is emitted from the resonator mirror on the semiconductor crystal.

1.17.2 Collimation

If a lens or lens system is placed in front of the laser source, we can form the beam. The light's parallelity can be increased or reduced. Making the light more parallel is called collimation and such a lens or lens system is named collimator.

With a collimated beam, we can irradiate from a distance and keep a high power density more or less constant at larger distances. The distribution of the light in the laser beam can be quite different in different parts of the beam

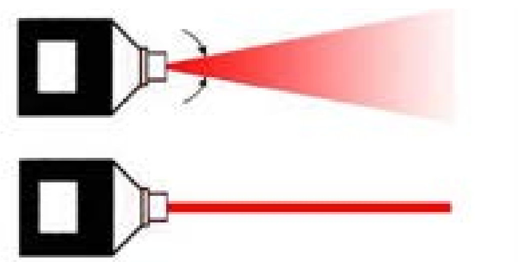


Figure 1.20 Collimation

Usually the laser light comes out through an opening - a hole. This is called the aperture. This opening can be small or large, be round or squared, covered by glass or transparent plastic, plane or in the form of a lens. The light distribution over the aperture can be different from laser type to laser type. This can be of importance in the practical treatment or illumination of objects.

In the figure below, we have shown some examples of typical beam profiles. They are here measured by means of a beam profile metre. The light distribution is not always of importance.

Some typical laser beam profiles.

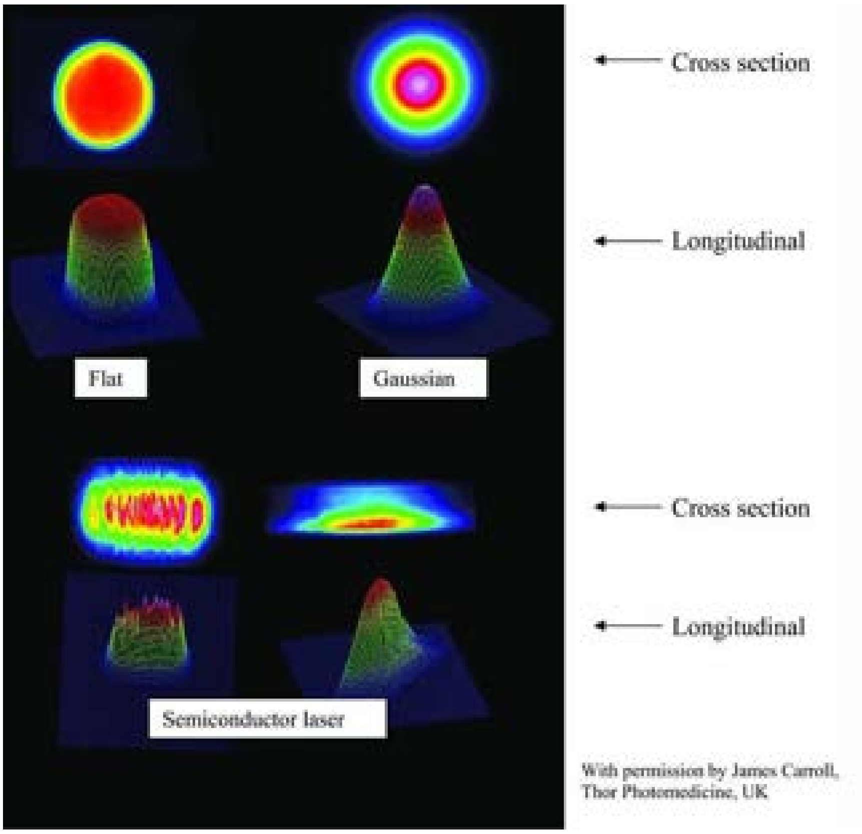


Figure 1.21 Laser beam profiles

1.18 Risk of eye injury

Already in the infancy of laser technology there was an awareness of the higher eye damage hazard, compared to the conventional light sources. Hence, rules were introduced to handle this hazard. Lasers were divided into four categories (class 1, 2, 3 and 4) according to their potential to injure eyes. Later laser class 3 was divided into class 3A and 3B. Lasers in the classes 1 - 3A were considered safe, whereas class 3B and especially class 4 were definitely risky. In class 4, the strong industrial and surgical lasers are found, i.e. lasers capable of burning and cutting. Note that this classification has nothing to do with the medical use, efficiency, or quality of lasers, but solely refers to the possible risk of eye injury.

Most people are afraid of lasers and though it is possible to cause eye injuries, almost all lasers are harmless. It is good to know that to date, only a handful of accidents involving lasers have been reported and the only severe accidents concern contact with high voltage power supplies. Very rare reports on injuries are found and in these cases very strong industrial lasers have been used and the protective measures have been ignored, or in laboratories where people, with time, had become careless. Furthermore, in many cases the person in question has not even been aware of an eye injury, although there has been a visible scar on the retina.

In the book "Therapeutic lasers", David Baxter writes: "In the only reported case of eye injury during therapeutic laser treatment, a chartered physiotherapist using a treatment unit on loan from a supplier suffered 60% corneal abrasion from the protective wings on the side of the goggles provided with the apparatus".

Another aspect is that, in the treatment of diabetic retinopathy, a strong argon or diode laser beam is directed right into the eye, and often some hundreds of laser pulses are fired. Still, the patient is not aware of any injury and reports that his vision is fine. In the treatment of cataract, a strong Nd:YAG laser is directed and fired right into the eye. Vision corrections are performed with an Excimer laser, evapourating parts of the cornea. CO_2-lasers, too, are used in eye surgery. All these lasers are strong and capable of burning tissue!

So, even though there are lasers capable of causing eye damage, the risk should not be exaggerated. Too often the fear of laser light is a greater risk than the laser itself! For example: a car driver being blinded by a laser pointer can lose control of his vehicle out of fear because he realises that he has been hit by a laser (and he “knows” this is very dangerous). But if he is blinded by a sunbeam, he will not be frightened, just blinded for a spell. Usually a sunbeam blinds a person much more than a laser pointer, because the laser pointer can only hit one eye at a time and for a much shorter time due to the narrowness of the beam.

A lot has been written about the laser as a military weapon to make soldiers blind. Well, that is not possible. At close range and with large lasers, it would be possible to inflict eye injury if an invisible beam were to be used. But in reality, no laser makes a person blind. Pilots could be disturbed by visible laser light but not made blind. Also, the user of the laser weapon would reveal his position and turn himself into a target. Still, the common military use of lasers is as distance measuring devices, beam-riding missiles and target designators – a laser points at a target and a “smart” bomb or missile sees the laser spot and flies to it. Amendations have been proposed to the Geneva Convention to forbid the use of laser as a weapon, but we think it would be much more sensible to suggest that guns be forbidden, as a bullet can do much more harm than a beam of light.

There are light sources which are more hazardous to the eyes than the corresponding lasers [1294]. One such device usually called IPL (Intense Pulsed Light) using a powerful flash lamp with a band-pass filter. It emits light pulses in the wavelength region 600 to 900 nm and with pulse energies around 50 joules per cm^2 aperture area. The aperture is usually rectangular and in the order of one by three cm. Like ruby and alexandrite lasers, this instrument is used in hair removal – the light is absorbed in dark hairs and then converted to heat, which burns the surrounding follicle to destruction or injury. This is called photo epilation. If this aperture is directed towards an unprotected eye, this can cause a much more severe injury than staring into the beam of e.g. an uncollimated ruby laser with fibre-optic transmission made for hair removal. But as these flash lamp devices are not lasers, there are no restrictions in their use!

Our recommendation is to use protective googles on the patient when performing laser phototherapy in the head and neck area. This gives the patient a feeling of safety and "high tech" and saves the therapist from any negative physchological reactions. However, irradiating a naked eye with a visible non-collimated beam below 100 mW is completely harmless. We often do this on ourselves during lectures and it seems to suprise most participants who already "knew" how dangerous this is. And as can be seen later in this book, even invisible LPT in this energy range has been used to treat macular degeneration.

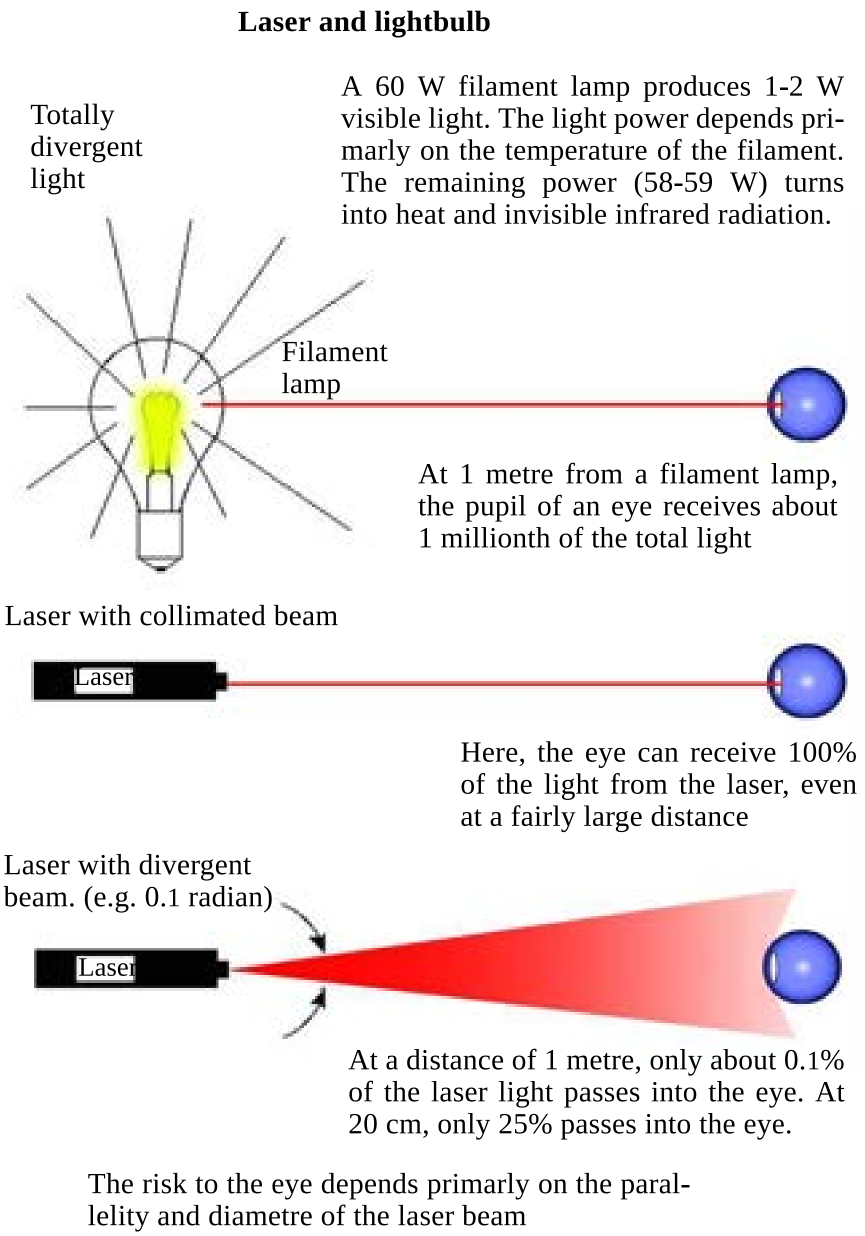


Figure 1.22 Laser and light-bulb

In 1998 there was an outbreak of laser hysteria in the Danish press. A train engineer was reported to have suffered a 20% loss of vision after having been irradiated by two young boys, using a laser pointer. In addition, a car driver was reported to have been injured in a similar fashion. This is, of course, pure nonsense. Laser pointers do not injure the eye! They are far too low-powered and the blink reflex will automatically reduce the exposure time. They are a cause of disorientation for a pilot or a car driver, though, and a good reason for the ban of green laser pointers in many countries.

Reidenbach [1303] has controlled the blink reflex of the human eye when hit by visible lasers of 1 mW. For 670 nm only 15.9% of the tested persons showed a blink reflex, for 635 nm 17.2% and for 532 nm 20.3%. This may seem alarming, but a 1 mW visible laser will never harm the eye and at higher power the blink reflex will increase gradually and work well long before the beam reaches a risky level.

The restrictions in the use of class 3B lasers as therapeutic instruments have been lifted in Europe since no reports of eye damages from these lasers have ever been reported.

1.18.1 Decisive factors in the risk of eye injury

The following factors are of importance in the eye risk of various lasers. (See figure on previous page.)

- The divergence of the light beam: A parallel light beam of small diametre is by far the most dangerous. It can enter the pupil in its entirety and be focused by the eye's lens to a spot with a diametre of hundredths of a millimetre. The entire light output is concentrated on this small area. With a 10 mW beam, the power density can be up to 12.000 W/cm^2.
- The output power of the laser: It is fairly obvious that a powerful laser (many watts) is more hazardous to stare into than a weak laser.
- The exposure time: The shorter the exposure time is, the stronger the light can be without risk of injuries. For visible light, the blink reflex affords a good protection.
- The wavelength of the light: Within the visible wavelength range, we respond to strong light with a quick blink reflex. This reduces the exposure time and thereby the light energy which enters the eye. Light sources which emit invisible radiation, whether an infrared laser or an infrared diode, always entail a higher risk than the equivalent source of visible light Radiation at wavelengths over 1400 nm is absorbed by the eye's lens and thus rendered safe, provided the power of the beam is not too high. Radiation at wavelengths over 2500 nm is absorbed by the cornea and is less dangerous.

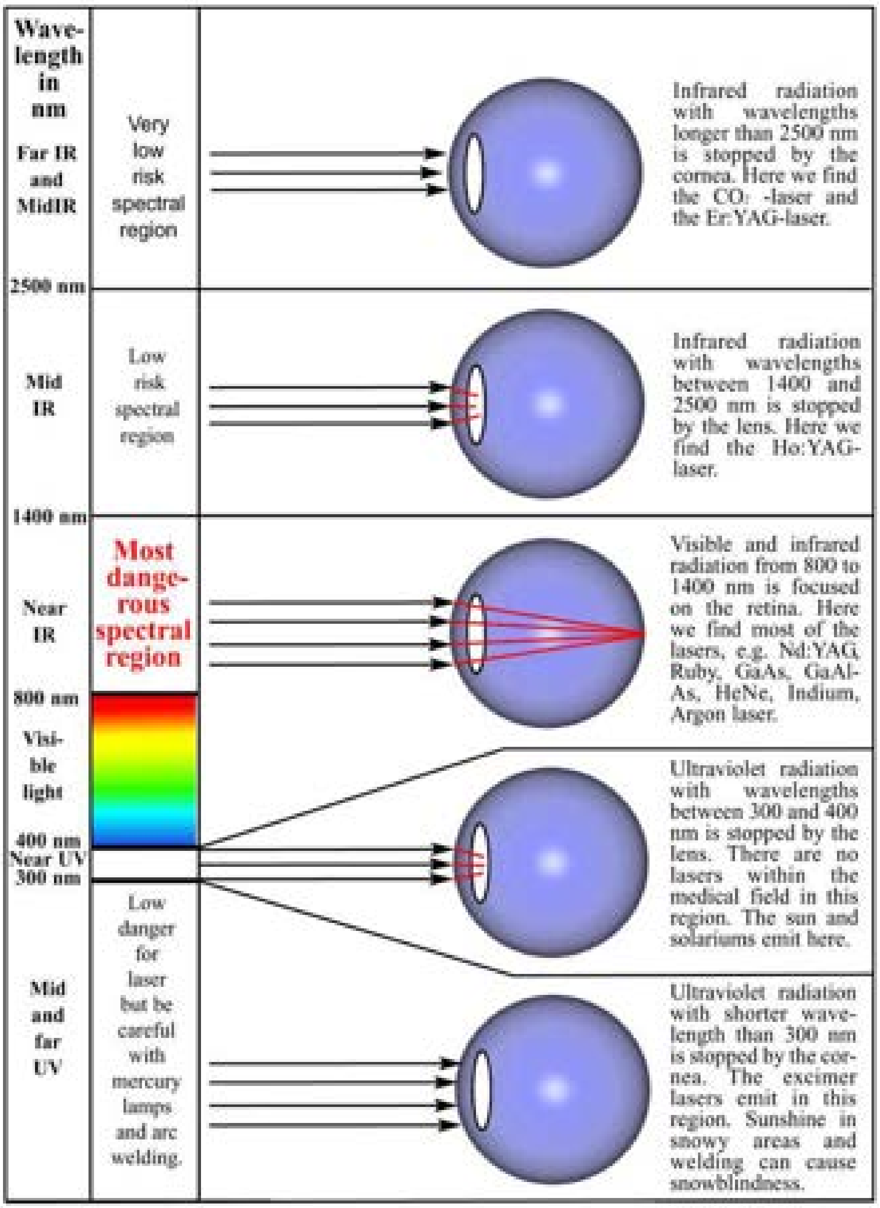


Figure 1.1 Differences of occular hazard in visible and invisible ligth

- <u>The distribution of the light source:</u> When looking at a light source, an image of the source is projected on the retina. If the light source is concentrated, as is often the case with lasers, the image will be projected as a point, provided it lies within our accommodation range, i.e. the area in which we can see clearly. A widely spread light source is projected onto the retina in a correspondingly wide image, with the light spread over a larger area, and with a lower power density as a consequence. For example: a clear light bulb (which is apprehended as a more concentrated light source) is worse to look at than a "pearl" light bulb. A laser system with several light sources spaced apart, such as a multiprobe with several laser diodes (the probe is the part of the laser you hold and apply to the area to be treated: a single probe means there is only one laser diode in the probe, as opposed to a multiprobe, which has several laser diodes) may be very powerful as a whole, yet constitutes a lesser hazard to the eye than it would if the entire power output was emitted by one laser diode, because the diodes' separate placement means that they are reproduced in different places on the retina.

We have often heard this kind of remark: "If it's a class 3B laser then it's fine, otherwise it is not effective!" This is, of course, entirely incorrect, and has led manufacturers to produce lasers that meet the 3B classification in order to sell higher volumes.

Let us look at two examples:
A GaAlAs laser with a wavelength of 830 nm, an output of 1 mW and a well-collimated beam (1 mrad divergence) is classified as laser class 3B as it is judged to be hazardous to the eye. The reason for this is partly the collimated beam, and partly the wavelength, which is just outside the visible range and hence provokes no blink reflex in strong light.

- A HeNe laser with a wavelength of 633 nm, an output of 10 mW (10 times stronger than the laser in the previous example) and divergent beams (1 rad divergence, which corresponds to a cone of light with a top angle of about 57°, which is often the divergence of light from a fibre-optic cable) is classified as laser class 3A because, owing to its divergence, it cannot damage the eye (only a small portion of the light will hit the pupil). The light from a laser diode is usually rather divergent unless it is fitted with a collimating lens or lens system.
- A CO_2-laser (10 600 nm wavelength) of EDL (defocused) type, with 15 watt output and with the radiation uniformly spread out over a surface with a diametre of 5 cm, will be classified as a class 4 instrument. If instead it is spread out over a surface of 10 cm diametre, it will be classified as a class 1 instrument (only class 1 and 4 have this wavelength) and is hence regarded as absolutely eye-safe in spite of its high output power.
- A laser pointer uses an InGaAlP laser with a wavelength usually between 650 and 670 nm (red light). The output power is in the order of 0.5 to 3 mW, focused in a well-collimated beam. The spot size is usually 5 to 10 mm in diametre at a distance of 1 metre. If you look straight into the beam, the light looks very strong. However, these devices are completely harmless and no

eye injury has been reported. But many people are afraid of them. As a comparison, an arrow or a dart can completely destroy an eye - a laser pointer is harmless.

As for therapeutic lasers, patients often ask: "Is it enough to shut your eyes if you receive laser treatment to the face, or must you have protective glasses?" Yes, it is enough to close your eyes! It is actually sufficient to shut your eyes even if a very powerful laser is being used. It is quite possible to treat a stye on the eyelid without risk, even if it is located right in front of the pupil [129]. The reason for this is that the eyelid spreads the light so that the lens cannot focus it. The light is spread over the entire retina and, with a 10 mW laser, we get a power density over the retina of 0.001 W/cm^2, which is about ten million times lower than if the eye were open and the beam parallel.

However, the use of protective glasses can be of benefit, particularly if powerful, collimated lasers in the infrared spectral region are used. In any case, protective glasses give the patient a sense of security. Furthermore, therapists never run the risk of a claim for damages from a patient if they make sure the patient always wears protective glasses during treatment. (Patients may well convince themselves that the laser has a negative effect on their eyes.)

Bear in mind, though, that protective glasses for HeNe or InGaAlP lasers are of no use whatsoever when using other laser types.

Warning: The use of normal sunglasses increases the risk of eye injury. The filtration mechanism of sunglasses is a wide band attenuation, giving a much lower absorption of a particular laser wavelength than real protection goggles give. In addition to this, the darkness of the glasses makes the pupil dilate and let in more light. They provide a false sense of security!

Summary: Although most lasers are harmless, some lasers certainly can cause eye injury. The most dangerous types combine power (> 100 mW) with a collimated beam and have a wavelength in the interval 700 nm – 1400 nm. So called laser pointers are harmless. A divergent beam can be quite strong and still carry a low risk; the more divergent, the less risk.

Literature:

Dushin [1783] reports that 60 patients with chronic dacryocystitis with partially retained patency of the lacrimal duct were treated by HeNe laser. The patients received 3-5 min sessions twice a week, 5-8 sessions per course. Positive effect was attained in 56 patients: complete cessation of excessive lacrimal discharge in 38 patients and subjective improvement in 18. HeNe laser exposure brought about a good antiinflammatory effect; in *combination with antibiotic therapy it promoted rapid sanitisation of the lacrimal duct, removed oedema, and rapidly normalised lacrimal discharge.*

Safe doses of LPT exposure for the structures of the eye were searched for in rabbit experiments by Prokofeva [1217], and the potentials of such lasers in ophthalmology were assessed. A 890 nm diode laser was used. The doses varied from 0.0001 to 1.0 J/cm^2, corresponding to exposure duration of 0.3 to 45 min. Experiments were carried out on 20 animals. The right eyes were exposed, and the left ones were control. An increase of intraocular pressure was recorded at a dose of 0.1 J/cm^2 (4.5 min) and higher; morphological study showed dilated, well-filled and newly formed vessels in the ciliary body and iris, as well as oedema and destruction of the external layers of the retina. Exposure to a dose of 0.05 J/cm^2 and lower did not lead to destruction of ocular structures and increase of intraocular pressure. The maximal LPT dose causing no side effects for the organ of vision was established at 0.05 J/cm^2, this corresponding to 2.5 min exposure.

1.19 The laser instrument

There are many different laser types. They can be classified in different ways. They can have different wavelengths, different output powers, different lasing medium, different type of pulsing, different use etc.

In this case we can limit them to medical/surgical use and leave out industrial lasers, communication lasers, lasers for printers, for pointers, for measuring tasks and more. Basically we can divide them according to the lasing medium (solid state, gas, semiconductor and liquid). These basic types are described in tha table on the following page.

1.19.1 Properties of some laser types:

Solid state lasers	Laser medium is a crystal.
Wavelength	Exact wavelength. Very narrow-banded. Highly coherent.
Temperature	The wavelength is not changed, but possibly the output power.
Beam configuration	Rather parallel beam (Typically 1 mrad)
Pulsing	Usually pulsed. Can be extremely pulsed (Q-switched). Can be made to run continuously.
Polarisation	The light is usually not polarised.
Energy supply	Light from flash lamp or other laser, e.g. semiconductor laser.
Gas lasers	Laser medium is a gas mixtur
Wavelength	Exact wavelength. Very narrow-banded. Highly coherent.
Temperature	The wavelength is not changed, but usually the output power.
Beam configuration	Rather parallel beam (typically 0,1 – 1 mrad)
Pulsing	Usually continuous but can be switched.
Polarisation	Normally not polarised light.
Energy supply	Current conduction through the gas. Sometimes radio wave excited.
Semiconductor laser	Laser medium made of semiconductor crystal. Also named diode laser.
Wavelength	Usually individual; usually within ±5 nm of specified wavelength An 820 nm diode laser can hence have a wavelength between 815 and 825 nm. Rather wide-banded; typical half width 2-3 nm. Small coherence length. The wavelength increases with increased temperature typically with 0.3 nm per 1 °C (the diode temperature can increase with 5 - 20 °C during a treatment session)
Temperature	Output power decreases with increasing temperature.
Beam configuration	fan-shaped, strongly divergent beam e.g. 2°× 20° angle.
Pulsing	Usually continuous. Can be switched. Exception: GaAs-laser, always super pulsed – can not work continuously.
Polarisation	The light is usually polarised.
Energy supply	Electric current through the semiconductor crystal.
Dye laser	Laser medium is liquid: water + dye.
Wavelength	The wavelength can be changed continuously, also when running. Small spectral half-width, high coherency.
Temperature	Relatively small temperature dependant output power.
Beam configuration	Rather parallel beam (typically 0,1 – 1 mrad).
Pulsing	Can be continuous or pulsed. Can be Q-switched.
Polarisation	Normally not polarised.
Energy supply	Light from other laser (e.g. Argon laser) or flash lamp.

Laser type	Typical wavelength	Often used in:
CO_2-laser	10 600 nm	Surgery, laser peeling
Nd:YAG laser	1064 nm	Surgery, coagulation, cataracts
Ho:YAG	2130 nm	Surgery, lithotripsy
Er:YAG	2940 nm	Dentistry, laser peeling
Argon laser	514 nm	Retinopathy, hemangiomas
KTP laser	532 nm	Telangiectasia, hemangiomas
Ruby laser	694 nm	Hair removal, tattoos
Alexandrite	755 nm	Hair removal, tattoos
GaAlAs laser	780-890 nm	Surgery, hair removal
Dye laser	400-900 nm	Research, lithotripsy
Excimer laser	193, 248, 308, 351 nm	Lasic, cornea sculpturing

Table 1.2 Types of laser in medicine

Apart from the output power we need to be able to concentrate their light on to a small enough surface to get a high intensity (measured in watts/cm^2), it must be powerful enough to heat up the tissue to temperatures over 50 °C.

A surgical laser can either be used in continuous wave or pulsed mode. These lasers can be broadly divided into three groups, according to their output:

1. vapourising (superficial complaints, e.g. condyloma) 1-5 W.
2. light cutting (superficial incisions, e.g. plastic surgery) 5-20 W.
3. deep cutting (conisation, major surgical operations) 20-100 W.

1.20 Description of common surgical laser types

The main aim of this book is not to instruct colleagues in the profession who work with or are thinking of working with surgical lasers - a great deal of literature on this subject already exists. Nevertheless, in this chapter we will be describing some of the surgical lasers on the market so that the reader can appreciate the difference between surgical and medical lasers and thereby answer their patients' questions.

1.20.1 The CO_2 laser (carbon dioxide laser)

As mentioned earlier, most types of lasers are named after one or more of the components (or the main component) of the lasing medium. The main component of the CO_2-laser is thus carbon dioxide. This laser usually produces radiation with a wavelength of 10.6 micrometres (10.600 nanometres), which is high in the infrared band of the spectrum. The advantage of radiation with this long wavelength is that it is absorbed by water to a great extent, and by objects which contain water, such as tissue. This makes the CO_2-laser largely non-hazardous to the eye. Further, this wavelength is highly absorbed by glass and plastic and every organic material. This means also that ordinary spectacles or glass or plastic discs in a suitable frame are a sufficient protection for this wavelength.

Another concequence of this is that we can not use optical fibres as light conductor between the laser light source and the handpiece, because there are very few materials that are transparent enough. Because of that, the transportation of the laser beam uses a so called articulated arm or mirror arm. Different solutions have been tested, such as small plastic tubes, internally coated with dielectric layers, have been tested as wave-guides. Internally coated metal tubes are also being used in spite of some disadvantages. The most promising wave-guide technique may be small flexible glass tubes, internally coated with dielectric layers.

A CO_2-laser can be made very powerful - with an output of millions of watts - though such a laser would be as big as a house and very nearly require its own power station! Powerful lasers of this kind are used in industry to cut and process metal. CO_2-lasers with an output under 200 W may be radio-wave excited with sealed gas systems, and do not require, as their predecessors did, any gas supply, gas refilling, or high voltage. Their lifetime is usually very long.

Today's surgical CO_2-lasers can also be superpulsed. This means that the laser light is emitted in a train of short but very intense pulses. In the case of tissue evapouration, this results in less burning under and around the vapourisation zone.

A useful accessory is the so called Fractional scanner. By applying the CO_2 laser energy in a fractionated manner, very small areas of thermic damage are created in the dermis. The fractional scanner delivers a precise matrix of microspots in fractional mode that penetrates into the dermis and stimulates the formation of new collagen. At the same time, immediate shrinkage of damaged tissue is caused by the high temerature in the small spots. The result is more youthful skin.

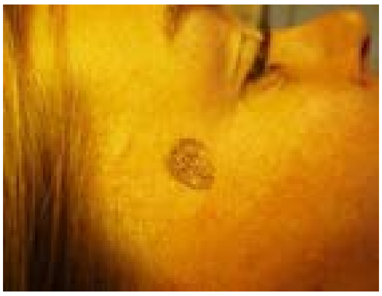
The fractional scanners are able to be connected to almost any type of CO_2 surgical laser. It is used for skin resurfacing procedure, and found to be effective in wrinkle reduction; acne scars; texture, tone, elasticity, colour improvement and pore size minimisation. Usually at least 3 treatments are needed for optimal results. Four to six treatments may be needed for patients with significant scarring and wrinkles. Treatments are usually performed 4 for 6 weeks apart.

Side effects are minimal and typically involve mild-to-moderate swelling and redness which usually subsides within several days. Skin may also appear to have a bronzed appearance for several days. Routine activities can be resumed immediately after treatment. Most patients return to work within 1-3 days. Many patients see improvement in discolouration and texture immediately followed by improvement in wrinkles and scars within months.

1.20.2 Carbon dioxide lasers in surgery

One of the advantages of the carbon dioxide laser is that the radiant energy it produces is strongly absorbed by water and all organic matter. This means that layer after layer of tissue can be removed without nearby tissue being affected to any great extent. At the same time, the CO_2-laser coagulates blood in small vessels, making it possible to work in a controlled fashion. When we use CO_2-laser on superficial skin problems we don't use any anesthesia except sometime EMLA crème.

When comparing a scalpel with a carbon dioxide laser it is not difficult to see the advantages of the laser. The scalpel causes profuse bleeding, making it difficult to see where the healthy tissue starts, and the practitioner is working with a knife close to well-vascularised tissue.



With the laser we can evapourate fractions of a millimetre at a time and our vision is not impeded as there is generally no bleeding, and, furthermore, sutures are unnecessary.

The picture is showing a very superficial pigment spot. In this treatment a power of about 1 watt was used and a spot size of not quite 1 mm in diameter. Single pulses were used and the shots were done side by side until the whole area was covered. The whole procedure took about one minute.

After the burning, the coagulated (and a little bit carbonised tissue) was wiped off with a cotton pin wiped in alcohol. Only a hypo-pigmented area is left. Normal skin colour came back in half a year.

Problems like haemangioma on lips can be treated in the same way; no bleeding, no sutures. The whole operation takes usually a minute or two and can be done on an outpatient basis. Subsequent check-ups are generally unnecessary. By focusing the beam, it can also be used like a scalpel, so it is possible to take a biopsy.

Another interesting property of the CO_2-laser is that, when cutting, evapourating or coagulating the tissue, pain persists for only a few seconds after the burning has stopped. This is in contrast to when you burn yourself on a hot iron, your oven or hot water, leaving a pain for 20 to 30 minutes, unless cold water or ice is applied to the site of the burn. The reason for this difference in pain perception is not known.

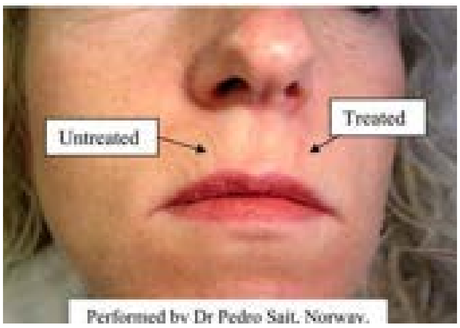
Gynaecology was the first main field of use for the CO_2-laser. It can be used to evapourate genital condyloma, cervical neoplasia etc. In the case of conisation a rather strong CO_2-laser is needed, due to the deep incision needed in the blood rich tissue.

The healing process after an operation using a carbon dioxide laser is a little slower than after conventional surgery, but, on the other hand, the post-operative discomfort is considerably milder and the final cosmetic result much more acceptable (the latter is of course more important in cases of treatment of the face). The absence of bleeding may be the cause of the slower healing. The laser beam also kills off any residual infection in the operating area, which contributes to the healing process.

The disadvantages of carbon dioxide lasers used to be their size and price. You can buy many scalpels for the price of one CO_2-laser. Carbon dioxide lasers can be made very powerful, but for dermatological and ENT use, 1-10 W usually suffices.

In general surgery, the CO_2-laser has been used for a long time. One good indication for the laser is haemorrhoidectomy. Other good indications are fimosis and circumcision. The healing after excision of penis cancer has proved to be very good. Typical benefits of laser surgery are less pronounced postoperative oedema and pain compared to conventional methods. Sutures are often not required.

In dermatology, the CO_2-laser is very well suited for excision of superficial tumours, evapouration of angioma, verrucae, syringoma, tricho-epithelioma, adenoma sebaceum, steatocystoma, hidradenitis suppurativa, condyloma, neurofibromatosis, xanthelasma, rhinophyma, actinic cheilitis, venous lacuna, spider naevi, hematoma, telangiectasia, superficial basaloma, lentigo solaris, lentigo senilis etc. A good field for the CO_2-laser is plastic surgery, such as eyelid operations (blepharoplasty).



As mentioned above the CO_2-laser can be used for so called laser peeling - a very superficial tissue ablation in the face - for the removal of wrinkles and acne scars. The mechanism is partly thermic by remodelling and contraction of the collagen, partly biostimulative.

This can be done also without a fractional scanner. In the picture here the peeling is done by hand and instead of the wrinkle a normal erythema is seen.

1.20.3 Carbon dioxide lasers in dental applications

Many attempts were made to adapt the carbon dioxide laser to other dental procedures than the purely surgical procedures. With the advent of the Nd:YAG and the erbium lasers, there was no longer any need for the CO_2 for procedures such as gingivectomies, dental necks, root canal disinfection etc. The new lasers were safer, easier to operate and more versatile. Still to this day, however, the CO_2 lasers are superior to any in certain situations.

Haemangiomas are also appropriately removed with laser once the size of the tumour has been carefully determined. Bear in mind that many haemangiomas are like the tip of the iceberg. The majority of laser-treated oral soft tissues are left to heal "per secundam", that is, by secondary intention without sutures.

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Figure 1.23 Heamangioma preop, directly postop and at one month

Hyperplasia of various kinds is appropriately removed by incision. After anaesthetics, the tissue is stabilised with a pair of tweezers, and then an incision is made using single pulses.

Figure 1.24 Gingivalyperplasia preop, directly postop and one month later.

Preprosthetic surgery can be performed with a carbon dioxide laser. Hypertrophic tubera and "flabby ridges" can be peeled off layer by layer. The patient can start using dentures much quicker than after conventional surgery because the oedema is much smaller than if a scalpel were used.

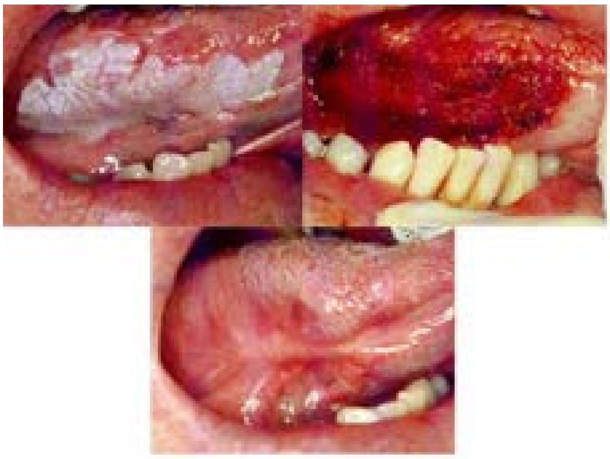


Figure 1.25 Benign hyperkeratosis of the tounge preop, directly postop and at one month.

Retention cysts such as ranula and mucocele can either be removed in their entirety or fenestrated by laser. By comparison with conventional surgery, a lower recurrence frequency has been reported when lasers are used.

1.21 The Nd:YAG laser

Laser operation of Nd:YAG was first demonstrated by J. E. Geusic et al. at Bell Laboratories in 1964. It is a laser with the very complicated name; Neodymium-doped Yttrium Aluminum Garnet (Nd:YAG) or colloquially, just "YAG laser". Its wavelength has become classic in the laser world - 1064 nm. Normally this laser is pumped by a very strong flash lamp or, in smaller versions, with a powerful semiconductor laser with the wavelength 808 nm. Neodymium-YAG is the most widely used solid state laser - from low-power continuous-wave lasers to high-power Q-switched (pulsed) lasers with power levels measured in the kilowatts.

Most Nd:YAG lasers produce infrared light at a wavelength of 1064 nm. Light at this wavelength is rather dangerous to vision, since it can be focused by the eye's lens onto the retina, but the light is invisible and does not trigger the blink reflex. Nd:YAG lasers can also be used with frequency doubling or frequency tripling crystals, to produce green light with a wavelength of 532 nm or ultraviolet light at 355 nm, respectively. The dopant, Neodymium, was discovered by Baron Carl Auer von Welsbach from Vienna 1885. The name is from the Greek "neos didumous", meaning new twin.

1.21.1 Nd:YAG lasers in surgery

The Nd:YAG laser has been used in general surgery for many years but is being replaced more and more by the CO_2-laser, which has better evapouration and cutting properties. However, the Nd:YAG laser is very good for coagulation, also of tumours.

In the treatment of cancer, it is used for laser-induced thermotherapy, in which benign or malignant lesions in various organs are heated by the beam. The effect on cancer is based on the fact that healthy tissue can be heated to a higher temperature than the tumour cells before being killed. Usually the laser beam is brought to the centre of the tumour by means of an optical fibre. It has also been used to remove skin cancers and to reduce benign thyroid nodules and to destroy primary and secondary malignant liver lesions.

To treat benign prostatic hyperplasia (BPH), the YAG lasers can be used for laser prostate surgery - a form of transurethral resection of the prostate. It is also used in ophthalmology to correct posterior capsular opacification, a condition that may occur after cataract surgery, and for peripheral iridotomy in patients with acute angle-closure glaucoma, where it has superseded surgical iridectomy.

Using hysteroscopy the laser has been used for removal of uterine septa within the uterus. It has also been used to treat onychomycosis, which is fungus infection of the toenail. The mechanism here is biostimulation.

In aesthetic use it has been marketed for laser hair reduction, though it is not the best choice. In the treatment of vascular defects such as spider veins on the legs it is also not the best tool. For larger veins, though, it is a good and effective tool. The treatment starts with inserting an optic fibre inside along the whole vein to be coagulated. The fibre is then connected to the laser. When the right power of emission is set, the laser starts and the fibre is slowly pulled out, coagulating the vein, centimetre by centimetre.

1.21.2 Nd:YAG lasers in dentistry

The Nd:YAG laser for "drilling" was a pioneer, but the procedure was very time consuming and has now been replaced by the erbium lasers, which are much better suited for "drilling". It soon became obvious that this laser was better suited for other dental procedures. Some of the possibilities of the dental Nd:YAG lasers are briefly presented below.

Aphthous ulcers. By reducing the power of the Nd:YAG laser, it can be used as a "therapeutic" laser in many cases. The problem is the difficulty of dosage calculations. Even at the lowest setting, the power density is high, since the probe is very thin. By using the laser in a sweeping motion, this problem can be overcome.

Analgesia. It is possible to cut soft tissue without causing much pain. The mechanism is unclear.

Anaesthesia of teeth. By irradiating a tooth for a few minutes with increasing intensity, local anaesthesia of the tooth can be brought about using energy densities ranging from 2 to 40 J/cm^2, preferably starting with short pulses, slightly below the pain threshold, and gradually increasing until anaesthesia is achieved. No lasting damage to the pulp as a result of this treatment has been observed. The anaesthesia is most easily achieved on young teeth. The more sclerotic the pulp chamber, the poorer the effect.

Fissure sealing. Laser-treated enamel is restructured and made more acid-resistant. This restructuring is possible through laser influence of the fissure system. It is also thought that bacteria in the bottom of the fissure can be killed and that it is possible to fuse the fissure. It is then still possible to seal with resin, if so desired. The enamel can be etched by the laser but acid etch is considered to give better bonding. However, as always, the outcome is within the parametres used.

Herpes simplex. As any other dental laser, with proper dosage, Nd:YAG will successfully treat herpes simplex lesions. When treated with a higher intensity than in conventional laser therapy, the lesions will shrink within seconds and will then fall off after a few days. In the blister stage, the laser can first be used to open the blister for drainage, collecting the infected fluid in a piece of gauze.

Hypersensitive dentine. The sensitive root surface is "painted" with the laser, using water-cooling. Organic matrix is coagulated and the tubuli are closed.

Periodontics. Nd:YAG laser has been tested for a number of purposes within periodontics. A typical treatment could be as follows. The probe is moved in a sweeping motion and at a slight angle in contact with the pocket epithelium. When the infected epithelium has been removed, a blood free opening of the pocket has been created and calculus can be visualised and easier removed by scaling and root planing. Anaesthetics are generally not required. Substantial regeneration of bone has been observed after Nd:YAG treatment in deep bony pockets. Different outputs and pulsation times are used for different operations. Nd:YAG lasers can be used with and without water cooling. Water cooling reduces the speed of tissue removal but also reduces the risk of thermal damage and tissue carbonisation. Bacteria are not supposed to be killed by the heat of the laser but by selective absorption of the light in dark pigments. The laser application is an adjunct therapy in periodontics; traditional scaling and root planing are always needed. Bi- and trifurcations are a challenging indication for Nd:YAG treatment. The flexible fibre will reach areas where the curette often fails. Conventional scaling and root planing is unable to remove the infected epithelium, which plays an important part in the reinfection of the pocket.

Figure 1.26 Perodontal pocket with a water cooled Nd:YAG; after removal of the infected epithelium (calculus visible), directly after scaling and two weeks postop. Performed in one session without anaesthetics.
Photos: Talat Qadri.

Figure 1.27 Oedema and pain, before Nd:YAG treatment and situation at two weeks postop. Photos: Talat Qadri.

<u>Soft tissue treatment.</u> It is possible to cut soft tissue without causing bleeding and without the need for anaesthetics. The uncovering of preparation margins is also possible, as are smaller operations, such as the removal of hyperplasia and minor frenectomies. The cutting output is, however, low and the operation takes longer time than with carbon dioxide lasers. The tissue tends to stick to the probe and needs to be cleaned frequently, especially if water cooling is not used. Unlike electrocautery, there will be no tissue retraction

<u>Sterilisation of root canals.</u> The biggest problem with the treatment of non-vital teeth is the apical infection. By moving the thin laser probe down into the apical area, and slowly moving it back, it can kill off parts of the bacterial load in the apex delta as well as in the side canals.

<u>Biostimulation.</u> LPT is always an integral part of the laser application, nolens volens. An Nd:YAG laser is not intended to be used for LPT, but by removing the fibre and setting the lowest possible output, the Nd:YAG can fairly successfully be used as a "therapeutic laser". The calculation of dosage is cumbersome and the probe has to be kept at a distance to let the beam diverge, and then the probe should be kept in a slow sweeping motion.

Literature: [926, 927, 1582, 1583, 1584, 1585, 1792, 2129, 2431, 2432, 2433]

1.22 Erbium lasers in dentistry

In dentistry, the Er:YAG family is excellent for dental hard tissue and is therefore much more suited for the treatment of caries than Nd:YAG-lasers. The wavelength 2940 nm is absorbed by the water in the tooth substance and by the OH-ion in the hydroxyapatite. To avoid overheating, a jet of water accompanies the laser beam, in the same way as with a conventional drill. The treatment is almost painless but pain levels depend on the power settings and the skill of the operator. Enamel, dentin and composites can be removed with this laser, but not metals such as amalgam. Apart from working as a "drill" the Er:YAG laser can be used in minor surgical procedures such as frenectomies, tongue ties, pulpectomies, debridement of periodontal pockets and uncovering of implants - frequently with just topical anaesthesia. It can also be used to treat aphthae and herpes simplex. Using thin fibres, it is also possible to reduce the microbic infection in root canals and to reduce bacterial growth in periodontal pockets. The Er:YAG "drill" is a bit slower than the traditional drill but has the advantage of requiring less anaesthesia, so several quadrants can be treated during the same session. There is no temperature rise in the pulp; on the contrary, the temperature is reduced by the water spray. With the Er:YAG laser, dentistry has taken a large leap from the old "extension for prevention" to "minimal invasive dentistry".

The Er:YAG laser is excellent for treating hypersensitive dentine. Several studies have confirmed this fact but have only been looking at morphological changes as possible explanations. Zeredo [1311, 1588] has, however, shown that this wavelength has a pain modulating effect in itself, just like all the other lasers used in dentistry. As always, it is not a matter of the laser used but of the dosage applied. Pourzarandian [1606, 1646] confirms the pain relieving effect of Er:YAG as well as the stimulatory effect.

A member of the Er:YAG family is the ErCr:YSGG laser (Erbium-Chromium:Yttrium-Scandium-Gallium-Garnet) with a wavelength of 2870 nm. The water spray is claimed not only to serve as a coolant but also to give a "hydrokinetic" action in order to make the ablation more effective. If so, this is take same with the Er:YAG as well, since water is always needed for "drilling".

An example of the technological advancements in laser dentistry is Photon Induced Photoacoustic Streaming (PIPS). This technique harnesses the power of the Er:YAG laser to create photoacoustic shock waves within the cleaning and debriding solutions introduced in the root canal. The containment of the shockwave streams these solutions through the entire canal system, enhancing their effectiveness. The canals and subcanals are left clean and the dentinal tubules are free of smear layer.

One of the difficult parts of the Erbium lasers is beam delivery. The first lasers used articulated arms with mirrors, a solution that is expensive and clumsy since the dentist has to move it at different angles. To make an optical fibre, the light conducting materials available were not transparent enough. Typically a one metre fibre reduced the output to 50% and a two metre fibre reduced it to 25%. Also, the fibres were easily burned at the input end. Today, there are flexible fibres of very pure quartz, transmitting more than 80% over a length of two metres. Another method is to use a hollow wave guide with a dielectric surface material reflecting the beam. There are basically two problems with this solution, namely that the output power depends on the bending angles and that it easily breaks if bent too much.

Literature: [201, 160, 1156, 1157, 1158, 1581, 1792]

1.23 “Strong” diode lasers in dentistry

Today the most common laser in dentistry is the so-called diode laser. The name is a bit misleading, because many other lasers are also diodes. Nevertheless, a dental "diode laser" generally means a laser in the 808-980 nm range and with outputs between 500 mW and 5 W. The reason for its popularity is the small size and the low price - compared to other lasers, that is. These lasers can be used for minor surgical procedures and are well suited for periodontal pocket curettage. Although initially marketed as surgical lasers, manufacturers have realised that these lasers also can be used as biostimulators, by reducing the output to the lowest value. This is generally 500 mW.

Diode lasers are far from optimal for biostimulation, but once you own one, it is well worth using for LPT. The problem is the high output, but to a degree this can be compensated by irradiating from a distance. If the fibre is in place when doing LPT, the local power density becomes very high, so a rather rapid movement with the probe over the target is needed. Some manufacturers are now offering special LPT handpieces to improve the situation. Still, the control of dosage remains a problem.

808 nm offers the best penetration into tissue, which is an advantage in many LPT situations. On the other hand, the reduced penetration of 980 nm would be an advantage when performing surgery, avoiding collateral damage.

In this context it is important to highlight the fact that all "surgical" lasers have a biostimulatory effect, even when used for surgery alone. The picture below illustrates this effect, which is becoming more recognised by manufacturers and users.

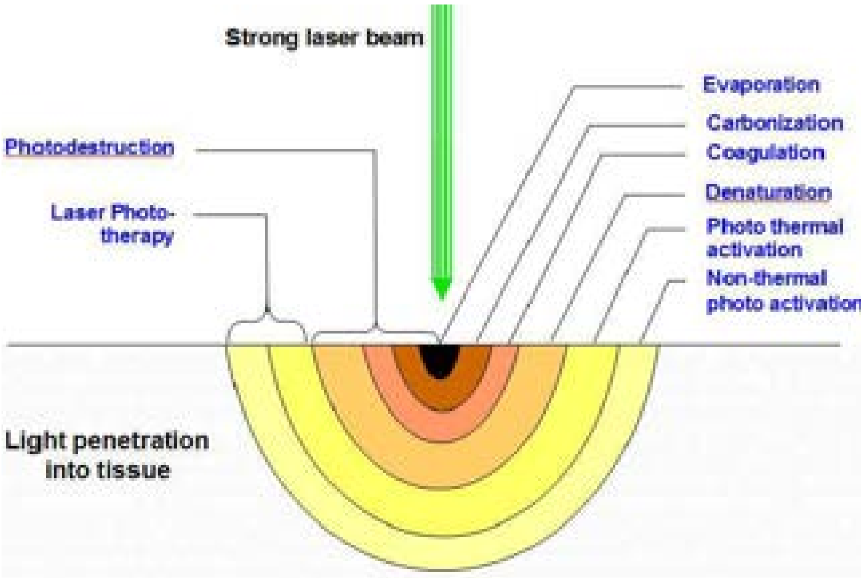


Figure 1.28 Laser - tissue interaction.

1.24 The KTP laser

The full name of this laser is KTP/532-laser frequency doubled Nd:YAG laser). Here, the Nd:YAG laser is combined with a non-linear crystal (such as KDP, KTP, LiNbO3, etc.), light can be converted to other wavelengths. One such combination is a Nd:YAG laser and a KTP crystal (Potassium Titanyl Phosphide), which is used for frequency doubling and hence also halves the wavelength of 1064 nm to 532 nm (green light). Such instruments are often called KTP/532 or just KTP laser. This laser is used to treat superficial blood vessels (as in the left figures) or haemangiomas (as in the figures to the left).

In the left figures the top picture is taken before and the lower picture is taken after one single treat-ment with KTP-laser.

The photos to the right show a haemangioma before (top) and after 6 treatments. Another two treat-ments were done before satisfaction. The time between treatments was about 6 weeks. Further, it has been observed that the KTP-laser radiation also has an effect on wrinkles, sometimes called "Non-Ablative Skin Rejuvenation" of wrinkles. The energy density is set lower than the pain threshold, which makes the treatment painless. Practically no side effects have been noted. The mechanism behind this is biostimulation. The 532 nm wavelength used to be exclusive but is now available in inexpensive laser pointers. The wavelength has also sucessfully been used for wound healing but the literature is still scarse. Frequency-doubled Nd:YAG lasers are also used for panretinal photocoagulation in patients with diabetic retinopathy.

1.25 Q-switching

Q-switching, sometimes known as giant pulse formation, is a technique by which a laser can be made to produce light pulses with extremely high (gigawatt) peak power, much higher than would be produced by the same laser if it were operating in a continuous wave (constant output) or switching mode. Especially the solid state lasers are suitable for this technique. The most common Q-switched laser is the Nd:YAG-laser. This can also be combined with frequency doubling.

The primary use today of Q-switched lasers is in bleaching of tattoos. Due to the extreme peak power a local explosion occur in the tattoo pigment. As the overlaying skin is fairly transparent (if not pigmented) it will not be injured. For black and blue colour of the pigment the 1064 nm wavelength is good, but for red and orange colour, the frequency doubling (532 nm, green light) is needed.
The Q-switched laser can also be used to remove unwanted brown spots and sun freckles from your skin.
In 2012 a new variant of tattoo removal turned up. It got the name R20. Instead of just normally cover the area of the tattoo with laser puses, four passes was performed. After the first treatment, you take a break of 20 minutes. After that, the treatment is repeated and a new break of 20 minutes is made. After that, a third treatment is performed. After another pause of 20 minutes, the fourth and final treatment is

done. This method makes the fading faster than with just a conventional treatment.

A year later, in February 2013 a new treatment variant appeared. In this case, a substance named perfluorodecalin (PFD) is combined with the laser treatment. PFD is a chemically and biologically inert biomaterial with high solute capacity for gases such as oxygen. This method got the name R0, as the break time between treatments is reduced to only seconds.

Research established that topical PFD clinically resolved immediate whitening reactions within a mean of 5 seconds (range 3-10 seconds). Tattoos treated with R0 method demonstrated excellent fading in an average total treatment time of 5 minutes.

Visualised imaging of whitening demonstrated epidermal and dermal hyper-reflective "bubbles" that dissipated until absent at 9-10 minutes after PFD application, and at 20 minutes without intervention.

In conclusion, multiple-pass tattoo removal using PFD delivers rapid sequential passes in a total treatment time averaging 5 minutes, and more effective than single pass treatment. Visualised whitening associated "bubbles," upon treatment with PFD, resolve twice as rapidly as spontaneous resolution.

After the first laser pass with the Q-Switched laser, apply few drops of PFD over the tattooed area of the skin to be treated. Use a cotton swab, over the tattooed area of the skin to be treated. Allow few seconds for white bubbles to resolve. Apply the second laser pass.

Absorption spectrum of some typical targets in aesthetic treatments.

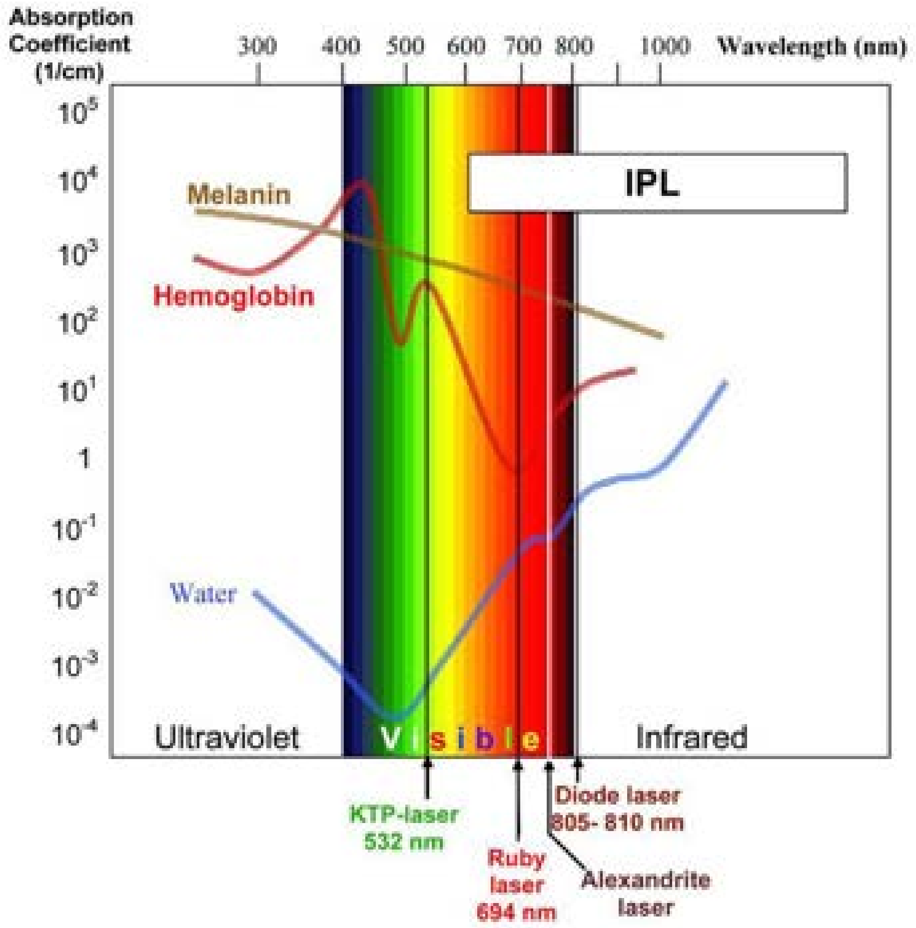
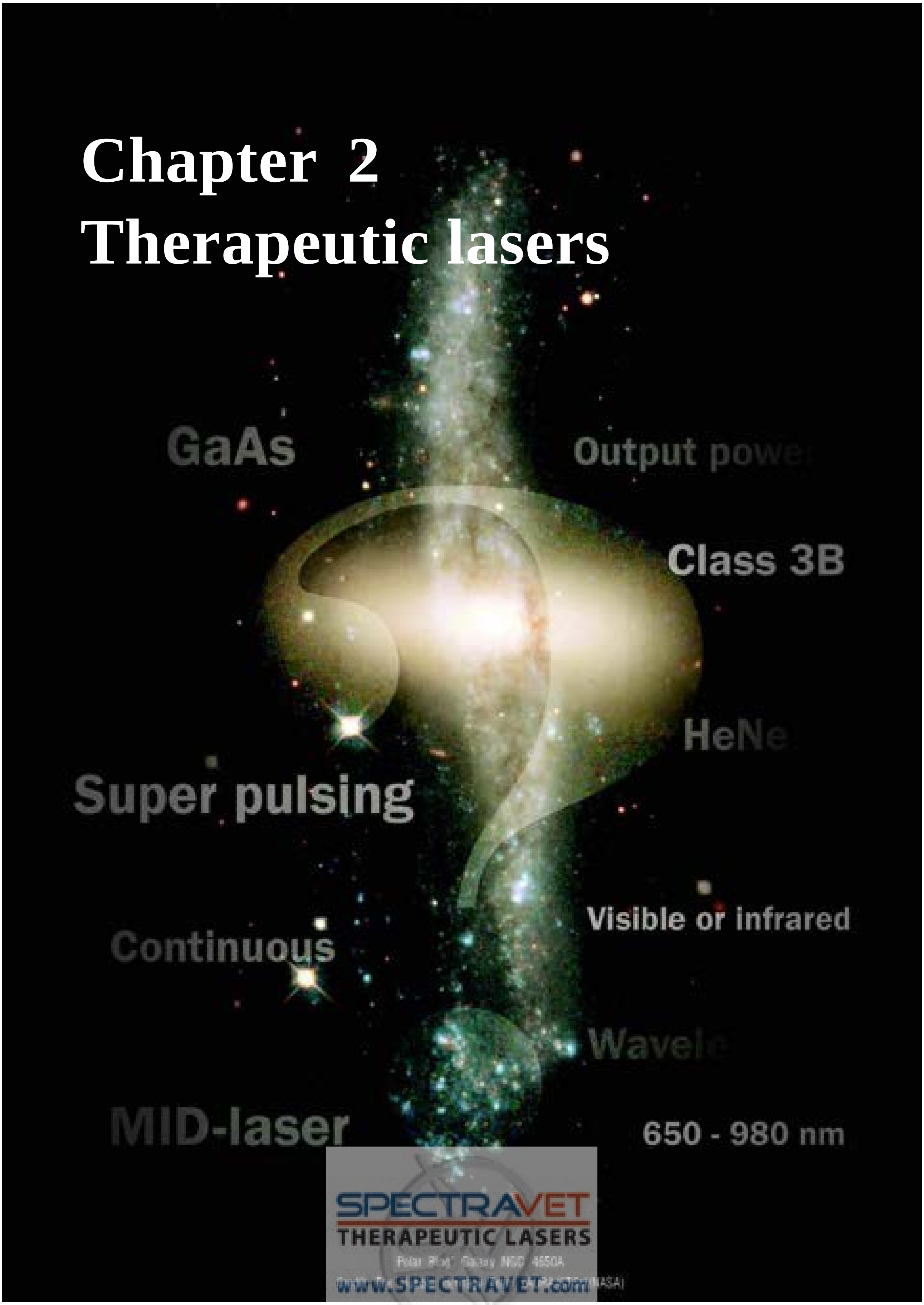


Figure 1.29 Absorpion with IPL for hair removal

In this diagramme the wavelengths of three different lasers for hair reduction is shown (Ruby, Alexandrite and Diode laser) and the width of a typical IPL device. Also the wavelength of the KTP laser (for removal of haemangiomas and superficial blood vessels) is shown.

Chapter 2
Therapeutic lasers



2.1 Therapeutic lasers

Compared to the thermal lasers (the strong/surgical/esthetical lasers) the medical lasers are smaller, lighter and cheaper. Historically all medical lasers were red light Helium-Neon-lasers. By the second half of the eighties, semiconductor lasers started to emerge. The first type was the super pulsed Gallium Arsenide laser with the wavelength 904 nm. Later the GaAlAs lasers arrived, with typical wavelength 820 or 830 nm and then the InGaAlP lasers with red light output, usually 650 or 660 nm.

2.1.1 The first generation 1975-1985

The first laser therapy instrument on the market was a HeNe-laser, a gas laser with a typical output of 1 to 5 mW. It emits visible, red light with a wavelength of 633 nm, or to be more exact, 632.8 nm. This laser contains a relatively large laser tube of glass, having a low-pressure gas mixture, connected to a high voltage power supply. The laser generally works continuously, but can be pulsed by switching the electric power supply or by means of a beam chopper. In that case, half of the output is lost (if the duty cycle is 50%) compared to the continuous working mode. Typical output of these lasers today is 5-20 mW. The beam directly from the laser tube is rather narrow and parallel and the spot size at a metre's distance is around 3 mm in diametre which gives a good power density.

In a therapeutic instrument, the HeNe laser light is aimed at the area to be treated, either directly, via scanning mirrors, or transferred via a fibre optic light conductor. The light conductor can either be a mono-fibre or consist of a number of small, thin fibres (fibre bundle). Mono-fibres have less power loss (typically 1-10%), but are more expensive. Fibre bundles often give a power loss between 20% and 30%, depending on quality. This optical fibre usually ends in a handpiece or in a syringe (for illumination of problems deeper in tissue). With the fibre end held in contact with the skin, less reflection from the skin is achieved and it is also possible to make a mechanical pressure forcing the nearest blood away, which also increases the light penetration.

2.1.2 The second generation 1985-1995

In the second part of the eighties, the first semiconductor laser emerged on the market. Semiconductor lasers, usually called diode lasers, in general are small, rugged and easy to drive electrically (no high voltage is needed). Another detail is that the light is linearly polarised, which usually is an advantage in this medical application. A laser diode emits a divergent beam (usually 10 to 20 degrees), which can be made parallel by the use of a collimating lens. In the beginning they had a relatively low output compared to today's devices.

The first diode laser on the market (around 1985) was named gallium-arsenide (GaAs) and has a wavelength of 904 nm (in the infrared) and is super pulsed. This means that the light is pulsed in a very extreme way; very short (100-200 nanoseconds) and very strong pulses (in the order of many watts). The reason for this is practical - the GaAs crystal could only lase if the current density was very high, meaning about 50 amperes through a crystal in the size of a salt grain. In order not to burn the crystal, the on-time (during which the crystal was heated) could not exceed 200 ns and the off-time (during which the crystal was cooled by its heat-sink) had to be more than a thousand time longer. It was quickly noted that this infrared super-pulsed laser light had a higher tissue penetration than the light from the HeNe-laser. It gave us a tool to treat musculo-skeletal problems. This laser is till much in use and with a higher output.

Another semiconductor laser, the Gallium-Aluminium-Arsenide lasers (GaAlAs) arrived around 1987. It had a wavelength of 820 or 830 nm and a typical output of 10-20 mW. Actually, this is a group of lasers with wavelengths in the region 750-850 nm and 980 nm. Today, mainly two variants are used, the 808 and 980 nm. Especially the 808 nm diodes can be made very strong - up to hundreds of watts. The 808 nm type is now dominating as the tissue penetration is better than the 980 nm type (see “How deep does light penetrate into tissue?” on page 79).

Further, the Indium-Gallium-Aluminium-Phosphide lasers (InGaAlP) came around 1988 and started to replace the HeNe-laser. Also this is a group of diode lasers with wavelengths between 630 to 690 nm. Due to its long name, it is often called just Indium laser. The most common type today has a wavelength of 650 nm.

2.1.3 The third generation 1995-2005

Due to the high efficiency of the diode lasers, battery powered devices started to come. However, the batteries were still not good enough. Especially for stronger types of diode lasers (consuming more power) the battery time could be irritatingly low. This is similar to the situation with mobile telephones. One new thing appeared - the first units for the consumer market, usually powered with conventional non-chargeable batteries. Small and relative cheap units for treatment of e.g. herpes, acne and skin problems were produced in different countries. From China came a small unit for intra-nasal treatment, targeting the small blood vessels in the nose.

During this period also light emitting diodes (LED) became more frequent, competing with lasers. (See “The light-emitting diode (LED)” on page 16.) In the marketing often laser studies were used to "prove" the efficiency of the product. In some devices, LEDs and laser sources were mixed, claiming that "the more wavelengths - the better effect!" One marketing trick is that "this is NASA Light Emitting Diodes", implying that they should be better or more efficient than others. NASA is not developing or producing LEDs. True or not, it has been known for long time that narrow banded red light has a positive effect on wound healing. More of this in Chapter 6. The typical treatment laser during this period consisted of a base unit (driving unit) to which one or different laser probes could be connected, offering different wavelengths and often with possibilities to set different

2.1.4 The fourth generation 2005 and onwards

During this period "new" wavelengths appeared. Such wavelengths are 532 nm (KTP) and 440 nm. It is not quite clear what they are useful for, except to kill bacteria. Some success is noted in the treatment of open wounds. The battery quality is now much better than before and more and more units can be run for many hours without charging. Also devices using a base unit have become smaller and often with a built-in power metre, assuring that the output power is what it is said to be. Another thing that has changed is that instruments have to be medically approved by authorities (CE, FDA etc).

2.2 What is a good laser therapy instrument?

Some questions to consider before you choose a laser

To choose a laser instrument is not easy for the layman. You talk to a salesman, and then you know which laser is the best. You talk to another one and then you don’t know. Now, read this:

- **Should I choose a laser, an LED, or a combination of both?**

There are about 25 scientific studies comparing effectiveness of laser (coherent) light with non-coherent light, (e.g. LED’s). In almost all of these comparisons, the laser has come out on top, even though the other light sources, under certain conditions, can give a similar effect.

- **Is a cluster probe with different types of laser diodes (different wavelengths) optimal?**

Mixing lasers with LED is not as good as pure laser light. In general, it seems that the narrower the bandwidth, the better the therapeutic effect. It can also be said that the closer we are to common daylight (i.e. the more wavelengths we mix in) the less is the therapeutic effect. So, the fewer the wavelengths the better the results.

- **Is a laser with built-in “recipes” better than an instrument giving fix doses?**

Some producers offer instruments with built-in treatment “recipes”, or treatment programmes. While this may sound good (“The instrument knows!”), it is actually unfortunate. Let’s look at an example: You choose “arthritis” from the menu of an instrument with built-in treatment programmes. The instrument may give the following programme:

“30 Hz for one minute, 156 Hz for 2 minutes, and 5000 Hz for 45 seconds.” Then the owner of the instrument thinks that this is the best treatment for arthritis. But this is wrong! Why? First of all, the area to treat is not involved, meaning that you will get the same number of joules for a finger joint as for a knee. Secondly, the pulse frequency is one of the least important parametres. If you chose one pulse frequency and keep power, power density, dose and treatment time constant, the result will probably be just as good as if another pulse frequency is chosen. Pulse frequency is probably on the fifth or sixth place of parametre importance. So, “recipes” are of little value, maybe a good initial help for the beginner. It is important that you choose a laser system that is flexible and allows you to control the frequency and dose depending on what and where you treat.

- **Is super pulsing better than switching with a 50% duty cycle?**

Yes, it can be, if the average power to tissue is high enough. The high peak powers that you often get with super pulsed lasers increases the penetration of the light into the tissue due to bleaching of collagen in the skin. So as long as the average power is high enough, super pulsing may be an advantage over regular switching (“chopping”).

- **Does pulsed light penetrate deeper than continuous light?**

No. Not if they have the same power and peak power respectively. However, super pulsed lasers usually have higher peak powers than continuous or switched lasers, which allows for a non-linear penetration profile (see below). Though tissue has the highest transparency for wavelengths of about 800 nm, super pulsed lasers with a wavelength of 904 nm (GaAs-lasers), and with high enough peak powers have a higher penetration depth than the 800 nm lasers. See question above.

- **Are there optimal laser types for certain indications?**

Basically, YES. An additional factor is the power. However, since the penetration also depends on the tissue, it is not possible to give a simple answer to that question. More important is “working depth”, i.e. the actual penetration plus the cell cascade effect passing from one cell to the next (systemic effects).

- **Is an expensive laser better than a cheap laser?**

That depends. If it’s not easy to use and doesn’t produce good results for your clients, then it doesn’t matter what it costs. A therapeutic laser is always an investment, so the important thing is that you carefully evaluate what you get with your purchase. Is the service good? What support is given with your purchase? Is the company that manufactures / distributes the laser knowledgeable? See also other FAQ:s on this web page: www.laser.nu.

- **Which laser type has the best documentation?**

For many years, the HeNe laser was number one, being around for such a long time. But now it is the GaAlAs and on second place the GaAs laser (904 nm).

- Are strong lasers better than weaker ones?

YES and NO. Output power should not be too low for its purpose. If the power is too low, it causes unnecessarily long treatment time in order to achieve the required total dose. Also, if output power is too low, it could result in the power density being too low which is an important parametre in treatment. Nor should output power be too high for its purpose. If the power is too high, the light could burn tanned, coloured, tattoos or skin with dark hair. Furthermore, in most countries, there is a power limit of 500 mW (= 0.5 watt), above which the laser may be a Class 4 laser. If so, it usually means that it requires oversight by an MD or DDS. Also, if the power is too high, it can result in unintentionally high doses which can give less good treatment results than necessary (see the Arndt-Schulz curve "Treatment dose" on page 684). And finally, time is also an important treatment parametre. Administering a certain number of joules over a certain area using a certain laser power during a certain time, may not give the same result as using a ten times stronger laser during one tenth of the time with unchanged optical configuration. Another way to say this is that the rule of reciprocity is not valid. Some laser companies claim that a Class 4 laser 'by default' is better than a Class 3B laser (4 is higher than 3, so it has to be better… right?). This is simply not true. The classification of lasers is a measure of eye hazard, nothing else. While defocused Class 4 lasers may well be used successfully in laser therapy, this does not have anything to do with the laser classification. See below for a more detailed explanation.

- Does the instrument have a power metre?

This is important. The human eye is a lousy power metre (visible light) and not working at all in the infrared spectrum. So, the output can be zero without you knowing it. A power metre can be built-in or separate.

- How much do spare parts cost?

This is an important question to ask a salesman. A laser producer has a monopoly on many spare parts such as printed circuit boards and can hence charge customers up to the cost of a new laser.

- What happens if it breaks?

For some therapists, the laser instrument is their main source of income, so this question is highly relevant. If it breaks, will you be offered a replacement unit during repair time?

- Is any educational support included?

In order to get good results, you need two things: a good instrument and good knowledge.

- **What literature is included with the purchase?**

It is important that your laser comes with documentation and educational materials to enable to use it successfully.

- **Is it important who manufactures and distributes the laser?**

In the beginning (from about 1985 to mid 90's) many laser producing companies went bankrupt. For many of their customers, this became a big service problem. Often their customers had to buy a new instrument. It is important to choose a stable company with a good reputation.

- **Instrument start-up time**

When you work with an instrument daily, it is important that you can use your time efficiently. Some instruments have to be “programmed” before you can start the treatment. Sometimes this is a long procedure. Be sure that your instrument can start quickly. To spend a minute with settings is not so much work, but to do it thousands of times is a waste of valuable time.

- **Quality of buttons**

Whenever you need to set parametres, the buttons, thumb wheels, slide switches or other electromechanical components must be both safe and easy to manoeuvre. The most common problems emanate from such components.

- **Quality of cables**

For a stationary unit, it is important that the cables are of good quality, flexible, resistant to massage oil (and similar), and are long enough to reach the whole patient from the place where the laser base unit is placed.

- **The aperture**

The opening where the light comes out is called aperture. This opening can be open or closed with a lens or a glass window. It is better if it is covered, so that dust and skin particles are not collected in the cavity in front of the laser diode. The area of the beam where it hits the skin, when the probe is held in contact is of importance – it influences the lights penetration into the tissue. If this area is in the order of a square millimetre, and if the laser is relatively strong, the power density can be so high that bleaching effect radically can increase the penetration through the skin. This is specially noticed for the super pulsed GaAs-laser. Small apertures create high doses (fluences) in the contact area while the applied energy still is low.

- **A flexible instrument**

The development will go on and new laser types may come. A professional instrument is built so that it can include coming wavelengths or powers, usually by updating of the software. A professional instrument should also be rugged and be able to stand large temperature differences, mechanical mishandling, static electricity, cleaning procedures and transport.

- **Service**

All instruments can break. Even a Rolls Royce breaks. That is not a problem if the service is good. Find out if you can borrow a replacement probe or instrument during the time of repair. In the beginning, almost every therapist is uncertain of treatment parametres and treatments. Can you get a mentor to contact? Is there a laser society that you can join? Are there regular meetings you can join?

Ideal but not necessary

Figure 2.1 a. Wisdom tooth with symptoms due to caries; apex location close to the IAN
b. Red laser over the suture line
c. Infrared over the projection of the IAN
d. GaAs extra-orally to reduce oedema

2.3 The basic instrument

Practically all instruments produced today use one or more laser diodes as the light source

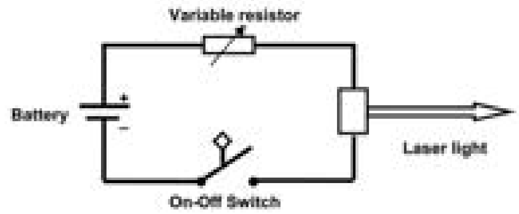


Figure 2.2 Basic construction of a laser

Basically the construction is very simple - a power source (e.g. a battery), a current limiter (e.g. a resistor) an on-off switch and a 100 mW laser diode. They can be bought for, let's say, 200 USD together if you know where to buy them. Higher output means a bit more, of course. But still, most instruments on the market cost thousands of dollars. So what do we pay for? First of all, we need more parts to get a useful instrument. A casing and maybe a heat sink to cool the diode. Still not very expensive.

Now, let us assume that a small company wants to build lasers. They will need some place to rent for the mounting. They have to have it CE-marked or FDA approved. This costs a great deal of money. They have to write and print a manual and sales material. They need to advertise and build a web site. Exhibitions, demonstrations, travelling, making boxes for packing, arranging courses etc. Unless it is a pure hobby, they will also need money for salary, VAT and tax payment. And how to compete with the already established companies? To get around this, they start using sales tricks.

2.4 Sales tricks

The collected evidence about the many advantages of laser phototherapy is rapidly increasing. The knowledge about the basic mechanisms as well as about the optimal dosage intervals has improved dramatically in recent years. It should be easy to sell laser equipment to all kinds of therapists just using the available scientific knowledge - which is truly amazing in itself. But this is not always the case. Too many manufacturers deliver poor equipment and training, and too many of them use sales gimmicks in order to make their equipment look unique. It is not that the devices they're selling are incapable of producing therapeutic effects. Even a $10 lecture pointer has some therapeutic potential. It is that they are simply NOT capable of delivering upon many (in some cases, most) of the claims that are made about them, whether those claims be about the range of treatable indications, therapeutic outcomes, depth of penetration, speed of treatment, method of application, or patented waveforms, etc. Such sales techniques and outright dishonesty are confusing for consumers and risk draining the therapy of the credibility it deserves. Let us look at some examples!

2.4.1 Sales trick 1: Soliton waves

One laser manufacturer in the USA claims that their lasers produce "soliton waves" by "piggybacking one wavelength upon another", and that these "penetrate deeper into the body than is possible with any other type of laser". This sounds impressive and unique, but it is a sales trick, no more, no less. No therapeutic laser on the market produces "solitons". And, even if it were possible and financially viable to do so, what evidence is there to support this manufacturer's claims of therapeutic benefit? We have studied one of these soliton lasers and there is nothing unique about it, just cheap conventional diodes!

2.4.2 Sales trick 2: Scalar waves

The "inventors" of the Scalar Wave Laser claim to have developed the "most advanced low level laser technology with state of the art quantum scalar waves" that supposedly employs a "unique approach to accessing the quantum neutral unified field state" to "dissolve cellular memory, normalise body systems, optimise anti-aging capabilities, and activate the glands and higher dimensional subtle body that yogis and mystics have tapped into throughout the ages". This is, of course, a complete fabrication, a crackpot theory. No laser equipment designed for laser phototherapy is producing scalar waves and again, even if such waves existed, there is no evidence whatsoever that they should have a positive or negative effect of cell functions.

2.4.3 Sales trick 3: Treating through clothes

One manufacturer claims that their device, emitting a very low intensity thin line of red laser light, can be used to treat patients effectively through their clothing. Yet it is obvious to anyone who wears a shirt in the sun that clothes are a very effective blocker of light. A simple experiment on the penetration of 650 nm 20 mW red laser light through different types of textiles can be watched on a Youtube presentation: http://www.youtube.com/watch?v=MkGJvvWD1vw. Representatives of this company also claim that these photons go right through our bodies. Whilst it is possible for very high-energy particles such as neutrinos and for x-rays, being very different waves, to penetrate through our bodies, the low energy photons of visible and infra-red light do not.

2.4.4 Sales trick 4: Class IV laser therapy

The international system of laser classification is concerned only with the risk for eye injury and, at higher powers, skin damage. It has nothing at all to do with suitability for laser treatment, nor does it mean a generational change, nor ensure any improvement in efficacy. Many different parametres are considered in eye risk evaluation (laser wavelength, beam diametre, beam divergence, exposure time, pulsing vs. continuous emission, type of pulsing and more). Actually there are Class I lasers that are higher powered than many Class IV instruments! So, there is no sense in or reason for, other than deception, the term "Class IV laser therapy".

For example, one manufacturer claims that their Class IV laser offers superb penetration through tissue (from 6 to 9 inches), and that the so-called "weak" Class IIIB lasers (e.g. 500 mW, 808 nm laser) hardly penetrate the surface skin barrier at all. However, the very opposite is the truth! Due primarily to its absorption by water in the tissue, 970 or 980 nm penetrates much less than 808 nm, and this is not compensated by the higher power. At around 808 nm we actually have the best penetration into tissue, and increasing power only increases the depth of penetration marginally. With the higher superficial absorbance of the 980 nm laser there will be considerable heating, and, while heat is fine for many conditions, the biostimulative effect does not depend on heat [1447]. There is one good side of giving more heat in the skin and that is that the patient "feels" the treatment better which might give a better placebo effect. There is more than one laser company using the same flawed argument to promote high-powered lasers.

It is also interesting to note the use of the term Class IV "technology". There is no specific "technology" that enables a manufacturer to choose a laser diode that produces more than 500 mW, thus the term "Class IV technology" is simply used to infer a differential benefit that does not exist. Apart from power, the only differences between Class IIIB and IV lasers are the potential hazards and, usually, the price.

It is interesting to see that a recently published study by Ottaviano [2437] is supposed to show that a "Class IV laser", i.e. a 970 nm laser of 5 W can treat oral mucositis better than a Class 3B laser. The authors claim to have been using a "standard 3B laser protocol" for comparison. In fact, they have not. The "standard" laser used is a laser pointer with a 635 nm diode of 2.5 mW, delivering 0.45 J per point and delivered from a distance of 1 - 3 cm, further reducing the power density. In spite of this, the authors refer to the review by Bjordal [2115] where 10 - 60 mW and 3 J per point is recommended. This is clearly a study to distrust. This study seem to have the primary purpose to prove that this "new treatment" (Class IV laser therapy) is the only one that is really effective. However, many companies around the world produce therapeutic lasers in laser Class IV (output power exceeding 500 mW) since more than 15 years ago so that is nothing new. Also, to make a laser that has a power of 600 mW (Class IV laser) is not more expensive than to make one that is 400 mW (Class IIIB laser) and not markedly more effective.

2.4.5 Sales trick 5: Claimed output vs. actual output

It is not uncommon that the output is lower than stated in brochures and manuals. This is only too well illustrated in an investigation from Brazil [2103]. In this report, forty lasers at 36 physical therapy clinics were tested. The output power was measured and compared with the stated data in the owner manuals, direct consultation and information from the manufacturers. In 30 cases, the power was less than it was supposed to be. In three of the remaining cases, the power was correct and in seven cases, the power was zero. The analysed equipment was out-dated and periodical maintenance not been conducted.

In another study [2456] 60 LPT devices were evaluated in two ways: first with the device cooled down and then with the device warmed up for 10 minutes. Only one device had the correct output power. The study also showed the need for periodical calibration of LPT equipment and a better technical knowledge of the therapists involved. Even though these two studies were performed in Brazil, there is no reason to believe that the result will be different in other countries. It is quite clear that if the owners/users had had a power metre and been using it, they would at least have been aware of the low output power of their instrument.

2.4.6 Sales trick 6: The 904 nm trick

Restating the above, even though the peak power of the super-pulsed GaAs laser may be very high, it lasts for an extremely short time compared to the pulse cycle, resulting in an average output power that is usually a thousand times lower than the peak power. For clinical use, it is the average power that counts. The energy delivered from pulsed lasers is always the average output power multiplied by the exposure time. The average power is the important output of the laser. Some manufacturers prefer to label these lasers as "very strong" and state only the peak power which then can be in the order of 100 watts. This sounds impressive, but typically these lasers emit 10-100 mW average power, and this is what counts for the treatment. The GaAs lasers are quite useful in physiotherapy, but care has to be taken.

In some super-pulsed lasers the average output changes with the chosen pulse frequency, so that low pulse repetition rates deliver low average outputs. This means that with such lasers, with low frequency settings, the treatment time may be impractically long in order to deliver a reasonable dose. One manufacturer, for example, promotes its super-pulsed lasers as having 25.000 mW or 50.000 mW of power, and offers the user a small number of preset 'programs' which, essentially, only adjust the pulse frequency and, therefore, the average output power. One of these "programmes" sets a frequency of 5 Hz. The average output power is then only 0.050 mW or fifty micro watts. With this very low average output power it will take 5.6 hours for this to deliver one Joule! If that instrument had a built-in (or separate) power metre, the owner (or buyer) would be able to notice this low output for set low frequencies.

2.4.7 Sales trick 7: False super pulsing

One manufacturer claims that its dual-wavelength (800 nm and 970 nm) high-powered Class IV laser has better penetration due to its 'Intense Super Pulse' emission. However, these diode lasers are not super pulsed, they are "chopped", and chopping does not offer increased penetration. In this case of chopping the output simply reduces the tissue-heating effect of the high power laser by both reducing the average power and also allowing time for the tissue to thermally relax (i.e., dissipate heat) between each pulse of light.

2.4.8 Sales trick 8: Pre-programmed machines

There are many variations of so called pre-programmed lasers on the market. Some offer 'starter' protocols that employ simple variations of power, frequency and time, making these parametres known to the user and even affording them the option of changing them as their knowledge and experience improves. Others, however, provide the user with nothing more than a choice of letters or numbers that represent different "proprietary programmes", ensuring that the user is kept completely in the dark as to what they're actually doing. Such programmes may consist of various frequencies and exposure times, often in automatically-changing combinations of such; for instance, 20 seconds of 500 Hz + 40 second of 120 Hz + 10 second of 1500 Hz. The user is informed only that that "programme" is supposed to be the best for e.g. headache, and that another program and time/frequency combination is the best for arthritis, etc.

The buyer of such an instrument trusts that the designer of the instrument knows that this is a fact. However, there are no such optimal time/frequency combinations scientifically proved to be better than others. Also - how can a setting for "arthritis", for example, be the same for a finger joint as well as for a knee? Who can verify the pulse repetition rates recommended? Such preset protocols will generate nothing more than vaguely satisfactory outcomes, at best; neither what your patients expect of you, nor what you should expect of a clinical tool that has, most likely, cost you thousands of dollars.

One particular manufacturer has corrupted the use of the terms “Optical Window” and “Therapeutic Window”, well-known to many within the phototherapy field, to label their preset programmes as so-called “Therapeutic Optical Windows” that, supposedly, deliver optimal combinations of the many different parametres that influence clinical outcomes. As an exercise, let's consider the various device and treatment parametres and patient characteristics that affect variations in phototherapy outcomes, and determine how many iterations of these must be clinically tested and validated before one could claim, with even a hint of honesty, to have determined the optimal

"Therapeutic Optical Windows" for even a handful of indications. First we take the various parametres of, say, a switched continuous wave device (e.g., output power, spot size, wavelength, pulse frequency, duty cycle). Then we add the irradiation duration, treatment technique, number of points to be treated or the area of affected tissue, and the target tissue depth. Next, toss in a handful of such patient characteristics as skin colour and tissue type and whether their condition is acute, sub-acute and chronic. Finally, consider some desirable clinical outcomes such as analgesia, reduction of inflammation, enhanced tissue repair and/or nerve tissue regeneration. Although this gives us a very simplified set of factors, we are still left with potentially billions of combinations of variables that must be subjected to clinical testing in order to support this manufacturer's claims. In forty-something years of research into phototherapy, by hundreds of researchers, we have barely even scratched the surface in terms of determining upper and lower activity thresholds of irradiation duration and intensity, and yet we're now supposed to believe that one company only has considered and tested every possible iteration and distilled them into nine optimal "Optical Therapeutic Windows"? Even the most credulous among us must baulk at that … We recommend, instead, availing yourself of high-quality research published in peer-reviewed journals, informative manuals and qualified seminars, rather than automatic settings. Use palpation, your own physiologic knowledge, your patients' feedback and your experience to guide you in your choice of parametres.

2.4.9 Sales trick 9a: Home tailored theories

"Continuous Laser emissions act fast on inflammation, stimulating blood and lymphatic circulation and inducing fast re-absorption of fluid build-ups; however, they only have a secondary effect on pain, which is diminished after reducing the inflammatory process. Pulsed Laser emissions, on the other hand, have a practically immediate effect on pain, since they are able to induce analgesia, interfering with the very transmission of the pain impulse to the higher brain centers, but they are less effective at treating inflammation and oedema, only achieving results after a long period of application."

The authors of this book have been unable to find any scientific documentation behind these impressive claims. Actually, the weight of evidence could just as well support the opposite argument: CW lasers have an excellent and immediate effect on pain [1570, 1702, 1784], inducing analgesia directly by interrupting the transmission of pain signals to the brain; and pulsed 904 nm lasers are fine for reducing oedema [92, 1337] and inflammation and, secondarily, relieving pain. In short, one could swap the words “Continuous” and “Pulsed” in the two sentences above with the same degree of credibility. The literature review by Hashmi [523] finds very little support for specific effects of pulsing, other than that of the high peak power of the super pulsed lasers.

2.4.10 Sales tricks 9b: Home tailored theories

"Interferential laser therapy" is manufacturer-coined term, when two probes are used simultaneously, for instance one in the front and one in the back of a shoulder. Sounds like a good idea: more energy into the area and arriving from two sites. So far so good, but the idea of interference is a misconception. The potential additional advantage of two laser diodes is not the creation of interference, because this can only be obtained from a single source. Although basically a misconception, one would still think that the use of two probes is quite practical and time saving, but the first study to investigate this was negative. LPT in itself, in this high quality study had a clear effect, but the addition of the second probe did not improve the outcome.

The aim of the study by Montes-Molina [2457] was to test the safety of “interferential laser therapy” generated by two independent low level lasers and to compare its effectiveness with conventional single probe laser therapy in the reduction of shoulder musculoskeletal pain and associated disability. 200 patients with shoulder musculoskeletal pain were randomly assigned in two groups, 100 people each. Group I, experimental (n=100) received "interferential" laser, placing two probes opposite each other over the shoulder joint. Group II, control (n=100) received conventional laser therapy, using a single probe along with a second inactive dummy probe. Lasers used were GaAlAs diode (810 nm, 100 mW), in continuous emission. Laser was applied in contact mode through ten sessions, on 5 shoulder points (7 Joules/point) per session. There were no differences between both groups in the reduction of pain, either assessed by VAS scale or SPADI index, using the Mann-Whitney U-test. Comparison between the scores recorded before and after the treatment, within each group, showed significant differences for VAS during movement and SPADI index for both groups. In this study, the application of two lasers in order to generate interference inside the irradiated tissue showed to be a safe therapy. Both interferential and conventional laser therapy reduced shoulder pain and disability. Nevertheless, differences between them were not detected. The "interferential group" received a total of 700 J during 10 sessions, whereas the conventional group received 350 J. Maybe, again, we can conclude that "less is more"?

2.4.11 High power - low power

There are two extremes on the market - those promoting very low power output and those promoting very high power output. Which is best? The answer is: none of them. There is no "one size fits all" laser. Each one has its limitation. There is an increased awareness about the necessity to deliver fairly low doses over longer time to optimise anti-inflammatory results [1840]. This means that, at least for healing processes, low power over long time is more effective than high power over short time, for stimulation of cell proliferation. For temporary analgesia of painful conditions, high power over short time can give a better momentary effect, subject to certain minimum-time and maximum-power thresholds. The optimal dose windows for musculo-skeletal indications, based upon the current scientific evidence, can be found at http://waltza.co.za/. Conclusion: very high powered lasers are useful for treating large areas in short time and to obtain pain inhibition, but seemingly less effective for basic cell stimulation. And they do not penetrate much deeper due to the high output - in fact, the very act of making a high power laser 'safe' for long-duration exposures may make it less capable of penetrating as deeply as a lower-powered laser that can e.g. be applied in contact and with slight pressure to the skin. All types of medical lasers are useful within their own limitations, but the very high powered lasers are still lacking scientific documentation in spite of their increasing popularity with salesmen and their less informed customers.

And - N.B. - high power does not mean that a laser instrument has to be in laser Class IV. Let us assume that the probe has 10 laser diodes, placed at some distance from each other, each having an output of 450 mW, i.e. Class III. This instrument is then a less hazardous (by definition) Class III instrument with an output of 4.5 W (4.500 mW).

2.4.12 Laser or LED

You will find many different configurations of phototherapy instruments in the market, some offering laser output only, some offering only LEDs, and (excluding LEDs that are provided for indication only) other devices combining both lasers and LEDs as active therapeutic components. The two latter types are sometimes deceptively called "laser" with no reference made to other emitter types; this is inaccurate, at best. Often the buyer is unaware of the distinction, thinking they have bought a true laser device. The primary reason for replacing laser sources with LED sources, or to add such, is not that LEDs are better or more efficient, but simply that they are cheaper to buy and to drive electrically. Although LED instruments also can elicit good clinical results, they are not lasers and it is technically and ethically incorrect to call them such; doing so serves only to benefit the manufacturer and/or marketer of the device, not the purchaser.

2.4.13 High or low price

If you are in the process of buying a laser instrument without experience of the market, you are vulnerable to the sweet arguments of the salesmen. One aspect is the price. Is high price indicating high quality and good treatment results? No. Not necessarily the opposite either. We can recommend that you acquire a power metre (separate or built-in). Also find out the service level of the company - what happens when it breaks?

2.5 Penetration of light into tissue

When light hits matter, three things may happen. It may be reflected. It may be transmitted. It may be absorbed. Or all three at the same time. This is general and not only valid for light, it is true for all types of electromagnetic radiation. (See also chapter 1).

2.5.1 "A story of a young scientist"

At some time or another in every young scientist's formative years, he or she has experimented by shining a flashlight through their fingers or, even more fun, up their own nose, to discover that the flashlight's white light not only penetrates through their appendages but also glows red on the other side, thus leading them to the conclusion that some light, but not all, can pass through tissue. Now our young scientist is older and more learned, and she understands that living tissues are a highly-complex, dynamic turbid medium, the optical properties of which are defined by varying rates of absorption, scattering, transmission and reflection. She also knows that different imaging techniques, such as optical coherence tomography (OCT), laser Doppler flowmetry (LDF) and transmissive laser speckle imaging (TLSI), rely upon an understanding of these complex optical properties. Penetration of living tissue depends on parametres like wavelength, intensity, polarisation and coherence of the light source, tissue compression and those of the tissues themselves, like pigmentation, fibrotic structure, hydration and composition, in addition to more obvious factors such as hair and clothes. (Thanks, Peter Jenkins for this elegant formulation!) For many indications in laser phototherapy, a good penetration through tissue is an advantage.

Now, our young scientist already noticed that red light goes well through the tissue. But what happens then with the rest of the light - the blue, green and yellow parts? It is absorbed by the tissue and is converted into heat energy. You can test this yourself: compare a red and green laser pointer of the same power, i.e. of 5 mW (legal in most countries) - the red light goes through your finger, the green does not. For infrared light we need an IR-to visible converter that is enough sensitive for the wavelength used. One thing to know is that laser light does not penetrate better or deeper than ordinary (not coherent) light of the same wavelength.

2.5.2 The wavelength

Some wavelengths penetrate very poorly; one example is the light from CO_2-lasers. That's why these lasers are very useful as surgical lasers for cutting and evaporating. Also the Er:YAG lasers light is highly absorbed in both water and hard tissue.

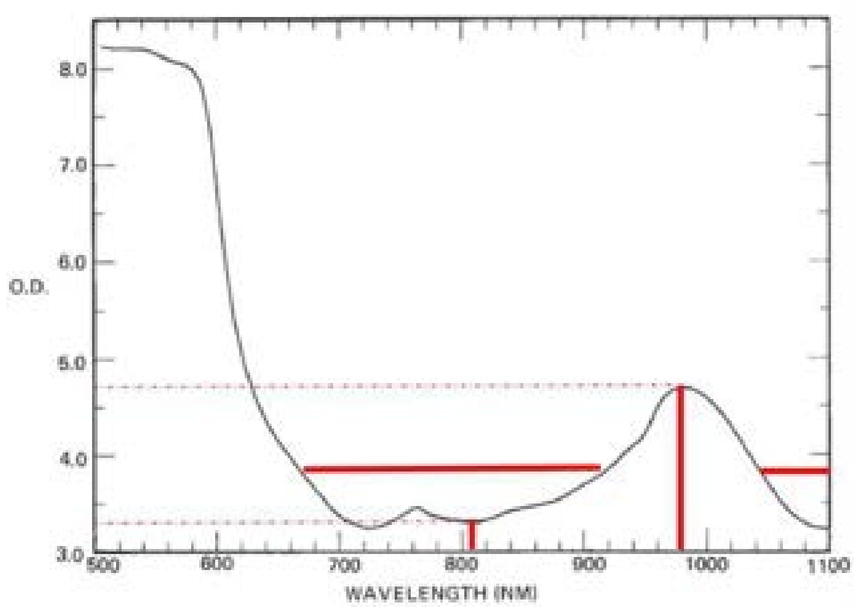


Figure 2.3 The absorption spectrum of a human hand. This spectrum was recorded with a very sensitive spectrophotometre with the hand in close juxtaposition with the photocathode (unpublished data of Karl H. Norris, from The Science of Photobiology, KC Smith, ed., Plenum Press, 1977; p. 400).

As can be seen, the best transmission through a hand is approximately between 670 nm and 910 nm and then from about 1050 nm and up. Original website: *http://www.photobiology.info/PhotobioInArt.html*

Here we can estimate that the O.D. (Optical Density) for 980 nm is about 4.7 while for 810 nm it is about 3.3. Transmission (T) and Optical Density (OD) are two common ways to express the throughput of a filter or another object like tissue. Transmission can be expressed as T = l0 - OD. This mean that the transmission is 25 times higher for the 810 nm light than it is for the 980 nm light (T3.3 = 0.0005 and T4.7 = 0.00002 respectively).

Another interesting diagramme is the one below, Figure 2.4:

Here we can see the spectral transmission of different tissue. This coincides fairly well with the shown spectral transmission of a hand. In both cases we are using continuous (or switched) light.

As can be seen from this diagramme, skin is the least sensitive to the wavelength while muscle, connective tissue and vertebral column is much more wavelength dependant. Conventional pulsing does not influence penetration.

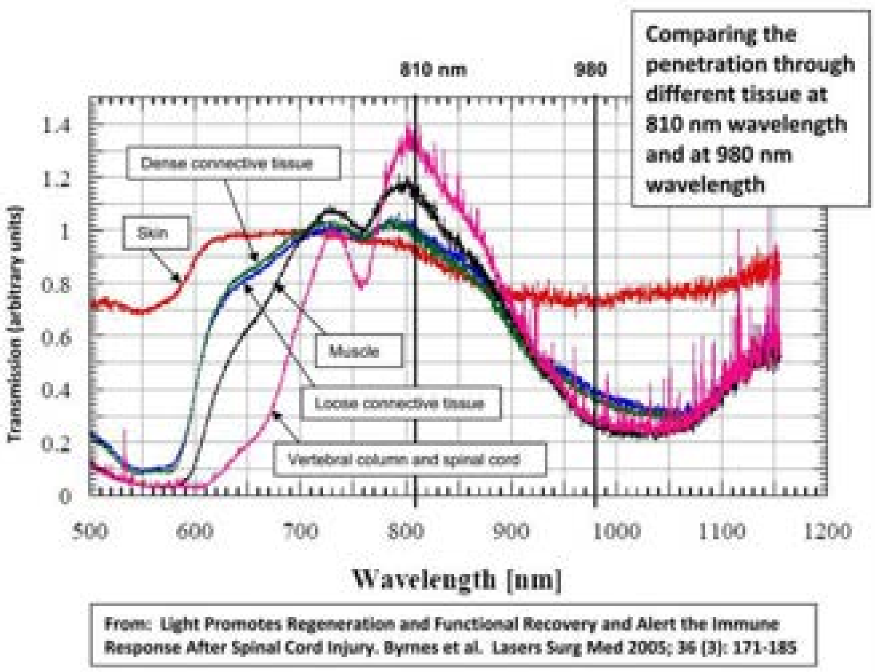


Figure 2.4 Variations of laser penetration

The first barrier for the light is usually the skin. Transmission through skin has been investigated in several studies. Bjordal [588] has summarised skin transmission with different lasers.

Energy loss due to the skin barrier:
for continuous HeNe (632 nm) laser is 90%,
for continuous GaAlAs (820 nm) 80%
for pulsed Nd:YAG (1064 nm) IR lasers, 80%.
for super pulsed GaAs (904 nm) infrared laser, 50%.

The most surprising part of this is that the GaAs differs so much from the other. What is so special with that wavelength - 904 nm? Nothing! It is not the wavelength, it is the extreme pulsing (super pulsing). Today it is possible to find GaAlAs-lasers with the 904 nm wavelength and then the energy loss due to the skin barrier is about 80%. Bjordal further states:

"In vivo trials with 904 nm pulse lasers, have demonstrated that these lasers achieve similar effects on collagen production with far lower doses on the animal´s skin than lasers with continuous output (Enwemeka 1991a; van der Veen and Lievens 2000)." This effect can be attributed to the photobleaching phenomenon, where the first strong pulse bleaches the opaque barrier of tissue, letting the second pulse pass through the tissue barrier with less loss of energy [2452].

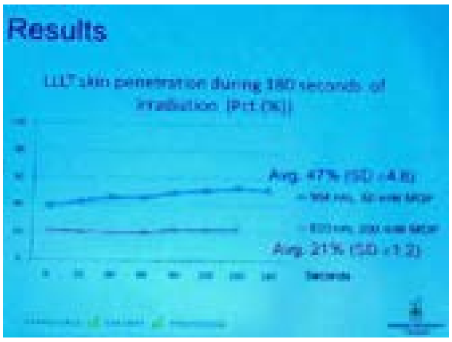
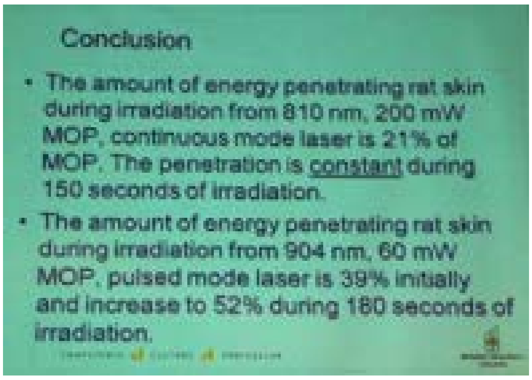


Figure 2.5 Time aspect of the penetration of 808 nm and 904 nm

This has further been studied by Joensen (2155). Surprisingly, the penetration of the super pulsed laser light is markedly increasing by the time, while the 810 nm laser light transmission remained constant. The very high power peaks of the GaAs laser "bleaches" the collagen and thus gradually creates a more transparent tissue. This gradually increasing transmission supports the theory of bleaching.

Other factors



Strong light penetrates deeper than weak. However, twice the power does not mean twice as deep, but maybe 5-10% deeper. Let us say that a 100 mW laser, at 10 mm depth has certain intensity. If we drive the same laser harder so that it emits 200 mW, the mentioned certain intensity will be found on 10.5 - 11 mm depth and if we increase the power to 400 mW, the depth will increase to between 11 and 12 mm. Another factor influencing the penetration is tissue compression - a probe that is mechanically pressed against the skin will force the blood in front to move away from the penetrating beam. Pigmentation can absorb a great deal of the incoming light.

2.6 How deep does light penetrate into tissue?

The question is not so simple. There is not an exact limit. It's not like hitting a nail into a board - it ends here! From the point of impact on the skin surface, the light penetrates the skin and is then spread diffusely into the tissue. In the picture below we can see a piece of tissue being hit by a narrow parallel beam and then being spread diffusely and filling a volume.

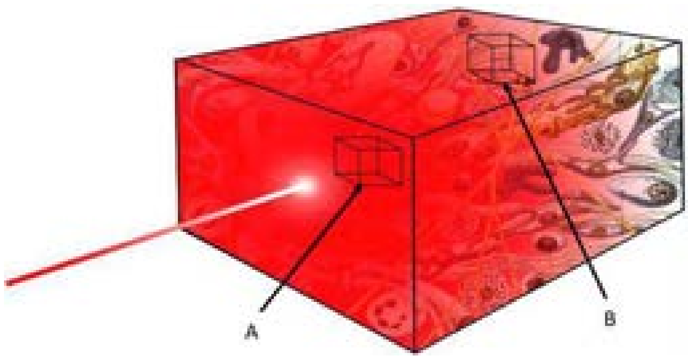


Figure 2.6 Light spread diffusely

As can be seen, inside the tissue, the light get weaker and weaker, the further in it reaches. We can also see two small cubes, A and B. Let us assume that they have the size 1×1×1 millimetre. In the box A we have more light energy than in the deeper lying box B of the same size. It means that the cells in respective box get different influence by the light, i.e. get different dose.

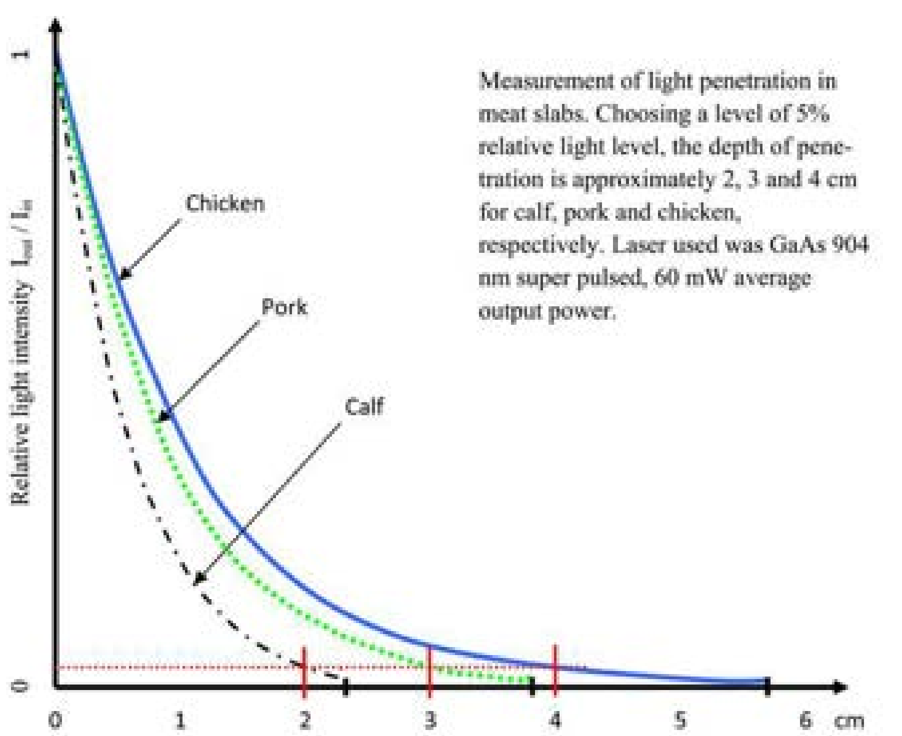
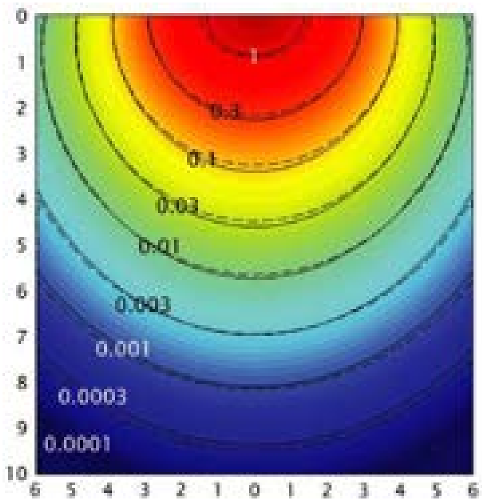


Figure 2.7 Light penetration thruogh different types of tissue

These curves are only valid for the wavelength used in this setup and for the more or less bloodless meat. For living muscle tissue, the blood content will influence, especially for wavelengths below 600 nm. In general, the light intensity as a function of distance z is given by

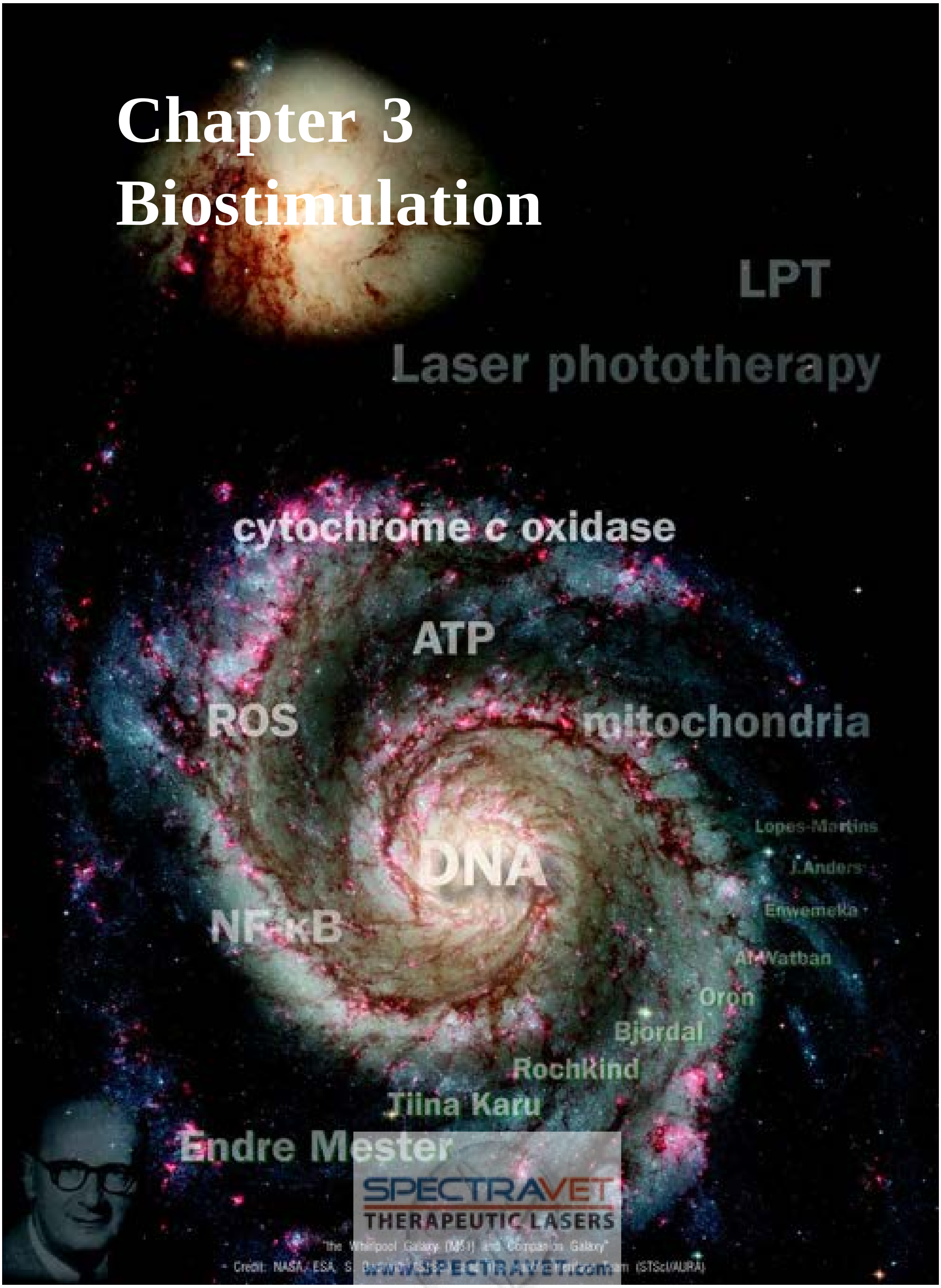
$$I(z) = I_0 \, e^{-\alpha z}$$



where alpha is the absorption coefficient which is a property of the tissue material. One consequence of this is that in different tissue the penetration varies (see figure above for penetration in chicken, pork and calf meat respectively). This then means, expressed in words that the light intensity in tissue decreases exponentially and hence never reaches zero level.

Bottom line
The most important factors influencing light penetration in tissue are wavelength, super pulsing, integral power (over the illuminated surface), intensity, tissue contact and compression. Other factors influencing penetration is of course pigmentation, fur and tattoo ink in skin. Blood vessels absorbs differently than adipose tissue, collagen, bone tissue and mucosa.

Chapter 3
Biostimulation



3.1 History

Initially, researchers' interest was focused on the use of lasers in surgery. Thus, rather high doses were used in early experiments.

Torsdagen den 31 oktober 1963

Forskarrön i USA:

Ljusstråle visar effekt på cancer

BOSTON. (AP) Laserstrålen, en koncentrerad ljusstråle med hög energi, har med gott resultat använts för att döda framkallade cancersvulster på försöksdjur, rapporterar en amerikansk läkargrupp.

I rapporten sades att experimenten ännu är inne i ett tidigt skede och att man inte har några planer på att använda den nya metoden på människor förrän man helt klarlagt dess effekt.

Drygt 50 proc. av de cancerceller som ympats in på hamstrar förstördes helt av strålen. Kort efter ingreppet syntes ett mindre brännsår, men efter ett par dagar hade svulsten börjat krympa och hade helt försvunnit efter två veckor. Läkarna står ännu frågande för exakt hur behandlingen gått till och varför inte hälften av försöksdjuren kunde botas.

Laserstrålen har ofta omnämnts som en motsvarighet till science fictionsförfattarnas beryktade "dödsstrålar". Med sin starka energi skär den med lätthet igenom metaller och andra fasta föremål.

Nordisk konferens för blindkonsulenter

De lokala blindkonsulenterna bör själva vara synskadade. Det ger dem en genväg i kontakten med de nyblinda. Detta fastslog deltagarna i den första nordiska konferensen för blindkonsulenter, som under tre dagar är samlade på Almåsa söder om Stockholm. Fem norska, två danska och två finska blindkonsulenter deltar tillsammans med

Figure 3.1 The Swedish daily Svenska Dagbladet, October 31st, 1963

Boston (AP). An American group of physicians report that laser light, a concentrated beam of light of high energy, has successfully been used to kill cancer tumours induced in laboratory animals. In the report it is stated that the experiment still is in an initial stage and that there are no plans to use it in humans until the effect is fully documented. Some 50% of the cancerous cells that had been implanted in hamsters were completely destroyed by the laser. Shortly after therapy, a minor burn was visible but within a few days the tumour had started to shrink and was completely gone in two weeks. The researchers still do not understand exactly how the therapy worked and why the other half of the experimental animals could not be cured. The laser beam has often been referred to as an equivalent of the feared "death beam" of science fiction. With its strong energy it easily cuts metals and other solid objects.

STUDIES OF THE SURGICAL APPLICATIONS OF LASER (LIGHT AMPLIFICATION BY STIMULATED EMISSION OF RADIATION)

Paul E. McGuff, David Bushnell, Harry S. Soroff, Ralph A. Deterling

Surgical Forum, **14**:143-145, **1963**

Method
Ruby Lasers varying from 0.5 to 360 joule energy. Pulse length 0.5 to 3 msec.

The effects of either single or multiple exposure upon the following tissues were studied: Post mortem canine tissues, specimens of human tumors and living induced and human malignant tumors transplanted to the cheek pouch or flank of the hamster.

Solid hepatic **metastatic nodules**, adjacent normal liver, and **primary lung** and **gastric tumors** were exposed to equal doses of Laser. The local destruction of the metastatic tumor tissue was significantly greater than that observed in the adjacent normal tissue exposed to the same dose.

A **Pitt-41 malignant tumor** of human origin was treated with 2 doses of 130 joules each. After 14 days microscopic and gross examination revealed that the tumor was eradicated.

Transplanted fibrosarcomas did not respond as well, but did show gross pathologic and microscopic destruction from 60 to 80% of the malignant tumor.

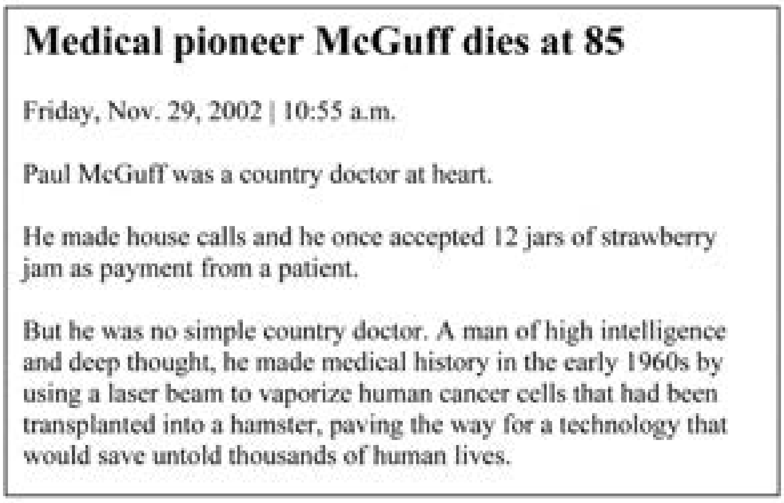
The effect of Laser on **malignant melanomas** in the cheek pouch of hamsters was also evaluated. Approximately 50% of these treated tumors were destroyed. The control tumors had remained unchanged. The treated tumors of these animals were free of gross and microscopic evidence of tumor cells by the thirty-ninth day after exposure to Laser.

Discussion
It would appear from the experimental data that Laser has a selective effect upon tumors since the treated tumors were destroyed while the adjacent normal tissue was relatively unaffected. The effect of the Laser appears to be both immediate and delayed. This is indicated by the observations that the destruction of the tumor is **progressive over a period of several weeks**

Above: Excerpts from McGuff's original article from 1963.

In this article it is no doubt a biostimulation effect that is described. This is, according to our knowledge, the first time this effect was described, though the researchers were not aware of it.

From having seen the article in the Swedish paper, we tried to locate the research team for many years. We had no names to search for and 1963 was long before Internet. In our sixth book, Laser Therapy - Clinical Practice and Scientific Background, printed in 2002, we sent out a call: "If any of our readers can find out which group in Boston did this experiment we would be glad to know". When we finally (2003) found out that it was the team of Paul MacGuff, he had passed way.



Medical pioneer McGuff dies at 85

Friday, Nov. 29, 2002 | 10:55 a.m.

Paul McGuff was a country doctor at heart.

He made house calls and he once accepted 12 jars of strawberry jam as payment from a patient.

But he was no simple country doctor. A man of high intelligence and deep thought, he made medical history in the early 1960s by using a laser beam to vaporize human cancer cells that had been transplanted into a hamster, paving the way for a technology that would save untold thousands of human lives.

After that we found more articles from the same groups [1853-1859]

Initially, researchers' interest was focused on the use of lasers in surgery. Thus, the doses and pulse energies used in these early experiments were rather high. This is, according to our knowledge, the first time this effect was reported, though it was not understood. The report refers to studies by McGuff [1853-1859] in which ruby and HeNe laser had been used in hamsters with experimental tumors.

In 1965 Laor [589] used 700-900 J with high power densities, causing high mortality among the laboratory rats. However, doses below 20 J rarely resulted in any microscopic changes. In the same year, Derr [28] published a report on the occurrence of free radicals in irradiated biological materials. In 1967, Carney [520], using a ruby laser, demonstrated an increase in collagen synthesis in skin wounds treated with power densities of 0.4 - 2.5 J/cm^2.

In 1966, (Orvosi Heitlap 1966, 107:1012, in Hungarian, abstract in English) Mester's group at the Semmelweiss hospital in Budapest published the first scientific report of the stimulatory effects of non-thermal ruby laser light (694 nm) on the skin of rats. (See figures on next page.) These pictures were published in [733, 734]. The following year, articles were published on the effects of lasers on wounds (see figure on next page) and leukocytes in culture [10]. Mester demonstrated that cells in culture and in tissue can be stimulated by a certain dose (input energy, measured in joules per cm^2 of skin) of laser light. Too low a dose has no or an insufficient effect. Too high a dose is also less effective, or has no effect at all, while a dose that is much too large can lead to inhibiting effects. A ruby laser was used. Along with Endre Mester, Viktor Injushin in Kazakhstan was researching early about the possible biological effects of low laser energies.

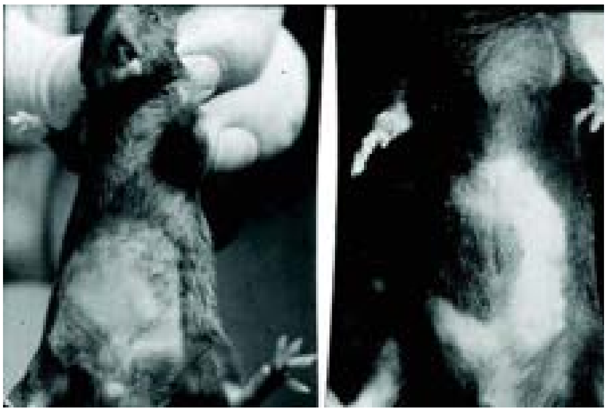


Figure 3.2 "The historic mice" I. Courtesy: Andrew Mester

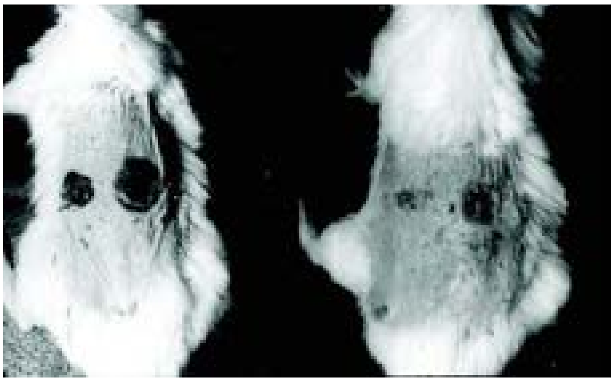


Figure 3.3 "The historic mice" II. Courtesy: Andrew Mester

The following year, articles were published on the effects of lasers on wounds (see figure on next page) and leukocytes in culture [10]. Mester demonstrated that cells in culture and in tissue can be stimulated by a certain dose (input energy, measured in joules per J/cm^2 of skin) of laser light. Too low a dose has no or an insufficient effect. Too high a dose is also less effective, or has no effect at all, while a dose that is much too large can lead to inhibiting effects. A ruby laser was used.

Endre Mesters group was the first that systematically investigated this new phenomenon. They published a lot of (for the time) well done studies both in vitro and in vivo. Most of the doses and other parametres that they suggested are still valid. They are definitely the true pioneers in this field.

Figure 3.4 Endre Mester in the 70-ies

3.2 A few words on mechanisms

Biostimulation is an important part of lasermedicine. Here is an overview of the laser medical field.

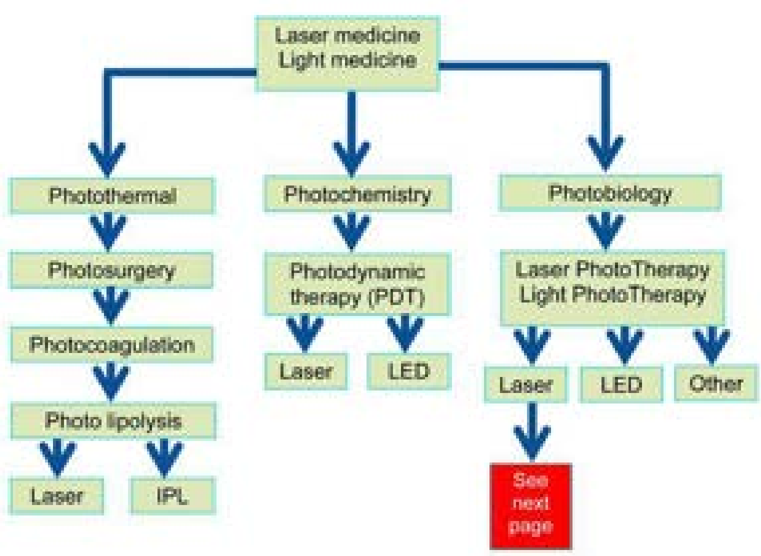


Figure 3.5 Branches of laser medicine

In the figure above, we can see the three branches of laser medicine; photo thermal principle, photochemical methods and photobiologic effects (phototherapeutic methods). Sometimes these effects can be unseparable. For instance, when a beam from a thermal laser hits tissue and penetrates, we will get biostimulation whether we want it or not.

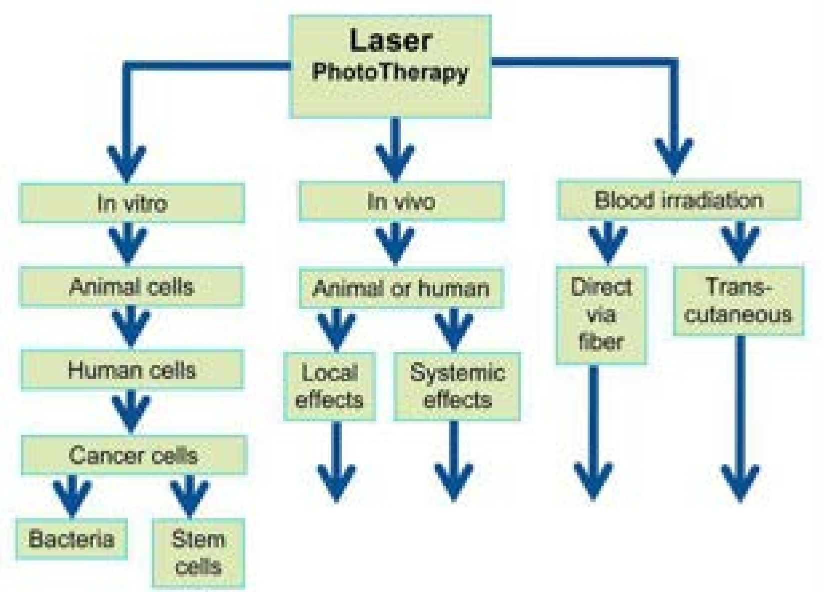


Figure 3.6 Photo Therapy pathways

In this chapter we will only give a brief overview of the mechanisms behind successful laser therapy. A much more detailed description is given in chapter 11.

Treatment with laser therapy is not based on heat development but on photochemical and photobiological effects in cells and tissue. What happens when this relatively weak laser light encounters our cells?

Firstly, quite a lot happens locally, where the light hits (primary response). As mentioned above, it has been observed that if laser light is administered in the right dose, certain cell functions are stimulated, and this is particularly evident if the cell in question has an impaired function. (See chapter 3.5.7 “The importance of the tissue and cell condition” on page 145.)

As will be discussed in chapter 11, it is known that chromophores, in the form of e.g. porphyrins, play an important role. It is known that small amounts of singlet oxygen build up when tissue is irradiated with laser light [28]. Rochkind's and Lubart's group in Israel has demonstrated this [29] using the NMR technique (Nuclear Magnetic Resonance). Singlet oxygen is a "free radical" which itself influences the formation of ATP (adenosine triphosphate) [30, 140, 2019, 2020], which constitutes the cells' fuel and energy store.

Another recently suggested photoreceptor is NADPH oxidase [1336], which has been found to exist in non-blood cells. It possesses a flavoprotein which can be the target of light. Several chromophores are photosensitisers and generate reactive oxygen species (ROS) following irradiation. ROS, such as singlet oxygen, NO and H_2O_2 are cell destructive in large amounts but in small amounts they serve as "secondary messengers" in the cascade of events following laser irradiation. The influence of ROS has been demonstrated by irradiating fibroblasts and establishing the stimulative ratio of the laser light. The antioxidant catalase was then added to the Petri dish and new irradiation was performed. The previous stimulation did not appear. Catalase is a ROS scavenger and the inhibition of the ROS obviously blocked the stimulation.

It is also known that nitric oxide can play an important role [432, 469]. Additionally, it has been observed that the calcium ion balance [31] in the cell is affected. The influence of laser light on the oxidative processes has been demonstrated by Karu [180] and others. Karu [512] suggests cytochrome a/a3, a respiratory chain component, as an important photoreceptor. Lilveria [1848] has, for instance showed that laser therapy significantly increased the activities of complexes II and IV (cytochrome c oxidase) but did not affect succinate dehydrogenase activity.

This leads in turn to a number of secondary effects (secondary responses) which have been studied and measured in various contexts: increased cell metabolism and collagen synthesis in fibroblasts [8], increased action potential of nerve cells [32], stimulation of the formation of DNA and RNA in the cell nucleus [33], local effects on the immune system [34], increased new formation of capillaries by the release of growth factors [35], increased activity of leukocytes [36], transformation of fibroblasts to myofibroblasts [37], and a great number of other measured effects.

Secondly, there is a systemic effect, well illustrated through the use of CO_2-lasers as biostimulators. The wavelength of CO_2-lasers cannot penetrate the tissue for more than a fraction of a millimetre, so there is no other primary responding tissue than the outer part of the dermis. The stimulative effects found when using CO_2 are in many cases quite similar to those observed in treatment with the classic wavelengths. We can thus draw the following conclusions:

1. CO_2-lasers work through a secondary response; and
2. Deep light penetration is not a necessity per se in biostimulation, at least not for some of the biostimulative effects.

The possible reason for this is that cells in the tissue subjected to the light produce substances that then spread and circulate in blood vessels and the lymphatic system.

Literature:

In case of biostimulation with deeper penetrating laser wavelengths, the systemic effects are often due to treatment of blood cells, which in turn influence other cells, tissue and mechanisms in the system. This is illustrated by Zhuk [1141] who treated patients with chronic tuberculosis by treating the blood in a vein. The patients were divided into two groups, both getting conventional medical treatment but only one group getting laser treatment as well. The laser group showed significantly shorter recovery times. (See chapter 4.1.58 "Tuberculosis" on page 437.)

Yet another illustration of the systemic effect is a report by Braverman [50]. In a study using experimental wounds, laboratory animals were treated with a HeNe or GaAs laser, or both in combination. The tensile strength of the newly healed wounds was greater in all the laser therapy groups than in the control group. There was also a group of animals on which two wounds were inflicted, only one of which was treated with laser. Even the untreated wound showed better results than in the control group. The authors of the report drew the following conclusion: "The laser irradiation can thus have released substances in the circulatory apparatus so that the tensile strength increased even in the wound on the opposite, untreated side."

The same observation has been made by Rochkind [39]. HeNe laser treatment on only the right-hand side of bilaterally inflicted skin wounds increased the healing process on both sides as compared to the control group. This also applied in the case of bilateral burn wounds.

In a crossover study, Airaksinen [302] treated patients with chronic neck and shoulder pain unilaterally with HeNe. The pressure pain threshold increased significantly on both the non-treated and the treated side, although the increase was larger on the treated side.

Inoue [405] has demonstrated that GaAlAs 780 nm laser irradiation suppressed the tuberculin reaction in sensitised guinea pigs. The suppression was seen not only on the irradiated side but also on the contralateral, non-irradiated side.

Schindl [350] induced the arthus phenomenon (an anaphylactic effect) in the corneas of 57 rabbits. The healing effect of a HeNe laser as compared to control was obvious. Consensual co-reaction could be observed in the contralateral non-irradiated eyes in the experimental group.

The above studies may explain why studies involving contralateral untreated control lesions on the same animal/patient have not always produced good or clear results. The non-irradiated "control" lesion in fact benefits from the treated lesion because of the systemic reaction just discussed.

This theory is supported by a study by Halevy [467]. Using a 780 nm 30 mW laser, 6 patients with cutaneous fissures located in the hands and feet were treated every 2-3 days. There were similar fissures on both sides of the body. On the irradiated side, 4 of the 6 fissures healed completely and in the remaining 2 there was a decrease of 40%. On the non-irradiated side, 3 healed completely and 1 healed partially.

Friedmann [513] draws the following conclusion: "Due to transmission of neural excitation and calcium waves, photobiomodulation is a systemic effect."

Villaplana [424] irradiated the anterior pituitary gland with HeNe laser through the surgically exposed lamina dura in two groups of rats (n = 30 per group). The calculated incident power at the gland was 2.75 mW. Population I Leydig cells of the central part of the rat testicles showed signs of increased but non-specific activity in the entire series of experimental animals as compared to sham-irradiated controls. Thus, laser therapy may have a systemic effect on testosterone production under these experimental conditions.

Hall [673] failed to find any systemic effect in a wound healing study in rats using GaAs. However, the parametres used did not enhance wound healing in the irradiated wound, so obviously there could be no systemic effectn the first place.

Systemic effects, however, are not always found, even when there is an effect on the irradiated side. In a wound healing study on diabetic rats by Reddy [657] the following conclusions were reached: 1) the GaAs laser therapy had no apparent systemic effect on the wound on the opposite side of the treatment side; and 2) laser photostimulation decreased the healing time for full thickness skin wounds in diabetic animals, but had no effect on the biomechanical properties of the tissue once the wound was healed.

Further literature: [1456]

3.2.1 Photoreceptors

In order for the laser light to be absorbed, there must be receptors. Such receptors are well known in plants, but are there human light receptors other than those in the eyes and in the skin? The following is quoted from Enwemeka [1160]:

“We may have to step back in time in order to begin to understand the mechanisms involved. That low energy light particles can produce significant, and at times, life-supporting changes in various organisms, is not at all new. Our primordial ancestor, the purple bacteria, provides a vivid example. Found in abstemious habitats below that of plant life – e.g. the bottom of ponds and topsoil, depending on the species – the purple bacteria inevitably lives on a meagre amount of light. Only the reminder of light unharvested by plants penetrates to those depths. But with the carotenoids in its light-harvesting complexes absorbing light at 500 nm wavelength, and its bacteriochlorophyll absorbing at 800-850 nm, this life form is able to carry out complex life-supporting metabolic processes with relatively minimal light energy.

To date, more than three hundred photochemically reactive proteins, capable of harvesting low light energy, have been identified in both prokaryotic and eukaryotic organisms. Many more are being discovered yearly. In humans, the most commonly known photochemically active receptor proteins are rod and cone pigments in the eye. However, other human photoreceptors have been discovered in recent times. Examples are encephalopsins in the brain and pinopsin in the pineal gland. Given the discovery of photoreceptor proteins in the pineal gland, the hypothalamus, and other tissues of lower vertebrates, it is only a matter of time that it will become clear that other human tissues have photoreactive proteins as well". (See chapter 11.1.9 "Bright Light Phototherapy" on page 711.)

Literature:

Adenosine triphosphate (ATP) is an important molecule in biology because it stores chemical energy and releases it to the biochemical processes occurring in the cell. In the study by Amat [1533] the authors analysed the biochemical behaviour of ATP after irradiating it with 635 and 830 nm diode lasers. They analysed the luminescence peak, the reaction rate and the area under the luminescence curve at 2×10^{-9} mol/l of ATP in the luciferine-luciferase luminescence reaction before and after irradiating the molecule at several irradiances and radiant exposures. The absorption spectrum of ATP at 3×10^{-3} mol/l concentration was measured between 650 and 900 nm after laser irradiation at 635 nm (Argon-Dye) and 830 nm (diode laser). It was found significant differences in the measured parametres when ATP was irradiated with both wavelengths. The absorption spectra of non-irradiated and irradiated ATP showed a physical-chemical difference in the ATP molecule after irradiation with both lasers. It can concluded that visible and near-IR laser light with the parametres that were used in this study changed the biochemical behaviour of ATP molecules.

Previous studies using 670 nm light-emitting diode (LED) arrays suggest that cytochrome c oxidase, a photoacceptor in the NIR range, plays an important role in therapeutic photobiomodulation. If this is true, then an irreversible inhibitor of cytochrome c oxidase, potassium cyanide (KCN), should compete with LED and reduce its beneficial effects. This hypothesis was tested on primary cultured neurons in a study by Wong-Riley [1499]. LED treatment partially restored enzyme activity blocked by 10-100 micromol KCN. It significantly reduced neuronal cell death induced by 300 micromol KCN from 83.6 to 43.5%. However, at 1-100 mm KCN, the protective effects of LED decreased, and neuronal deaths increased. LED significantly restored neuronal ATP content only at 10 micromol KCN but not at higher concentrations of KCN tested. Pretreatment with LED enhanced efficacy of LED during exposure to 10 or 100 micromol KCN but did not restore enzyme activity to control levels. In contrast, LED was able to completely reverse the detrimental effect of tetrodotoxin, which only indirectly down-regulated enzyme levels. Among the wavelengths tested (670, 728, 770, 830, and 880 nm), the most effective ones (830 nm, 670 nm) paralleled the NIR absorption spectrum of oxidised cytochrome c oxidase, whereas the least effective wavelength, 728 nm, did not. The results are consistent the hypothesis that the mechanism of photobiomodulation involves the up-regulation of cytochrome *c oxidase, leading to increased energy metabolism in neurons functionally inactivated by toxins.*

In a search for chromophores responsible for photobiostimulation, endogenous porphyrins, mitochondrial and membranal cytochromes, and flavoproteins were found to be suitable candidates This is described in the review article by Lubart [1506]. The above-mentioned chromophores are photosensitisers that generate reactive oxygen species (ROS) following irradiation. As the cellular redox state has a key role in maintaining the viability of the cell, changes in ROS may play a significant role in cell activation. In the present review, we summarise evidence demonstrating that various ROS and antioxidants are produced following laser illumination. It was found that very little evidence for NO formation in illuminated non-vascular smooth muscle cells exists in the literature. The author suggests that the change in the cellular redox state, which plays a pivotal role in maintaining cellular activities, leads to photobiostimulative processes.

Further literature: [1451], [1452, 1525, 1526]

3.3 What parametres to use

For laser therapy systems, we know that the following parametres (among others) significantly affect treatment results: choice of laser wavelength, size of dose, level of power density, the laser's method of working, pulse repetition rate, depth of penetration, treatment methodology, treatment frequency and total number of treatments.

3.3.1 Laser parametres

There are basically two types of parametres – laser parametres and patient parametres. The laser parametres will sometimes have to be changed from patient to patient depending on the patient parametres.

3.3.1.1 Which wavelength?

It is important to use the right wavelength (i.e. laser type) for the right indications. Although it has not yet been possible to determine the "best" wavelength for each indication, the authors believe that the HeNe or InGaAlP laser (633-670 nm) is the best option for ulcers and nerve regeneration. Due to the poor penetration of light of this wavelength (up to one cm), other wavelengths must sometimes be used, although they may not be optimal.

In addition, we consider that the GaAs laser is a better choice for the treatment of deeper problems such as sports injuries and that it has a greater effect on postoperative pain and swelling than the shorter wavelength lasers. Further about this laser in chapter 11.1.8 “How deep does light penetrate into tissue?” on page 709.

GaAlAs lasers are usually the best choise for tendinitis but it can also be a good alternative for treating pain and oedema, and we have positive experience of treating chronic ulcers with this laser type. The high power density of modern GaAlAs lasers has also proved to be advantageous in physiotherapy.

It must be stressed that any wavelength, with a reasonable dose in the target area, will have a biological effect. If “the best” wavelength is not at hand, it is of course recommended to use other wavelengths. Probably, the correct dose may be just as important as the wavelength. However, that dose is sometimes not known or obtainable, e.g. due to the lack of penetration.

Karu [180] found, by measuring chemiluminescence, that the oxidative processes of blood cells were influenced by various laser wavelengths during the initial phase of acute viral respiratory illness. Of the four different wavelengths tested (660, 820, 880 and 950 nm), 660 nm was found to be the most effective. The dose range in this *in vitro* study was 0.1 - 1 J/cm^2.

Some studies have shown improved results when two wavelengths were combined. However, it could be asked whether the clinical results of these studies are sometimes just as much dependent on the combined doses as on the two different wavelengths.

3.3.1.2 Output power

Of course you should know what laser type you have as well as its wavelength. But it is just as important to know the output power of your instrument in order to calculate the right dose to administer. A significant advantage of a higher output power is that it takes less time to reach a given dose. This has a financial significance for the patient but is not a decisive factor in achieving good results. Dosage is the primary factor. Output power is, however, of great consequence in that a higher output power gives a higher power density, which very often is beneficial. Output power is also of some importance with respect to light penetration in tissue.

3.3.1.3 Average output power

When a laser works in pulsed mode, it is the laser's average output power that is significant in terms of dose calculation. If you do not know the average output power of your pulsed laser, you cannot calculate the dose to administer.

3.3.1.4 Power density

Power density is the same as the “intensity” of the light and is measured in watts or milliwatts per cm^2. Spreading the light over a large area gives a low intensity. As biostimulation is based on local effects, with the transport of various substances through cell membrane and tissue, power density should not be too low, even if the number of joules is high. Low power cannot entirely be compensated by increased time. Since the dose can easily become too high locally when the laser is held directly against the skin/mucous membrane, one must ensure that the treatment time is not too long when using point treatment. The power density (I) can be calculated as

$$I = \frac{P}{A} \quad [\ W/cm^2\ ]$$

(See chapter 10.3 “Power density” on page 678.)

Literature:

van Breugel [228] studied the effects of HeNe laser light on human fibroblast cultures. Irradiation was administered on three consecutive days at various power densities with exposure times of between 30 seconds and 10 minutes. The laser output power varied between 0.55 and 5.98 mW. It was apparent that the most significant effects were obtained by laser output power below 2.91 mW, while 5.98 mW had no effect. The stimulative effects were strongest during irradiation periods between 30 seconds and 2 minutes. The study demonstrates that power density and exposure time are important parametres. Another conclusion is that power density is important in itself. Treating an area with 40 mW for 10 seconds is usually more beneficial than using 10 mW and 40 seconds, although the dose would be the same.

Trelles [458] found that the effects of HeNe laser light on mast cells were accomplished faster at 50 mW than at 4 mW, although all cell lines were irradiated with 2.4 J.

Further literature: [291]

3.3.1.5 Energy density

Energy density is the same as dose or fluence. The difference between power density and energy density is simply the time. As mentioned above, the power density is measured in watts per cm². The energy density is measured in watt-seconds per cm², which is the same as joules per cm². For calculation of energy density, see chapter 3.4.2 “Calculation of doses” on page 100.

Looking at a specific situation with laser light penetrating into tissue, we will have points and areas with high power density and other areas with low power density. If this distribution of light is held constant over a certain period, we will have an <u>energy</u> distribution that, in every point, is exactly proportional to said <u>power</u> distribution. If we keep the same situation going on for ten times as long, we have an energy density (i.e. dose) that is ten times higher in every point reached by the light. (See chapter 10.3 “Power density” on page 678 and chapter 10.7 “Energy density” on page 683.)

Just like the power density, the energy density is not constant - it has a two-dimensional distribution over a surface (this is also true of the area that is hit by the laser light when a treatment probe is held in skin contact) and has a three-dimensional distribution in the treated tissue volume.

3.4 The dose

Since the first reports 1968 that laser light in certain doses promotes cell functions, wound healing and pain relief, the method has been argued and debated. A large number of studies show clear effects and some do not.
Why are the results so conflicting?

A. The physical and technical parametres are not well enough described.

This means that it is in practice impossible to repeat a study - every attempt ends up in a new study with new parametres!

B. There is no consensus in the definition of dose within Laser Phototherapy.

In Laser Phototherapy there are many important physical parametres. The most important ones are the wavelength (laser type), dose, intensity (power density), treatment time, type of pulsing (if any), polarisation etc. Medical people often do not realise how important physical parametres are. In most scientific reports, these parametres are not well specified. The most complex of the mentioned parametres is the "dose". Very often we can read: "… and the dose was 3 J/cm^2." However this does not say anything! Dose means simply "quantity". Dose in Laser Phototherapy means a certain quantity of light, such as:

- A number of joules [J] per treatment
- A number of joules [J] per month
- A number of joules per unit area [J/cm^2]
- A number of joules per unit volume [J/cm^3]
- A number of joules per point etc.

In the literature we find that the dose usually is defined as the amount of energy applied to 1 cm^2 of skin or mucosa. But, what is the dose 1 cm down in tissue? Should the unit instead be joules per cm^3, or, would it be better using joules per mm^3. In a blood vessel under an illuminated square centimetre of skin, we might perhaps use joules per ml. The light gives both local effects on cells and tissue and systemic effects - which is the most dominating? The energy that we feed into the tissue will cause a three dimensional light distribution.

Joules per cm^2 may be suitable if we are illuminating cells in vitro with a beam of uniform power covering the whole area of the cells treated. It is also useful when illuminating an open area of an ulcer with a beam of uniform power covering the whole area of the ulcer. In most other cases, more information is needed to describe the situation.

Sometimes the dose is described as joules per point, but then we need to know what we mean with "point".

If you are a practitioner with not very much interest in the scientific side of this and if you already have a laser, you can jump to the next chapter. For practical treatment values, you can use the WALT recommendations. For a complete list and latest recommendations see www.waltza.co.za

WALT

Recommended treatment doses for Low Level Laser Therapy

Laser class 3B, 904 nm GaAs Lasers

(Peak pulse output >1 Watt, mean output >5 mW and power density > 5mW/cm2)

Irradiation times should range between 30 and 600 seconds

Diagnoses	Min. area/points	Min. total dose	
Carpal-tunnel	2-3	4	Minimum 2 Joules per point
Lateral epicondylitis	2-3	2	Maximum 100mW/cm2
Biceps humeri cap long	2-3	2	
Supraspinatus	2-3	4	Minimum 2 Joules per point
Infraspinatus	2-3	4	Minimum 2 Joules per point
Trochanter major	2-3	2	
Patellartendon	2-3	2	
Tract. Iliotibialis	2-3	2	Maximum 100mW/cm2
Achilles tendon	2-3	2	Maximum 100mW/cm2
Plantar fasciitis	2-3	4	Minimum 2 Joules per point

Example of WALT recomendations for tendinopathies

To better understand this, and to se how complex the dose is if we go into detail, we have made some examples.

First, we have to decide if we are going to treat a shallow or a deep lying problem. In order to treat a deep lying problem we have to choose if we want to use direct effect (the light is illuminating the cells in the problem volume) or systemic effects only.

In the first case we need to choose a wavelength that is penetrating tissue well enough and also to choose a treatment method that makes the light go deep.

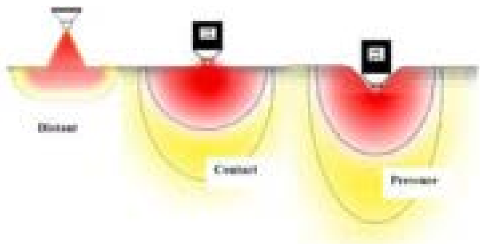
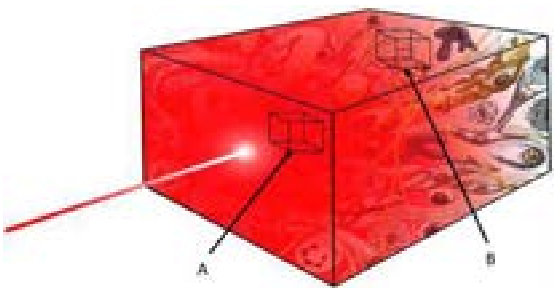


Figure 3.7 Modes of application

In the figure above we can see that the deepest penetration is when we treat in contact and apply a certain mechanical pressure on the tissue (skin) above the volume of problem.

Often the problem to treat is situated at a certain depth into the body, and normally we add the light to the surface of the overlying skin. Then we give a two-dimensionally light distribution on a surface and get a three dimensional distribution inside the tissue under the skin - joules per J/cm^2 is converted to joules per cm3 with a specific value in every point reached by the light. We want to get a certain dose in the volume of the injury - this gives the direct effect of the treatment.

What is the dose in this case? Power of the laser is 100 mW. Treatment time is 10 seconds. Answer: We don't know.



Let us look closer on this answer: The energy given in the treated point is 1 joule! But what is the dose? In the picture: It shows the light distribution in the tissue just under the skin. The intensity of the light is not the same everywhere and the energy density distribution is proportional to the light intensity. Two small volumes (squared) are shown (A and B). Let's assume that they are one cm^3 in volume. If we measure the dose in joules per cm^3 in this tissue, the dose in position A is higher than the dose in position B.

3.4.1 Treatment dose

Treatment dose is the same as the energy density. We will in future mainly use the term dose. The dose is the most important treatment parametre. Dosage refers to the amount of energy per unit area brought to bear on tissue or cell culture. Dosage and treatment intervals can only be specified schematically. This is because the various laser wavelengths mean that different doses must be given, and treatment conditions likewise vary. People are receptive to laser treatment to varying degrees - some can "feel the laser right down to their toes", others are entirely impervious. It is appropriate to begin with a low dose for a new patient to ensure that you do not enter a biosuppressive dose range or trigger a pain response on the first treatment.

3.4.2 Calculation of doses

The dose is the amount of energy administered to a surface area of tissue. In the calculation we will measure area in cm^2. Energy can be measured in joules or calories (old measure). A joule is the same as a Ws (reads watt-second) where W stands for watt and s for second. The dose D is hence measured in joules per square centimetre (J/cm^2) and is calculated as

$$D = \frac{P \times t}{A} \qquad [\ J/cm^2\ ]$$

where P is the laser's output power in watts, t is the treatment duration in seconds, and A is the area treated, given in cm^2. If the laser is pulsed, the average output power in watts should be used instead.

Choosing a variety of output powers and times, we can calculate the corresponding doses and present them in a table. The table below shows doses in J/cm^2, under various treatment durations, reached with lasers of different output power. Using a 20 mW GaAs single-probe laser or a 30 mW GaAlAs single-probe laser, for example, we can calculate, using the formula in the section on dose calculation below, that when treating an area of 1 cm^2 for a certain duration we achieve the dose (in joules) shown in the columns in the table.

Output power from the laser							
Time/ cm^2	**10 mW**	**30 mW**	**60 mW**	**120 mW**	**240 mW**	**500 mW**	**1000 mW**
1 sec	0.01 J	0.03 J	0.06 J	0.12 J	0.24 J	0.5 J	1.0 J
3 sec	0.03 J	0.09 J	0.18 J	0.36 J	0.72 J	1.5 J	3.0 J

Four different laser powers and exposure times per square cm area.
Table 3.1 Dose to skin surface

10 sec	0.1 J	0.3 J	0.6 J	1.2 J	2.4 J	5 J	10 J
30 sec	0.3 J	0.9 J	1.8 J	3.6 J	7.2 J	15 J	30 J
1 min	0.6 J	1.8 J	3.6 J	7.2 J	14 J	30 J	60 J
3 min	1.8 J	5.4 J	11 J	22 J	43 J	90 J	180 J
10 min	6.0 J	18 J	36 J	72 J	144 J	300 J	600 J

Four different laser powers and exposure times per square cm area.
Table 3.1 Dose to skin surface

N.B.! We have said it before; It is of the greatest importance that you know the output power of your laser! If you don't, you have no idea of the doses you give! It is not self-evident that the power of your laser is the same as when you bought it. Furthermore, the power specified in a brochure is frequently quite different from what you actually get out of your probe. The output should be measured from time to time! If you don't have a built-in power metre, you should check your laser with an external one regularly.

We often meet therapists who do not know what type of laser they are using. When asked, it is not unusual for them to respond "3B". Often they do not know what "dose" means, much less how to calculate one. Frequently, they have believed that the output power of the instrument was completely different from what it actually was.

One day we received a call from a clinic in Stockholm. They said there must be something wrong with their instrument; results were not good recently. It turned out to be a GaAs laser. The brochure stated that the average output power of the single probe (with one laser diode) was 20 mW, and the output of the multiprobe was 60 mW (with three laser diodes). Testing resulted in the following table

Pulse rep. rate	Single probe	Multiprobe
10 Hz	0.002 mW	0.02 mW
100 Hz	0.02 mW	0.25 mW
1000 Hz	0.20 mW	2.1 mW
10.000 Hz	1.81 mW	20 mW

Table 3.2 Output power dependent on pulse repetition rate

As can be seen, the output from the single probe was less than 10% of the stated nominal output at the highest pulse repetition rate. Neither the brochure nor the manual mentioned that the output power was dependent on the pulse repetition rate setting.

3.4.3 Dose ranges

Biostimulation has been reported in the literature with doses from as low as 0.001 J/cm^2 to 10 J/cm^2 and more. How is this possible? Can we just use any dose? Certainly not - this is where we have to start thinking! There is a great difference between irradiating naked cells in the laboratory and treating a deep lying pain condition! In fact, a “dose” is a very complicated issue. It is a matter of wavelength, power density, type of tissue, condition of the tissue, chronic or acute problem, pigmentation, treatment technique and so forth. However, there is certainly a “therapeutic dose window”. Doses that are too low result in no or only a weak effect. If a dose above the highest one suitable is administered, weaker or no biological effects will result. With an even greater dose, the bio-suppressive range is entered (inhibiting effect result). This is most obvious in wound healing and stimulation of hair growth. (See Figure 10.6 “Arndt-Schulz law” on page 684.)

So which are the “correct” doses? You want to know - and we seem to be beating around the bush (for good reasons). The answer is: read this book carefully, think, and do the best you can with the laser you happen to have. Doses do not have to be “perfect” to produce a good biological response. Anyway, the table below gives you a rough view of suitable doses.

Indication	Laser type	Dose in J/cm^2
Open wound	HeNe	0.5-1.5
	InGaAlP	1-2
	GaAlAs	0.5-1.5
	GaAs	0.01-0.2
	CO_2	1-10
Wound periphery	HeNe	1-4
	InGaAlP	2-6
	GaAlAs	1-4
	GaAs	0.5-1
	CO_2	-
Superficial pain	HeNe	0.5-2
	InGaAlP	1-4
	GaAlAs	2-4
	GaAs	1-2
	CO_2	5-100
Deep lying pain	HeNe	-
	InGaAlP	-
	GaAlAs	4-10
	GaAs	2-5
	CO_2	5-100

Table 3.3 Dose ranges for different lasers and indications

Doses for other lasers, like the Ruby laser and Nd:YAG lasers are not as well known. Mester's group used Ruby laser and indicated 1-2 J/cm². Doses for acupuncture points: See chapter 3.4.18 "Acupuncture." on page 119.

As can be seen above, it appears that lower doses are required with GaAs laser than with HeNe laser. This has been observed by e.g. Abergel [8]. In general, tissue tolerates higher "overdoses" of HeNe, InGaAlP and GaAlAs than of GaAs, which more quickly reaches an inhibiting level.

In the treatment of healthy, optimally working tissue, almost any dose can be used without noticeably macroscopic negative effects. This is e.g. the case in the use of surgical lasers cutting, evapourating and coagulating tissue, using very high power and energy densities. Right outside the destructive zone, very high levels of power density and dose occur, but this is not found to be negative.

When irradiating "naked cells", in an open wound, for example, the optimal dose is much lower than when irradiating through overlying skin. The dose and the treatment interval differ depending on whether the condition in the tissue is chronic or acute, but also on whether we primarily want to treat pain or achieve a more long-term effect. As stated before, specifying the "right" dose for a particular condition is not easy. Numerous parametres must be taken into account: wavelength and output, contact or non-contact with skin/mucous membrane, type of tissue, acute/chronic, how deep in the tissue you want to reach, the patient's general condition, the skin's pigmentation, etc. "The right dose" may sometimes be whatever the instrument is able to deliver.

Literature:

Abergel [8] investigated the effect of HeNe-laser light and GaAs-laser light on the connective tissue metabolism. In this comparison the author writes: "Similar stimulation of collagen production was also observed with GaAs-laser. With this laser a two- to threefold stimulation in two separate cell lines was achieved with energy densities that were considerably lower than those required for stimulation with HeNe-laser."

Bolton [419] irradiated human fibroblasts with a 50 mW GaAlAs laser. The proliferation of fibroblasts and the succinic dehydrogenase activity increased at doses of 2 J/cm², but both were inhibited at doses of 16 J/cm².

Igarashi [579] irradiated neonatal rats with a 830 nm laser, delivering 0.9 J twice daily from birth to day five at two points located above the hippocampus. The mean body weight of the irradiated animals on day 20 was 22% lower than that of the control animals. The density of synaptic junctions was also reduced in the irradiated animals as of day 20. This may seem alarming, but don't worry! Suppose the weight of a newborn rat is 3 g. A newborn human weights around 3.000 g. Thus, the extrapolated dose would be 900 J. Another factor is the size of the neonathal rats; here we have millimetres when with human babies have centimetres, giving much higher power *densities and local doses for the rat fetus. This study is an example of bio-inhibition.*

The inhibitive effect of high doses of laser energy has also been demonstrated by Gross [779]. The effect of HeNe laser light on the cell cycle and the growth of rat kidney epithelial cells was studied. Daily doses of 11.9 - 142 J/cm² significantly inhibited cell growth, while less than 4.7 J/cm² had no effect.

Other examples of stimulation and inhibitions are [1095, 1101]. (See Table 11.3 "Examples of different dose levels in vitro" on page 714.)

3.4.4 Calculation of treatment time for a desired dose

The most common situation in laser therapy is that we wish to administer a certain dose **D** to a specified area **A** with our laser, having an (average-) output power **P**, and we need to calculate the treatment time **t** for the laser probe at hand. If the problem to treat is situated at a depth **d** (where d = 0 to 4 cm), the following approximate formula can be used to find the treatment time:

$$\mathbf{t} = \frac{D \times A}{P} \times (1 + d) \qquad [\text{ sec }]$$

N.B. For this formula to work, the correct units to be used are: **P** must be given in watts (not milliwatts), **D** must be given in J/cm², **A** must be expressed in cm² and **d** in cm. The treatment time will then come out in seconds. Values 1 - 4 of the parametre **d** are only applicable to the deeper penetrating laser types (GaAs laser and GaAlAs lasers). For CO_2-, HeNe- and GaAlInP-lasers, use value d=0. Usually your laser power is given in milliwatts. If you want to use the formulas in this book, you must use the power expressed in watts. To convert from milliwatts to watts, you simply divide by 1000. E.g. 40 milliwatts (40 mW) becomes 0.040 watts (0.040 W). A simple rule can be: Use 3 decimals and your power will be seen as: 0.040 W for your 40 mW probe and 0.250 W for your 250 mW probe.

3.4.5 "Ready reckoner"

For most people, mathematical formulas have negative associations. For the common therapist it is, however, not necessary to use a calculator for every treatment. We have made the process easy. For the treatment of larger areas, such as back, neck, shoulders, arms, knees, etc., we use "apples". If you cut an apple in two halves, the cut surface has an area of about 50 cm². Supposing that you know what laser type you have and its output power, you simply use the tables on the following pages. Find your laser's output power and then enter the depth of the problem: Is it deep or superficial? The table will show you the treatment time in minutes per "apple" at different depths.

Example 1: To treat an area with the size of an apple and with a problem situated 3 cm underneath said surface, using a **GaAs-laser** probe with an average output power of 50 mW at the chosen treatment pulse repetition rate, you need a minimum of 3 minutes. If the area is larger than an apple – e.g. the size of 4 apples – treat 4 times 3 minutes as a minimum. Maximum treatment time: Choose twice the minimum value. Move the probe evenly over the surface.

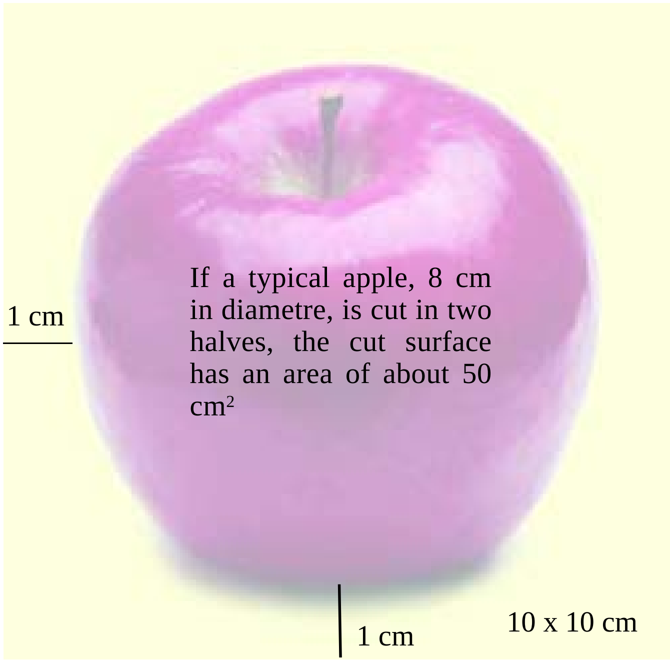


Figure 3.8 Apple ready reckoner

Treatment time for 50 cm² surface area with a GaAs-laser. The output powers are average powers. Treatment should be done with skin contact.

Depth	10 mW	25 mW	50 mW	100 mW	200 mW
0.5 cm	2.5 min	1 min	30 sec	15 sec	10 sec
1 cm	5 min	2 min	1 min	30 sec	15 sec
2 cm	10 min	4 min	2 min	1 min	30 sec

Table 3.4 Treatment time with a GaAs-laser

3 cm	15 min	6 min	3 min	1.5 min	45 sec
4 cm	20 min	8 min	4 min	2 min	1 min

Table 3.4 Treatment time with a GaAs-laser

Treatment time for 50 cm² surface area with a GaAlAs laser. If the laser is pulsed, the average output power should be used. Treatment should be done with skin contact.

Depth	10 mw	25 mw	50 mw	100 mw	250 mw	500 mw
0.5 cm	25 min	10 min	5 min	2 min	1 min	30 sec
1 cm	50 min	20 min	10 min	5 min	2 min	1 min
2 cm	*)	40 min	20 min	10 min	4 min	2 min
3 cm	*)	*)	30 min	15 min	6 min	3 min
4 cm	*)	*)	40 min	20 min	8 min	4 min

Table 3.5 Treatment time with a GaAlAs laser

*) Unrealistic depth and time

As can be seen, table 3.5, shows longer treatment time for corresponding powers and depths, reflecting the higher doses needed for the GaAlAs laser compared to the GaAs laser.

Example 2: Another approach, which many people find easier, is to ascertain the time it takes for the laser to produce 1 joule. If the laser has an output power that is 40 mW, it takes 25 seconds to produce 1 joule (calculate it by dividing 1 by your laser's power output given in watt in this example 1/0.04 = 25 sec). This means that if you radiate the area of 1 cm^2 for 25 seconds, you have given a dose of 1 J/cm^2.

The complexity of dosage is discussed elsewhere in this book. At this early stage we just want to underline the difference between irradiating with a laser of 10 mW for 100 seconds and a laser of 1000 mW for 1 second. Both will produce 1 joule, but the effect on cells is quite different. High power densities are useful for pain conditions, whereas lower power densities are better for wound healing. One difference is that the longer treatments times also mean more absorption by blood and consequent distant effects.

3.4.6 Dose per point

In the treatment of trigger points and acupuncture points the dose is often said to be a number of joules per "point" and it is assumed that a point is something small. We have defined a "point" as an area that is 5 mm in diametre (= 0.2 cm^2) or less. This means that if we hit the skin with the light concentrated to this small area and administer 1 joule, we have given 1 J “per point”, and in this “point” (= 0.2 cm^2) the dose value is 5 J/cm^2. This is also explained in chapter 10.10 “Dose per point” on page 692.

3.4.7 Pulsed or continuous light

As mentioned previously, a laser can work continuously (most typical for InGaAlP, HeNe, and GaAlAs lasers) or pulsed (the GaAs laser).

The GaAs laser (904 or 905 nm) is always superpulsed, with two possible consequences. Firstly, the pulsing of the laser light may interfere with other pulsing phenomena in the organism, and secondly, continuous/switched and superpulsed lasers may have different active depths. A superpulsed laser always penetrates deeper than a continuous or switched laser with the same wavelength and the same average output power. The extremely intense light flashes of the GaAs laser achieve greater light intensity extending deep into the tissue.

3.4.8 Pulse repetition rate (PRR)

Few aspects of laser therapy cause so much confusion as the concept of pulsing. So let us try to make it a bit easier.

1. It is important to understand the difference between “switching” and “super pulsing”. Continuous lasers can be pulsed through mechanical or electronical devices. This means that the continuous beam is shut on and off. The power of the beam remains the same. If the “on-time” and the “off-time are the same, then the so called “duty cycle” is 50%. This means that the average laser power is 50% of the continuous wave power. If the laser is in the on mode during 90% of the cycle time, then the duty cycle is 90%, i.e. close to continuous. With 50% duty cycle the treatment time has to be doubled in order to achieve the same dose as with a continuous beam.

´ In some cases, the “on-time” is very short, which means that the duty cycle is very low. This is often called super pulsing. Characteristic for super pulsing is that the power in the peaks - peak power - is very high compared to the average power. Some semiconductor lasers, like the GaAs laser, can only be powered with very, very short but strong current pulses. The reason for this is that the GaAs chrystal needs a very high current density to lase. Typically a current of 25 - 100 ampere is fed through a 1 cubic millimetre chrystal and such current pulses have to be very, very short (no more than 200 ns) not to burn the chrystal. After such a current pulse, it needs a long time (typically more than 100 micro seconds) to cool down before the next pulse heats it again. This means that the duty cycle for a GaAs laser typically is in the order of 0.1% or less, which in turn means that the peak power usually is about 1000 times higher than the average power. For a GaAs laser with 10 mW average power and 0.1% duty cycle, the peak power is 10 watt. The biological response to this type of pulsing is very likely different to a switched beam. Some manufacturers like to list the peak power only, to make the equipment look more powerful and impressing.

2. Even with a GaAs laser you still have to watch out when it comes to deciding a pulse repetition rate ("frequency"). Some GaAs laser will shift power along with the pulsing. If, for instance, the maximum average power is 10 mW and the highest pulse repetition rate is 10.000 Hz, then follows that using 1000 Hz reduces the power to 1 mW. And if 100 Hz is used, then the power drops further to 0.1 mW. Modern GaAs lasers can handle this problem and give the same average power over all pulse frequencies. But still, you have to select one particular pulse repetition rate and rely on anecdotal evidence.

3. Many *in vitro* studies have showed that different pulse frequencies give different effects. In such settings a particular isolated biological event is studied in cell monolayers. When irradiating such a complex target as a mammal, the situation is quite different. The selected pulse repetition rate may (or may not) work the way the laboratory study suggests, but several other biological effects may be negative at the same time or at least unknown.

4. Looking at the literature, it becomes clear that very few studies provide a rationale for the selected pulsing. The frequencies used seem to have been chosen at random or adopted from an older study, where the pulse repetition rate also was chosen at random. In a literature study on the effects of laser therapy on musculoskeletal pain Corral-Baqués [1260] identified 150 papers. Among these, 35 reported the used pulse repetition rate and only 25 all the laser parametres used. Before the 90ies the dominating wavelength was 904 nm but after the 90ies many 808-830 nm lasers were used in a pulsing mode. More than 30 frequencies were used, switched and super pulsed. The only conclusion which can be made from this analysis is that no conclusion can be made.

5. Many laser manufacturers favour certain frequencies, particularly for switched mode. One favourite is 73 Hz, used already by Walker [38] in 1983. This pulse repetition rate is initially recommended for electrotherapy and there is no evidence for its use in light therapy. Other frequencies originate from the auriculo-therapy field and there possible advantages there have not been documented in laser therapy or any other light therapy.

6. When an effort is made to evaluate studies using pulsing, several questions arise. Was the output power the same for both frequencies? Or was the time of irradiation changed to compensate for the reduction of power? Was the

laser well calibrated and the pulse mechanism quality verified? Too often the questions remain unanswered.

In short, pulsing probably has an effect but we know very little about it today. The general recommendation is therefore: use continuous unless you have a very good reason not to do so. In a reveiw from 2003, Corral-Baqués [1260] writes:

We've gone through more than 150 papers in search of conclusive data to develop new treating parametres for skeletal muscle injury. We were especially concerned, among the different parametres, on the frequencies used. Of those papers, only 35 reported the used PRR, but just 25 of them specified all the parametres (fluence, radiance, spot, etc) and just 6 were done in vitro.

In order to make the most of the gathered information, we built charts of each wavelength and the different frequencies used depending on the pretended effect.

Focusing just on the 904 nm wavelength we've noticed:

- That most of the articles were previous to 1990 (a big fall not understandable when considering that up to 84% of the reviewed papers showed positive effects) with a big increase on papers dealing with the 820 nm.

- From the 26 papers found dealing with 904 nm, we've identified 29 different frequencies (no related among themselves, that is, not based on previous studies).

- From that table we can conclude that, to get an analgesic effect we need a PRR in the range from 4 Hz to 5120 Hz (that means any PRR is supposed to be useful).

- The same happens with the trophic effect, any PRR from 5 Hz to 10000 Hz is supposed to be equally effective.

- If we are to compare other parametres (power density, energy density, etc.) we will get to the same point: it's impossible to make any sense out of it.

ERGO: it's impossible to extract any conclusions as a starting point to start new researches in order to find more suitable working parametres.

So, for super pulsed lasers, there is not yet much literature providing advice on which PRR:s are suitable for what (as regards pulsing, see chapter 1.16.3 “Continuous and pulsed lasers” on page 28)

Although the literature in this field has not yet made clear which frequencies are particularly suited to which treatments, the many users of laser therapy have still produced a large body of empirical material. The table below shows the frequencies that, on empirical grounds, are considered particularly suitable for certain types of problem. when a superpulsed laser is used. The column to the right shows the frequencies with which many acupuncturists consider various acupuncture points should be treated.

The table applies only to truly pulsed lasers.

Local treatment		Laser acupuncture	
Diagnosis:	Frequency range:	Point type:	Frequency:
Pain, neuralgia	1-100 Hz	Endpoints	73 Hz
General stimulation	700 Hz	Source points	146 Hz
Oedema	1000 Hz	Sedation points	584 Hz
General stimulation	2500 Hz	Tonification points	1000 Hz
Inflammations	5000 Hz	Alarm points	2500 Hz
Infections	10.000 Hz	Beginning points	5000 Hz

Table 3.6 Pulse pulse repetition rates - local and laser acupuncture

The frequencies discussed here have nothing in common with the different pulse frequencies recommended for laser acupuncture.

There are GaAs lasers that automatically vary the pulse repetition rate during treatment, going from low to high and back. As can be seen from the above studies, it is not self-evident that this concept is beneficial.

Literature:

Mohktar [161] studied the pain-relieving effects of 16 Hz and 73 Hz frequencies, with otherwise unchanged parametres, in a double-blind study of experimental ischaemic pain. Significant effects were obtained, compared to the reference group, at 16 Hz but not at 73 Hz. The equipment used was a combined laser/LED array.

In another comparative double-blind study, also by Mohktar [162], nerve action potential was measured under irradiation at 73 Hz and 5000 Hz, under otherwise unchanged conditions. 73 Hz gave no significant effect when compared to the placebo group, whereas 5000 Hz did produce effects.

Kim [283] studied the effect of different GaAs pulses by irradiating 360 cultures of candida albicans with 5, 500, 1500, and 10.000 Hz. Significant differences were seen amongst the groups depending on the pulse type with which irradiation was given.

Martin [308] has shown that photobiological effects upon lower limb blood flow can be PRR-specific.

Fagnoni [509] had better results using 30 Hz rather than 70 Hz when treating patients suffering from trigeminal neuralgia.

El Sayed [529] compared the effect of GaAs at different frequencies on mast cell number and degranulation. All frequencies were effective compared to the sham irradiated groups, but only 20 Hz and 292 Hz, among the frequencies used, were significantly effective.

Almeida Lopes [1330] performed three interesting studies on fibroblasts. In the first study the fibroblasts were irradiated with 2, 5, 10 and 15

Joules; 56 mW constant power at 664 nm. The best results were achieved with 2 J. In the next experiment the energy was set at 2 J and the power used was either 28 or 56 mW. Best results were achieved with the higher power. Finally, the power of 56 mW and energy of 2 J were used either in continuous mode or at different pulse modes. The continuous mode provided the best stimulation and among the frequencies used the higher pulse frequencies presented the best results. These experiments elegantly demonstrate the importance of a correct amount of energy, that the energy density is important and that continuous mode is better than pulsed modes.

Al-Watban [1495] compared the wound healing effect of pulsed and continuous 635 nm laser. Continuous beam provide the best results, and the 100 Hz pulse repetition rate the best among the different frequencies used. And this pulse repetition rate happens to be the one closest to continuous among the frequencies used, which further underlines the superiority of the continuous beam for wound healing procedures.

The effect of pulsing is also studied by Ueda [1181]. Osteoblastic cells isolated from fetal rat calvariae were irradiated once with GaAlAs laser (830 nm, 500 mW) in two different irradiation modes; continuous irradiation (CI), and 1 Hz pulsed irradiation (PI). The author then investigated the effects on cellular proliferation, bone nodule formation, alkaline phosphatase (ALP) activity, and ALP gene expression. Laser irradiation in both groups significantly stimulated cellular proliferation, bone nodule formation, ALP activity, and ALP gene expression, as compared with the non-irradiation group. Notably, 1 Hz markedly stimulated these factors, when compared with the continuous group. In this study the lowest possible pulse mode was compared to continuous, and the possible effect of higher frequencies is not known.

Hashmi [523] has performed a literature review on the subject of pulsing in LPT. The conclusion is that the available evidence is inconclusive.

Further literature: [773, 1158]

3.4.9 Patient parametres

Of course the laser parametres depend very much on what we are going to treat. For instance, if we are going to treat an ulcer, we choose other settings than if we are going to treat knee arthroses.

3.4.9.1 Treatment area

In order to calculate dose, power density and treatment time, it is necessary to know the treatment area. In the formulas for calculation, the treatment area must be expressed in cm^2 if the outcome is to be correct.

Also, it is of importance for deciding the dose to have a knowledge of the depth below skin surface of the site to be treated.

Practical experience indicates that it may be more beneficial to treat a smaller area more intensively and then treat nearby areas later, rather than treating a larger area over a longer period of time at a single session. This may well be related to the fact that certain substances are released, which can be traced in blood and urine, that can reach disturbingly high levels when large areas are treated. It can also be a question of saturation.

3.4.10 Treatment intervals

Treatment intervals must be assessed for each individual case. Those expecting detailed advice on how to treat each particular case will be disappointed by what follows here. The same rules apply to laser treatment as to all other forms of medical treatment: the best results are achieved by the therapist who possesses sound medical knowledge, can listen to the patient and has a good intuition. As a general rule, however, it is better to use 3-4 treatments a week with moderate doses than using higher doses and few treatments.

Mester demonstrated that small doses with appropriate periods of time in-between are more effective than treatments that are very close. Abergel [8] has also demonstrated this on fibroblast cultures. Because laser therapy treatment has been shown to be cumulative (the dose from one treatment lasts some time, and what "remains" of the dose is added to the dose at the next treatment), it is vital that treatments are not too close together, so as to avoid a situation where the accumulated dose eventually ends up above the biostimulating range or even in the bio-inhibiting range, with consequently poorer results.

Acute problems are usually dealt with by a few treatments, which can be closely spaced. Acute herpes simplex or herpes zoster, for example, can be treated every day for a few days. Acute pain conditions can be given close treatment. Chronic complaints are usually best handled with more widely spaced treatment.

It has been shown to be beneficial to treat at closer intervals in the beginning (e.g. every other day or every third day for two weeks) and then at longer and longer intervals (e.g. once a week for a few weeks). Experience shows that it is not disadvantageous to temporarily suspend treatment after a number of introductory sessions. In some circumstances, this can actually be beneficial.

Another aspect is that you always have to take the patients' economy into account. If we haven´t noted a clear reaction after 4-5 sessions, we may suggest that further therapy is to be postponed for some weeks (or even months), to see if there will be a "late reaction". Then we can "speed it up" with more sessions. This also convinces the patient that our primary aim is not the patients' "money", but the clinical results.

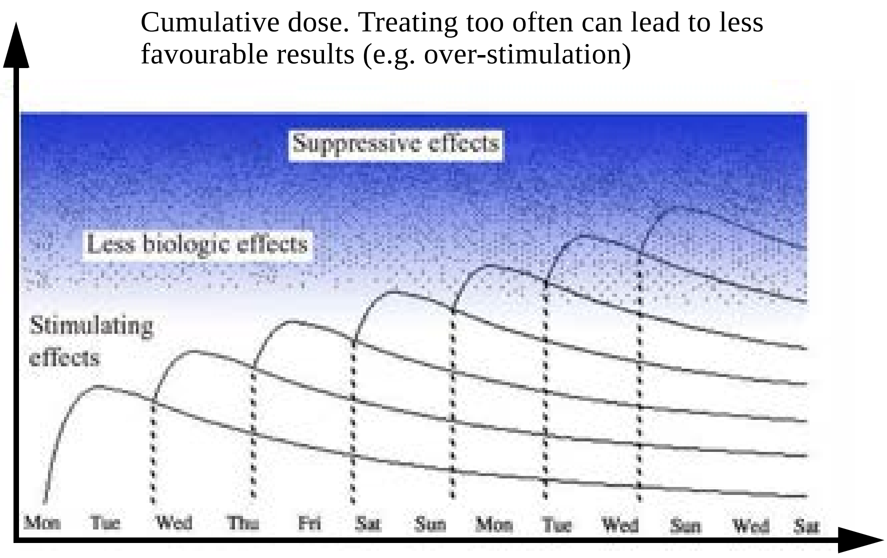


Figure 3.9 Cumulative dose

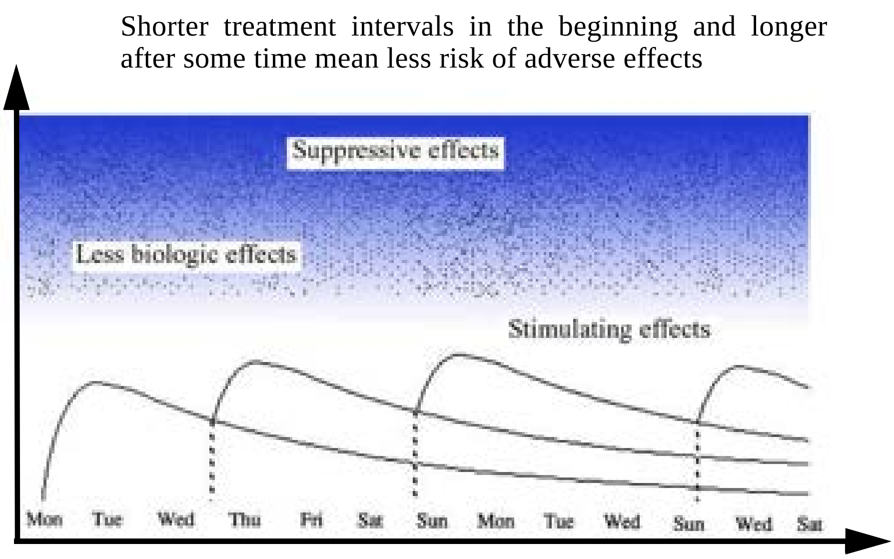


Figure 3.10 Shorter treatment intervals

Literature:

In the study by Ng [1508] sixteen rats were used, with 12 receiving surgical transection to their right MCL and 4 receiving a sham injury. Group 1 (n=4) received a single dose of InGaAlP laser therapy (wavelength 660 nm, average power 8.8 mW, pulse 10 kHz, dosage 31.6 J/cm²) directly to their MCL during surgery. Group 2 (n=4) received 9 doses of GaAlAs laser therapy applied transcutaneously on alternate days (wavelength 660 nm, average power 8.8 mW, pulse 10 kHz, dosage 3.5 J/cm²). The controls (Group 3, n=4) received one session of placebo laser at the time of surgery, with the laser equipment shut down, while the sham injured Group 4 (n=4) received no treatment. Biomechanical tests for structural stiffness, ultimate tensile strength (UTS), and load-relaxation were done at 3 weeks after injury. The stiffness and UTS data were normalised by expressing as a percentage of the left side of each animal before statistical analysis. The load-relaxation data did not show any differences between the groups. The normalised stiffness levels of Groups 2 and 4 were significantly higher than that of the control Group 3 . The normalised UTS of Groups 2 and 4 were also significantly higher than that of the control. Although, Group 1 had higher mean stiffness and UTS values than the control, no statistically significant difference was found between these two groups. Multiple laser therapy improves the normalised strength and stiffness of repairing rat MCLs at 3 weeks after injury. The multiple treatments seemed to be superior to a single treatment.

In the study by Carati [1337] post mastectomy oedema was treated with GaAs laser. One session of laser kept the oedema below the volume of that in the patients of the control group, whereas patients receiving two sessions showed a continuous improvement during a 3-months follow up.

The results of the cell study by Hawkins [1744] show that the correct energy density or fluence (J/cm²) and number of exposures can stimulate cellular responses of wounded fibroblasts and promote cell migration and cell proliferation by stimulating mitochondrial activity and maintaining viability without causing additional stress or damage to the wounded cells. Results further indicate that the cumulative effect of lower doses (2.5 or 5 J/cm²) determines the stimulatory effect, while multiple exposures at higher doses (16 J/cm²) result in an inhibitory effect with more damage.

A study by Houreld [1889] investigated the effectiveness of helium-neon laser irradiation at increasing intervals on diabetic-induced wounded human skin fibroblast cells (WS1) at a morphological, cellular, and molecular level. The controversies over light therapy can be explained by the differing exposure regimens and models used. No therapeutic window for dosimetry and mechanism of action has been determined at the level of individual cell types, particularly in diabetic cells in vitro. WS1 cells were used to simulate an in vitro wounded diabetic model. The effect of the frequency of He-Ne irradiation at a fluence of 5 J/cm² was determined by analysis of cell morphology, viability, cytotoxicity, and DNA damage. Cells were irradiated *using three different protocols: they were irradiated at 30 min only; irradiated twice, at 30 min and at 24 h; or irradiated twice, at 30 min and at 72 h post-wound induction. A single exposure to 5 J/cm² 30 min post-wound induction increased cellular damage. Irradiation of cells at 30 min and at 24 h post-wound induction decreased cellular viability, cytotoxicity, and DNA damage. However, complete wound closure as well as an increase in viability and a decrease in cytotoxicity and DNA damage occurs when cells were irradiated at 30 min and at 72 h post-wound induction. Thus, wounded diabetic WS1 cells irradiated to 5 J/cm² showed increased cellular repair when irradiated with adequate time between irradiations, allowing time for cellular response mechanisms to take effect. Therefore, the irradiation interval was shown to play an important role in wound healing in vitro and should be taken into account.*

3.4.11 Pre- or postoperative treatment?

Previously the predominant view was that there is nothing to gain by irradiating tissue pre-operatively. If the tissue is healthy, laser treatment has no effect. It may be time to reconsider the conventional wisdom, however, based on the results of several studies.

All irradiation, even of healthy tissue, activates a variety of processes, leading, for example, to the production of singlet oxygen. If no trauma exists or occurs later, these products disappear quickly and the normal state returns. If trauma occurs immediately after irradiation (planned surgery), however, the tissues' defence systems are in a more favourable state. If the tissue is already in poor condition prior to the operation (oedema, inflammation etc.), laser energy is even more beneficial pre-operatively.

Some conditions are cyclic and there are studies suggesting the possibility of treating these even in the inactive period. This has been demonstrated for herpes simplex [908] and asthma [1205].

Literature:

A study by Rosner [494] entailed crushing the optical nerve of rats. The object of the study was to investigate the capacity of the HeNe laser to delay or prevent nerve degeneration. Surprisingly, the effects were equally beneficial whether radiation was applied immediately before or immediately after the nerve was crushed.

In this study the tissue was intact before inflicting a trauma. In the following studies, the tissue was in a state of imbalance: Popova [147] removed muscle tissue from rats, irradiated it with X-rays, and then replanted the tissue. Improved healing was observed in those animals given laser therapy, prior to X-ray as well as after X-ray.

A study by Pourreau-Schneider [46] showed that mucositis associated with chemotherapy in cancer patients was alleviated by HeNe laser light. Alleviation resulted both from irradiation prior to chemotherapy and irradi-

ation following the debut of symptoms.This effect is confirmed by Bensadoun [929].

In an in vitro study by Karu [1107] it was found that the cell-glass adhesion increased in a dose-dependent manner after irradiation. The addition of different antioxidants eliminated this effect. Pre-irradiation was found to decrease (or normalise to the control level) the suppressive effects of these chemicals.

Bibikova [587] found that the process of regeneration in degenerated muscles can be markedly enhanced if the muscle is irradiated with HeNe laser prior to the injury.

Pöntinen [1285] has been using laser pretreatment in patients scheduled for various surgical intervention. Laser therapy has been performed on the day before surgery and immediately before surgery. This therapy has improved the rehabilitation process through reduced postoperative pain and oedema.

In the study by Zeredo [1588] the researchers tested the possible antinociceptive effect of laser irradiation when applied to a normal tissue before the onset of a painful stimulus. Male rats were used. A 1.5% formalin solution was injected into the right upper lip of the test animals (n=9) immediately after 10 min of low-power Er:YAG laser irradiation (energy: 0.1 J/cm^2 per pulse at 10 Hz). Control animals (n=9) were restrained for 10 min without laser application. The nociceptive response, i.e., the amount of time the rats spent rubbing the formalin injected area, was measured by an investigator blind to whether the animals had been laser irradiated or not. On laser irradiated rats, significantly less nociceptive behavior was observed only during the late phase (12-39 min) of the test. This result is similar to that reported for nonsteroid antiinflammatory drugs (NSAIDs) and other peripherally acting antiinflammatory agents.

The study by Santos [2508] aimed to evaluate the effects of LPT immediately before tetanic contractions in skeletal muscle fatigue development and possible tissue damage. Male rats were divided into two control groups and nine active LPT groups receiving one of three different laser doses (1, 3, and 10 J) with three different wavelengths (660, 830, and 905 nm) before six tetanic contractions induced by electrical stimulation. Skeletal muscle fatigue development was defined by the percentage (%) of the initial force of each contraction and time until 50 % decay of initial force, while total work was calculated for all six contractions combined. Blood and muscle samples were taken immediately after the sixth contraction. Several LPT doses showed some positive effects on peak force and time to decay for one or more contractions, but in terms of total work, only 3 J/660 nm and 1 J/905 nm wavelengths prevented significantly the development of skeletal muscle fatigue. All doses with wavelengths of 905 nm but only the dose of 1 J with 660 nm wavelength decreased creatine kinase (CK) activity. Qualitative assessment of morphology revealed lesser tissue damage in most LPT-treated groups, with doses of 1-3 J/660 nm and 1, 3, and 10 J/905 nm providing the *best results. Optimal doses of LPT significantly delayed the development skeletal muscle performance and protected skeletal muscle tissue against damage. These findings also demonstrate that optimal doses are partly wavelength specific and, consequently, must be differentiated to obtain optimal effects on development of skeletal muscle fatigue and tissue preservation. These findings also suggest that the combined use of wavelengths at the same time can represent a therapeutic advantage in clinical settings.*

Ushkova [2515] reports on the results of preventive measures introduction in 524 PC users, 98 jewelry polishers and 64 metallic ship hull assemblers are given LPT. The use of preventive measures, based on low-intensity laser radiation, was shown to prevent development of visual over-fatigue and occupational musculoskeletal system diseases. This abstract is short of details but the number of participants in the study is impressing.

Further literature: [564]

3.4.12 Treatment method parametres

There are several ways of administrating the laser light:

A. Local treatment (produces primarily local effects). This means that the laser light irradiates the affected area, e.g. a wound or an inflamed tendon.

B. Systemic or indirect irradiation (produces primarily systemic effects)

Examples of indirect irradiation are:

- irradiating acupuncture points
- irradiating trigger points
- irradiating spinal processes
- irradiating the dermatome
- irradiating the blood
- irradiating lymph nodes

In these instances we irradiate areas outside or far from the area where the patient would otherwise locate the problem. Direct and indirect treatment can be combined. In fact, even direct irradiation is a mode of indirect irradiation. The beam will always find blood, lymph and nerves, influencing the circulating metabolites. So every local treatment is also a systemic treatment but not vice versa.

3.4.13 Local treatment

This means that the laser light irradiates the affected area, e.g. a wound or an inflamed tendon. The treatment technique used depends on the depth of the tissue that you want to treat.

3.4.14 Shallow problems

1 Open wounds: The probe is held 1-2 cm from the wound. The depth of penetration is insignificant, which is of course the intention. Treat the periphery of the wound in skin contact. Give the open area of the wound a lower dose than the skin periphery.

2 Tissue lying close to the skin surface: Hold the probe in light contact with the skin.

3.4.15 Deeper problems

At medium depth: Press the probe against the skin. The deeper the tissue to be treated, the higher the pressure.
At great depth: Only the GaAs and high-powered GaAlAs laser can reach to these depths, but the therapist's knowledge of anatomy is also crucial. If the patient moves his/her arm/leg to various positions, an obstructing muscle mass can be moved aside to expose openings in deep muscle attachments. Pressing the probe firmly against the skin will also move the light closer to the target and decrease absorption through the ischemia caused by the pressure.

Literature:

For many skin treatments with light, it is important to have deep photon penetration into the skin. Because of absorption and scattering of photons by skin tissue, both the colour and the diametre of the incident beam affect the penetration depth of photons. In a study by Zhong-Quan [1748], the dependence of light transmission through human skin tissues (ear lobes and between the fingers) has been measured in-vivo at six wavelengths (532 nm, 632 nm, 675 nm, 810 nm, 911 nm, and 1064 nm). The same measurement was also made on pig skin in-vitro for comparison. It was observed that 1) the photons at 1064 nm penetrate deeper than the other colours studied for a given incident beam diametre; and 2) the transmittance at a particular wavelength increases asymptotically with incident beam diametre. For some skin tissues, the transmittance flattens at about 8 mm for 532 nm photons and approaches saturation at about 12 mm for all other colours. The results on pig skin are similar.

3.4.16 Treating inside the body

In some cases you may realise that the problem volume can not be reached through overlying skin, muscles, bone etc. A possible way to overcome this may be to use fibre optics or specialised probes to reach the place of a problem. Hence, the light can be brought into rectum, vagina, bladder, nose cavity etc by suitably designed probes. An optical fibre can be guided into blood vessels to treat angina etc. With an endoscope, ulcers in throat and stomach can be treated. A fibre can also be attached into a syringe needle, which can penetrate through lacerated muscles, emitting the light at its tip. Another, very simple method that has been used for problems in rectum and vagina, is to insert a test tube of glass or transparent plastic in order to expand the tissue and then to insert a laser probe inside the test tube. The light must then be properly spread or directed so that the right target is illuminated.

3.4.17 Systemic treatments

Systemic treatment means that we irradiate areas outside or far from the area where the patient would otherwise locate the problem. Examples of such treatment are treatment of acupuncture points and trigger points.

3.4.18 Acupuncture.

Acupuncture with lasers is an exciting phenomenon. A wide range of opportunities is open to a therapist with acupuncture training. The method is sterile and painless, and therefore highly acceptable to the patient and especially to children. Practitioners with little or no knowledge can use acupuncture with some success on a narrow range of indications. If well-known and uncontroversial points are used in laser acupuncture therapy, pain, tension, nausea, and anxiety can be influenced. Both laser acupuncture and conventional needle acupuncture affect the acupuncture points, but according to experienced therapists they do not always result in identical effects. They could be said to complement each other.

Lasers only cause a negligible rise in temperature in tissue [109, 170, 189, 1221], which is why laser acupuncture should not be confused with moxa treatment. Indeed, in some cases, even a small reduction in temperature has been reported [494]. Lasers seem to stimulate acupuncture points in a similar way to needles, although needles are more suitable for deep-lying points.

The pioneers of laser acupuncture come, unsurprisingly, from China. The oral surgeon Yo-Cheng Zhou worked with needle acupuncture between 1958 and 1965 and until 1971 experimented with acupressure on dental indications. Since 1971 he has worked with laser acupuncture, mainly as anaesthesia for extractions and minor operations. Zhou has developed an interesting technique that involves a small number of acupuncture points being subjected to high outputs. For extractions in the lower jaw, one single point is irradiated for five minutes with a HeNe laser (2-6 mW). The extraction starts immediately after, but the laser is held on the Hegu point (the thumb grip) during the whole process. Zhou also works with a CO_2-laser within the laser therapy range 0-100 mW, which he considers even more effective than the HeNe laser. His experience is that coagulation times are shorter with laser acupuncture than with normal anaesthetics and that subsequent discomfort is also reduced. Postoperative oedema and trismus are also less pronounced after laser acupuncture.

Bearing in mind that, since 1971, Zhou has performed over 10.000 tooth extractions with LAA (Laser Acupuncture Anaesthesia), the method cannot be dismissed as a placebo or something which only works on the Chinese - which was often the argument put forward before needle acupuncture was accepted in the West. LAA is not very well known amongst European authorities on acupuncture, despite the fact that Zhou, as early as 1984, published an account in English of his experience after the first 600 extractions. The points in the upper jaw for extraction are Sibai and Quanliao, and for the lower jaw, Jiache. The Hegu grip is used during extractions from both the lower and the upper jaw. Yangbai, Yuyao, Yintang, Sibai, Quanliao, and Jiache are the main points used for minor maxillofacial operations. Zhou also uses a HeNe or carbon dioxide laser directly on the alveolus after an extraction. In the thousands of extractions performed with LAA and its subsequent local treatment, not a single case of alveolitis or postoperative bleeding has occurred. Sutures are very rarely needed.

Even though it was the Chinese who pioneered laser acupuncture, it was a Canadian - Friedrich Plog - who, quite early on, highlighted the usefulness of the HeNe laser in this context. He was already testing lasers instead of needles in 1973 [227].

The literature in this area is rather large but the actual mechnisms have not been well documented. Recent studies using fMRI and comparing the effects of laser and needle acupuncture, have contributed to a more objective confirmation of the observed clinical effects and confirming the the fact that acupuncture points actually can be influenced by laser light [1833, 1835]. Thus, laser acupuncture has ceased to be controversial.

A new concept of laser acupuncture is the so-called “laser needles” [1519]. These are very thin fibres with an adhesive ring at the top. The adhesive ring can fix the laser fibre firmly to an acupuncture point. Since the fibre is thin, the power density over the point becomes considerable, even though output powers are in the 50 mW range. The system is equipped with several fibres and many acupuncture points can be treated simultaneously, making the situation more similar to the needle acupuncture situation. Further to that, single blind studies can now be performed, since the patient will not be aware whether the fibres are active or not.

Even tough laser are the tools in laser acpuncture and many practitioners use a combination of local irradiation and laser acupuncture, such combination is not acceptable in a research procedure [1802]. The effects are different and one cannot be compared to the other.

Literature:

Zhao [115] studied the changes in metencephalin in rat brains after HeNe laser irradiation of the Zusanli point. During irradiation, the pain threshold rose, while levels of metencephalin and diencephalin were redu-ced.

Yamamoto [406] has compared the effect of needle acupuncture and laser acupuncture in a rat model, using 830 nm. A selected acupuncture point was irradiated for 90 minutes. The pain threshold was elevated and reached a maximum after 60-90 minutes. After the end of the irradiation, the pain threshold gradually returned to the previous level. The analgesic effect was antagonised by naloxene but a difference between laser and needle was found using dexamethasone.

Bradley [117] studied the effects of laser acupuncture by means of thermography. St 6 was chosen as the standard point. Four minutes of stimulation with a GaAs laser (5000 Hz, 5 mW) and 30 minutes of needle stimulation were compared on the same subject. The facial tissue response showed up thermographically on videotape. It was observed that both needles and laser therapy caused vasodilatation in the facial region, both on the stimulated side and the opposite side. GaAs and needles produced the same results, but it took longer for GaAs stimulation to take effect. The effect was manifested immediately when using needles, and after 2-4 minutes with the laser. A comparison was also made of the effects of stimulation of a randomly chosen spot (instead of a known acupuncture point). The effects of stimulation of the acupuncture points were greater than those of the randomly chosen spots.

Kreczi [324] studied the analgesic effect of laser acupuncture in a single blind cross-over study. 21 patients suffering from radicular or pseudoradicular pain were given either laser or mock irradiation. Mean pain levels after laser treatment were significantly lower than after placebo treatment.

Smesny [445] compared the effect of needle and HeNe laser acupuncture. In a group of 112 patients with cervico-occipital headache, 50% were treated with needles and 50% with laser on identical points. Results in the two groups were equivalent (60% in both groups).

Hoffman [494] irradiated LI 4 in 5 subjects. The typical reaction was a temperature reduction of approximately 1 °C in the region of the fingers. Irradiation of placebo points failed to induce this reaction.

King [540] used HeNe laser in auricular therapy in 80 healthy volunteers, aged 18-39 years. 41 received laser therapy and 39 sham irradiation at appropriate acupuncture points in the left ear. Experimental pain threshold at the ipsilateral wrist was determined with an electrical stimulus immediately before and after treatment. The laser group demonstrated a significant increase in pain threshold after treatment, but the control group did not.

In a double blind, randomised, placebo controlled study by Schlager [892] the effectiveness of point P6 acupuncture on postoperative vomiting in children undergoing strabismus (eye) surgery was studied. A 10 mW 670 nm laser was used and the P6 point was irradiated for 30 seconds 15 minutes before anaesthesia and 15 minutes after arriving in the recovery room. In the laser group the incidence of vomiting was 25% and in the placebo group 85%.

These results are confirmed by Butkovic [1703] in a paediatric group scheduled for hernia repair, circumcision or orchidopexy. Laser acupuncture was equally effective as metoclopramide in preventing post operative vomiting.

Ilbuldu [1459] performed a placebo controlled, prospective, long-term follow up study with 60 patients who had trigger points in their upper trapezius muscles. The patients were divided into three groups randomly. Stretching exercises were taught to each group and they were asked to exercise at home. Treatment duration was 4 weeks. Placebo laser was applied to group 1, dry needling to group 2 and laser to group 3. HeNe laser was applied to three trigger points in the upper trapezius muscles on both sides. The patients were assessed before, post-treatment, and at 6 months after treatment for pain, cervical range of motion and functional status. The investigators observed a significant decrease in pain at rest, at activity, and increase in pain threshold in the laser group compared to other groups. Improvement according to Nottingham Health Profile gave the superiority of the laser treatment. However, those differences among the groups were not observed at 6-month follow up.

Zalewska-Kaszubska [1517] reports that fifty-three alcoholics were treated with two types of laser stimulation in four sessions. Each session consisted of 20 consecutive daily helium-neon laser neck biostimulations and 10 auricular acupuncture treatments with argon laser (every 2nd day). The Beck Depression Inventory-Fast Screen (BDI-FS) was used to assess their frame of mind before the session and after 2 months of treatment. Moreover, beta-endorphin plasma concentration was estimated five times using the radioimmunoassay (RIA) method. Improvement in BDI-FS and increase in beta-endorphin level were observed. These results suggest that laser therapy may be useful as an adjunct treatment for alcoholism.

However, in a study by Trümpler [1834] inpatients undergoing alcohol withdrawal were randomly allocated to laser acupuncture (n=17), needle acupuncture (n=15) or sham laser stimulation (n=16). Attempts were made to blind patients, therapists and outcome assessors, but this was not feasible for needle acupuncture. The duration of withdrawal symptoms (as assessed using a nurse-rated scale) was the primary outcome; the duration of sedative prescription was the secondary outcome. Patients randomised to laser and sham laser had identical withdrawal symptom durations (median 4 days). Patients randomised to needle stimulation had a shorter duration of withdrawal symptoms and tended to have a shorter duration of sedative use, but these differences diminished after adjustment for baseline differences. The data from this pilot trial do not suggest a relevant benefit of auricular laser acupuncture for alcohol withdrawal.

O'Reilly [1516] studied the effect of at-home laser acupuncture therapy. Interstitial cystitis (IC) is a debilitating condition which causes irritative bladder symptoms, pain and a decrease in health status. The pathophysiology is poorly understood so therapeutic options are diverse. Women meeting the National Institutes of Health National Institute for Diabetes and Digestive and Kidney Diseases criteria for IC were prospectively recruited and randomised to treatment (29) or placebo (27) cohorts in a double-blind trial. At home the patient performed laser therapy daily for 30 seconds over the SP6 acupuncture point for 12 weeks. Measures at baseline and at 84-day follow-up included the 7-day voiding diary, the Interstitial Cystitis Problem Index, Interstitial Cystitis Symptom Index and RAND 36-Item Health Survey questionnaires. There were no significant differences between the treatment and control cohorts on any of the measures. However, there was a significant decrease between baseline and 12-week follow-up in the amount voided, symptom problems and severity, and on all 8 SF-36 scales. There was no significant effect of fluid intake. This study demonstrated no difference between the active and sham device. However, it is interesting that treatment and control cohorts experienced similar improvements, suggesting that the control cohort improvements may have been due to participants' belief that they were receiving active treatment from the stimulator.

The paper by Litscher [1518] presents an experimental double-blind study in laser acupuncture research in healthy volunteers, using a new optical stimulation method. 18 healthy volunteers (mean age +/- SD: 25.4 +/- 4.3 years; range: 21-30 years; 11 female, 7 male) were included in a randomised controlled cross-over trial using functional multidirectional transcranial ultrasound Doppler sonography (fTCD; n=17) and performed functional magnetic resonance imaging (fMRI) in one volunteer. Stimulation of vision-related acupoints resulted in an increase of mean blood flow velocity in the posterior cerebral artery measured by fTCD [before stimulation (mean +/- SE): 42.2 +/- 2.5; during stimulation: 44.2 +/- 2.6; after stimulation: 42.3 +/- 2.4 cm/s, n.s.]. Mean blood flow velocity in the middle cerebral artery decreased insignificantly. Significant changes of brain activity were *demonstrated in the occipital and frontal gyrus by fMRI. Optical stimulation using properly adjusted laser needles has the advantage that the stimulation cannot be felt by the patient (painless and no tactile stimulation) and the operator may also be unaware of whether the stimulation system is active.*

In an experimental animal study Litscher [1519] investigated the effects of the new technique of laser needle stimulation (wavelength: 685 nm; energy density: 4.6 kJ/cm^2*. per point; application duration: 20 min). The results revealed changes in microcirculatory parametres of the skin resulting in an increase in blood flow. However, the quality and intensity of the laser light did not induce micromorphological alterations in the skin.*

In an open, randomised trial, Allais [1520] evaluated transcutaneous electrical nerve stimulation (TENS), infrared laser therapy and acupuncture in the treatment of transformed migraine, over a 4-month period free of prophylactic drugs. Sixty women suffering from transformed migraine were assigned, after a one month run-in period, to three different treatments: TENS (Group T; n=20), infrared laser therapy (Group L; n=20) or acupuncture (Group A; n=20). In each group the patients underwent ten sessions of treatment and monthly control visits. In Group T patients were treated for two weeks (5 days/week) simultaneously with three TENS units with different stimulation parametres (I: pulse rate=80 Hz, pulse width==120 ms; II: 120 Hz, 90 ms; III: 4 Hz, 200 ms). In Group L an infrared diode laser (27 mW, 904 nm) was applied every other day on tender scalp spots. In Group A acupuncture was carried out twice a week in the first two weeks and weekly in the next 6 weeks. A basic formula (LR3, SP6, LI4, GB20, GV20 and Ex-HN5) was always employed; additional points were selected according to each patient's symptomatology. The number of days with headache per month significantly decreased during treatment in all groups. The response in the groups differed over time, probably due to the different timing of applications of the three methods. TENS, laser therapy and acupuncture proved to be effective in reducing the frequency of headache attacks. Acupuncture showed the best effectiveness over time.

Wozniak [1521] reports that laser acupuncture can reduce postmenstrual obesity. The study population consisted of 74 postmenopausal females with visceral obesity that was divided into two groups according to an employed 6-month slimming procedure. In the first group (n=36) a low-calorie diet was applied, while women in the second group (n=38) were on the same kind of diet, having additionally one cycle of laser acupuncture procedure at the same time. At baseline and at the end of the study, body weight, body mass index and waist-to-hip ratio were determined in all women. After 6 trial months both groups exhibited a statistically significant drop in body weight, body mass index and waist-to-hip ratio. The mean reduction of body weight, body mass index and waist-to-hip ratio was significantly higher in the second group of women (laser acupuncture plus low-calorie diet).

A double blind, placebo controlled, crossover study was performed by Gruber [1522] to investigate the possible protective effect of a single laser *acupuncture treatment on cold dry air hyperventilation induced bronchoconstriction in 44 children and adolescents of mean age 11.9 years (range 7.5-16.7) with exercise induced asthma. Laser acupuncture was performed on real and placebo points in random order on two consecutive days. Lung function was measured before laser acupuncture, immediately after laser acupuncture (just before cold dry air challenge (CACh)), and 3 and 15 minutes after CACh. CACh consisted of a 4 minute isocapnic hyperventilation of -10 degrees C absolute dry air. Comparison of real acupuncture with placebo acupuncture showed no significant differences in the mean maximum CACh induced decrease in forced expiratory volume in 1 second (27.2 (18.2)% v 23.8 (16.2)%) and maximal expiratory flow at 25% remaining vital capacity (51.6 (20.8)% v 44.4 (22.3)%).*

As recent studies demonstrated, acupuncture can elicit activity in specific brain areas. The study by Siedentopf [1559] aimed to explore further the central effect using laser acupuncture. The researchers investigated the cerebral effects of laser acupuncture at both acupoints GB43 with functional magnetic resonance imaging (fMRI). As a control condition the laser was mounted at the same acupoints but without application of laser stimulation. The group results showed significant brain activations within the thalamus, nucleus subthalamicus, nucleus ruber, the brainstem, and the Brodmann areas 40 and 22 for the acupuncture condition. No significant brain activations were observed within the placebo condition. The activations observed were laser acupuncture-specific and predominantly ipsilateral. This supports the assumption that acupuncture is mediated by meridians, since meridians do not cross to the other side.

Fifty patients with chronic tension-type headache were randomly allocated to treatment or placebo groups in the study by Ebneshahidi [1569]. Patients in the treatment group received laser acupuncture to LU7, LI4, GB14, and GB20 bilaterally. Points were irradiated for 43 seconds, and the intensity was 1.3J (approximately 13 cm^2.). Ten sessions were given, three per week. The placebo group was treated in a similar way except that the output power of the equipment was set to zero. The outcome variables were headache intensity (VAS), duration of attacks, and number of days with a headache per month, by daily diary, assessed monthly to three months after treatment. There were significant differences between groups (P<0.001) in changes from baseline in months one, two and three, in median score for headache intensity (treatment group -5, -3 and -2, placebo group -1, 0 and 0), median duration of attacks (treatment group -6, -4 and -4, placebo group -1, 0 and 0 hours), and median number of days with headache per month (treatment group -15, -10 and -8, placebo group -2, 0 and 0).

Aigner [1700] used HeNe 5 mW, 0.075 J per point as an adjuvant treatment modality ina group of whiplash injuried patients. There was no additional effect of the treatment.

The Cochrane collaboration [1524] has performed a literature analysis on the effect of acupuncture, acupressure, laser therapy or electrostimu-

lation for smoking sessation. Quote: " …on the extracted data in duplicate on the type of smokers recruited, the nature of the acupuncture and control procedures, the outcome measures, method of randomisation, and completeness of follow-up. We assessed abstinence from smoking at the earliest time-point (before 6 weeks), at six months and at one year or more follow-up in patients smoking at baseline. We used the most rigorous definition of abstinence for each trial, and biochemically validated rates if available. Those lost to follow-up were counted as continuing to smoke. Where appropriate, we performed meta-analysis using a fixed effects model. MAIN We identified 22 studies. Acupuncture was not superior to sham acupuncture in smoking cessation at any time point. The odds ratio (OR) for early outcomes was 1.22 (95% confidence interval 0.99 to 1.49); the OR after 6 months was 1.50 (95% confidence interval 0.99 to 2.27) and after 12 months 1.08 (95% confidence interval 0.77 to 1.52). Similarly, when acupuncture was compared with other anti-smoking interventions, there were no differences in outcome at any time point. Acupuncture appeared to be superior to no intervention in the early results, but this difference was not sustained. The results with different acupuncture techniques do not show any one particular method (i.e. auricular acupuncture or non-auricular acupuncture) to be superior to control intervention. Based on the results of single studies, acupressure was found to be superior to advice; laser therapy and electrostimulation were not superior to sham forms of these therapies. There is no clear evidence that acupuncture, acupressure, laser therapy or electrostimulation are effective for smoking cessation."

Gottschling [1827] investigated whether laser acupuncture is efficacious in children with headache and if active laser treatment is superior to placebo laser treatment in a prospective, randomised, double-blind, placebo-controlled trial of low level laser acupuncture in 43 children) with headache (either migraine (22 patients) or tension type headache (21 patients)). Patients were randomised to receive a course of 4 treatments over 4 weeks with either active or placebo laser. The primary outcome measure was a difference in numbers of headache days between baseline and the 4 months after randomisation. Secondary outcome measures included a change in headache severity using a 10 cm Visual Analogue Scale (VAS) for pain and a change in monthly hours with headache. Measurements were taken during 4 weeks before randomisation (baseline), at weeks 1-4, 5-8, 9-12 and 13-16 from baseline. The mean number of headaches per month decreased significantly by 6.4 days in the treated group and by 1.0 days in the placebo group. Secondary outcome measures headache severity and monthly hours with headache decreased as well significantly at all time points compared to baseline and were as well significantly lower than those of the placebo group at all time points. It is concluded that laser acupuncture can provide a significant benefit for children with headache with active laser treatment being clearly more effective than placebo laser treatment.

In the study by Zeredo [1828] the authors tested the analgesic effects of high-intensity infrared laser for acupuncture-like stimulation. Twelve adult Sprague-Dawley rats weighing 230 to 250 g were randomly assigned to laser, needle, or restraint groups. Stimulation was directed to the meridian point Taixi (KI 3) for 10 min. For laser stimulation, a pulsed Er:YAG system was used. The laser settings were adjusted to provide a focal raise in the skin temperature to about 45 degrees C. The anti-nociceptive effect was evaluated by the tail-flick test. Both needling and laser stimulation significantly increased the tail-flick latency. Peak needling effect was observed immediately after treatment, while laser stimulation was effective both immediately and 45 min after treatment. High-intensity laser stimulation may be used alternatively or in combination with conventional acupuncture needling for pain relief.

In the work by Lihong [1829], 68 cases of acne vulgaris were randomly divided into a treatment group of 36 cases treated with HeNe laser auricular irradiation plus body acupuncture, and a control group of 32 cases treated with body acupuncture only. The results showed that the cure rate was 77.8% in the treatment group and 46.9% in the control group, indicating that HeNe laser auricular irradiation plus body acupuncture may exhibit better effects for acne vulgaris.

Quah-Smith [1830] performed a double-blind randomised controlled trial, conducted to test the efficacy of laser acupuncture in mild to moderate depression. Thirty patients with depression were randomised to receive either active or inactive laser treatment. The laser unit could be switched to one of two settings. One switch position delivered active laser acupuncture and the other was inactive (sham). In the active mode, 0.5 J was delivered to each of six to eight individually tailored acupuncture sites per visit. All patients were treated twice weekly for four weeks then weekly for a further four weeks. The patients and the acupuncturist were both blinded to conditions. At the end of the treatment period, Beck Depression Inventory scores fell from baseline by 16.1 points in the intervention group and by 6.8 points in the sham control group. The difference showed only a trend four weeks later, but was again significant after 12 weeks. Laser acupuncture was well tolerated with transient fatigue as the most common adverse effect.

The paper by Litscher [1833] presents an experimental double-blind study in acupuncture research in healthy volunteers using a new optical stimulation method. The authors investigated 18 healthy volunteers in a randomised controlled cross-over trial using functional multidirectional transcranial ultrasound Doppler sonography (fTCD; n=17) and performed functional magnetic resonance imaging (fMRI) in one volunteer. Stimulation of vision-related acupoints resulted in an increase of mean blood flow velocity in the posterior cerebral artery measured by fTCD. Mean blood flow velocity in the middle cerebral artery decreased insignificantly. Significant changes of brain activity were demonstrated in the occipital and frontal gyrus by fMRI. Optical stimulation using properly adjusted laser needles has *the advantage that the stimulation cannot be felt by the patient (painless and no tactile stimulation) and the operator may also be unaware of whether the stimulation system is active. Therefore true double-blind studies in acupuncture research can be performed.*

The aim of a study by Siedentopf [1835] was to investigate the effect of laser acupuncture on cerebral activation. Using functional magnetic imaging (fMRI) cortical activations during laser acupuncture at the left foot (Bladder 67) and dummy acupuncture, were compared employing a block design in ten healthy male volunteers. All experiments were done on a 1.5 Tesla magnetic resonance scanner equipped with a circular polarised head coil. During laser acupuncture, we found activation in the cuneus corresponding to Brodmann Area (BA) 18 and the medial occipital gyrus (BA 19) of the ipsilateral visual cortex. Placebo stimulation did not show any activation. We could demonstrate that laser acupuncture of a specific acupoint, empirically related to ophthalmic disorders, leads to activation of visual brain areas, whereas placebo acupuncture does not. These results indicate that fMRI has the potential to elucidate effects of acupuncture on brain activity.

A study by Litscher [1832] comprises scientific-theoretic fundamental investigations of laserneedle technology, a new and painless method of acupuncture stimulation. Laserneedles are not inserted in the skin, but are merely placed on the surface of the acupuncture point. The study documents the significant changes in peripheral microcirculation and surface temperature of the skin induced by laser, in 22 healthy volunteers. In addition, a randomised cross-over study to characterise the specific changes in cerebral blood flow velocity with laserneedle acupuncture is presented.

Several treatment modalities for children suffering from monosymptomatic nocturnal enuresis are available, but desmopressin is a well-established option. In the study by Radmayr [1836] forty children aged over 5 years presenting with primary nocturnal enuresis underwent a previous evaluation of their voiding function to assure normal voiding patterns and a high nighttime urine production. Then the children were randomised into two groups: group A children were treated with desmopressin alone, and group B children underwent laser acupuncture. All children were investigated after a minimum follow-up period of 6 month to evaluate the duration of the response. The children of both groups had an initial mean frequency of 5.5 wet nights per week. After a minimum follow-up period of 6 months reevaluation revealed a complete success rate of 75% in the desmopressin-treated group. Additional 10% of the children had a reduction of their wet nights of more than 50%. On the other hand, 6 months after laser acupuncture, 65% of the randomised children were completely dry. Another 10% had a reduction of the enuresis frequency of more than 50% per week. 20% of the children in the desmopressin-treated group did not respond at all as compared with 15% in the acupuncture-treated group. Statistical evaluation revealed no significant differences among the response rates in both groups. In comparison *with pharmacological therapy using desmopressin, the study showed that laser acupuncture should be taken into account as an alternative, noninvasive, painless, cost-effective, and short-term therapy for children with primary nocturnal enuresis in case of a normal bladder function and high nighttime urine production. Success rates indicated no statistically significant differences between the well-established desmopressin therapy and the alternative laser acupuncture.*

Read [1837] reports on a 28-year-old woman with acquired brain damage who suffered subsequent profound mental disability and an intense hyperphagic syndrome complete with life-threatening pica. She was the single subject of two consecutive experiments. In the first, Naltrexone, an orally administered opiate blocker, was given to reduce hyperphagia and distress, but was associated with even greater urgency when eating meals and a manifest increase in distress. While distress reduced to premedication levels on withdrawal of treatment, urgency of eating did not reduce so quickly. In the second experiment a laser acupuncture procedure was used at 2.5 Hz and 10 Hz for 10 days each with an intervening 10-day placebo condition to increase the availability of the subject's endogenous opiates, and thus hopefully produce opposite effects to the first experiment and effect a positive treatment. The 10 Hz condition produced a significant but transient reduction in pica measured by attempts at pica on a supervised walk shortly after each treatment. The subject was also easier to manage on walks, and appeared happier.

Further literature: [45, 111, 116, 118, 119, 175, 227, 876-891, 939]

Laser acupuncture – some thoughts by the amateur

In needle acupuncture there is always a sensory effect of the needle. This may or may not be of importance but it is a fact that the sensory input is absent in laser acupuncture. There is evidence enough to accept that laser acupuncture works, but there are even more questions involved in laser acpuncture that in needle acupuncture:

1. Is there a wavelength difference?
2. Which is the "correct" dose for an acupuncture point? Considering the difference in depth (for instance between ear acupuncture points and body acupuncture points) there should be a difference. The doses used in the literature differ a lot.
3. When an acupuncture point is irradiated, there is a large "light ball" surrounding the area of the light incidence. The energy of the beam is then greatest in the center of the beam, but how crucial is it to be on the exact anatomical spot?
4. When an acupuncture point is irradiated, a certain volume of blood is also affected. Is this significant?

5 The ideal acupuncture laser should have a very small aperture to be able to pinpoint the acupuncture point and to give a high energy density. But many therapists just use the laser that happens to be at hand and they all claim that their therapy is effective.

6 In auricular acupuncture several points will be affected whenever one selected point is irradiated, even if the laser has a very small aperture. This is not the case in needle acupuncture. What is the implication of this? Would a laser with e.g. yellow light (less penetration) be better?

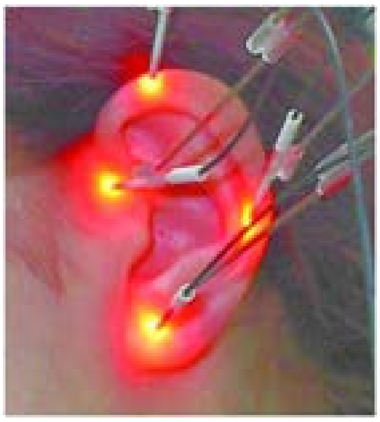


Figure 3.11 Laser needle auriculotherapy.
Courtesy: Michael Weber

7 When performing regular laser therapy, many random acupuncture points are irradiated, nolens volens. Which are the consequences?

8 Moxa (heat) is used on acupuncture points but laser acupuncture is not a heat phenomenon. However, some therapists use carbon dioxide lasers for acupuncture and actually burn the acupuncture point.

9 Several therapists use different pulsing systems (Nogier, Baar etc), others use continuous irradiation. Is pulsing important and, if so, what scientific documentation is there? The Nogier pulse repetition rate list was ”inherited” from electro-acupuncture – is it relevant to use that in the pulsing of light?

10 Goldman [2218, 2516] found that adenosine, a neuromodulator with anti-nociceptive properties, was released during acupuncture in mice and that its anti-nociceptive actions required adenosine A1 receptor expression. Direct injection of an adenosine A1 receptor agonist replicated the analgesic effect of acupuncture. Inhibition of enzymes involved in adenosine degradation potentiated the acupuncture-elicited increase in adenosine, as well as its anti-nociceptive effect. These observations indicate that adenosine mediates the effects of acupuncture and that interfering with adenosine metabolism may prolong the clinical benefit of acupuncture. Obviously, needle acupuncture stimulates ADP and LPT ATP. Are we close to an explanation? [378, 2019]

Summing up, it is obvious that a multitude of parametres are used in laser acupuncture and that there is no real consensus on these. However, since laser acupuncture seems to be an acceptable alternative to needle acupuncture, this possibility merits further research. Laser acupuncture is pain free, sterile and can safely be used on infected individuals, persons with needle phobia and on infants.

3.4.19 Trigger points

It is generally clinically advantageous to combine local treatment with trigger point treatment. The reduction in pain on palpating very often coincides with pain reduction in the inflamed area. However, only irradiating the trigger points in not a good idea, all laser therapy should primarily be aimed at "the heart of the matter".

Further literature: [253, 302, 313, 315, 647, 670]

3.4.20 Spinal processes

Irradiation of the spinal processes corresponding to the area where the pain is located will reduce the pain. In the case of golf or tennis elbow, it may be a false golf or tennis elbow. It may be a nerve entrapment in the nerve passage leading into the spinal cord and laser treatment of C6 may reduce an oedema around the nerve and hence give pain relief.

Further literature: [540]

3.4.21 Dermatome

In cases of skin eruptions such as herpes zoster, the entire dermatome should be irradiated.

Further literature: [57]

3.4.22 Blood irradiation

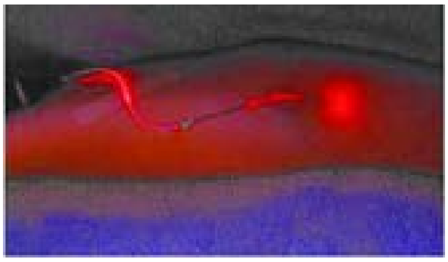


Figure 3.12 Laser blood irradiation.
Courtesy: Levon Gasparyan

An interesting treatment technique has been used in Russia for many years. The patient's blood is irradiated in order to improve the immune system and the microcirculation. The irradiation can be done through the skin via a fibre leading directly into the blood stream or via a dialysis-like machine. Wavelengths used are 633 and 890 nm.

Irradiating the blood is not a recent treatment modality [671]. In fact, as early as 1923 the US scientist Knott began to experiment with ways to irradiate the blood in order to destroy infectious organisms. In those days there were no lasers, so UV light was attempted. The works of Nobel Prize winner Ryberg Finsen spurred the idea.

This was a time when there were no antibiotics and scientists were trying every possibility in coping with infections. In initial experiments Knott irradiated the entire blood of experimentally infected dogs. He found that the irradiation cleared the blood of infection, but the dogs died in 5-7 days of profound depression and a progressive respiratory slowing and failure. This led Knott to experiment with irradiating different amounts of the blood of the dogs until he determined that the optimal approach was to irradiate 1.5-3 ml of blood for every pound of body weight (about 5% of the total blood) for about 10 seconds.

The first treatment of a human subject occurred in 1928. The patient was a woman moribund following septic abortion complicated by haemolytic streptococcus septicaemia. Treatment with UV blood irradiation rapidly returned her to normal health. Knott waited five years to make sure that the woman did not suffer from any subtle long-range effects before further treatment of a human subject was undertaken.

With the advent of antibiotics the idea of UV blood irradiation vanished. The new miracle therapy was used extensively, while the long term side effects and bacterial backlash were not yet discovered. Russian researchers [669] took a new look at the old idea in the 70s and since then the treatment has been extensively investigated in the laboratory and in the clinic.

Samoilova [482] names this “photohaemotherapy” or “photomodification” and states that it has been used for many years in Russia. There are reports of general effects on the immune system, including decrease of the blood viscosity, improvement of microcirculation, detoxification and oxygenation, normalisation of haemostatis, and activation of immune and proliferative processes. Some indications reported in the literature are: occlusive vascular diseases in the extremities, unstable angina, acute myocardial infarction, diabetic angiopathies, acute pneumonia, lung abscess, bronchial obstructive diseases of the lungs, drug resistant forms of schizophrenia, rheumatoid arthritis, acute calculous pyelonephritis, ischemic heart disease, circulatory encephalopathy, haemorrhagic shock, Tourette’s syndrome, and OPH gestosis.

The use of lasers instead of UV light only started in the 70s (in the former Soviet Union). Laser Blood Irradiation (LBI) seemed to have effects similar to UV Blood Irradiation (UBI). Although LBI seemed to be slightly less effective than UBI, the great advantage was that LBI was easier to perform. HeNe laser could penetrate the skin, whereas UV light does not.

Several treatment methods have been used. The most common is irradiation with HeNe laser via a thin light-guide and an IV needle, which is then withdrawn. HeNe lasers of 1-10 mW are used (most frequently 1 mW) and duration of treatment varies from 30 to 60 minutes. Usually the cubital vein is used. In some cases an artery is used.

Another method is to irradiate the blood outside the body in plastic or quartz tubes. Only a small amount of the patient’s blood is irradiated. This method is mainly used for UBI.

Transcutaneous irradiation is non-invasive and has several advantages, such as better patient acceptance, ease of application and lack of cross infection risks. Some researchers claim that 1 mW intravenous HeNe irradiation equals 20-30 mW transcutaneous irradiation. Intravenous irradiation is said to cause a sensation of warmth and sleepiness. This sensation is less obvious with transcutaneous irradiation [670]. LBI also seems to improve microcirculation, thus improving the uptake of pharmaceuticals. For transcutaneous irradiation, infrared lasers are used.

An interesting aspect of blood irradiation is the effect of normal sunshine. In the Nordic countries the solar power density varies from almost 0 in winter to 100 mW/cm^2 in the summer. Some of this energy comes in the infrared and can penetrate down to the aretrioles. One hour in the sun during a clear summer day thus would give a dose from penetrating light of roughly 0.05 W × 3600 seconds = 180 J/cm^2 of the bodily areas which are at a right angle to the incoming light. That area could be rather large, suppose 50 × 60 cm = 3000 cm^2. The biological effects of the sun are obvious, but they differ a lot from that of laser therapy. However, it has been demonstrated that the effects on cells from a laser can be eradicated if the cells later are subjected to broadband light (like the sunshine). So the question is - should patients avoid gross doses of sunlight after being treated by laser?

Literature:

Kipshidze [472] used HeNe irradiation in 900 patients with acute myocardial infarction. All patients were treated within four hours of the anginal attack. There was a painkilling effect as well as a limitation of the ischaemic area. Antioxidant blood activity and oxygen content of blood and tissue rose. The amount of drugs used was reduced and the duration of the hospitalisation decreased by an average of 7 days.

Koukoui [481] used the same procedure for this indication, but the blood was irradiated extracorporally.

The effects of laser therapy on the blood is considered to be a subject of great importance in elucidating the mechanisms of action between laser light and biological tissues. The study by Siposan [1325] investigates some in vitro effects of laser on some selected rheologic indices of human blood. After establishing whether or not damaging effects could appear due to laser irradiation of the blood, the author tried to find a new method for rejuvenating the blood preserved in haemonetics-type bags. Blood samples were obtained from adult regular donors (volunteers). HeNe laser and laser diodes were used as radiation sources, in a wide range of wavelengths, power densities, doses and other parametres of irradiation protocols. In the first series of experiments he established that laser therapy does not alter the fresh blood from healthy donors, for doses between 0 and 10 J/cm^3 and power densities between 30 and 180 mW/cm^3. In the second series of experiments he established that laser does have, in some specific conditions, a revitalising effect on the erythrocytes in preserved blood. It was concluded that laser irradiation of the preserved blood, following a selected protocol of irradiation, could be used as a new method to improve the performances of *preservation: prolonging the period of storage and blood rejuvenation before transfusion.*

Acc. to the study by Nascimento [1738] LPT elevates (1.0 J/cm^3*) or decreases (2.0 J/cm*^{3}*) the potential of long-term cryopreserved peripheral blood progenitor cells for growth of colony-forming units in vitro.*

Kirichuk [483] applied transcutaneous HeNe laser light to rats that had been exposed to pathological stress. It was shown that stress-induced platelet aggregation was reduced by 34% through the irradiation.

The work by Mehdi [1530] was designed to evaluate the effect of intravenously administered laser irradiation on the level of antibiotic in the blood. A locally constructed GaAs laser of 200 nsec pulse width, average power of 1 mW at 1 kHz pulse repetition rate was used. It had further an optical package containing a connector and optical fibre with fine canula fixed in its end. Twenty eight male adult New Zealand white rabbits were used in this study. They were divided into two groups (control & treated with the laser radiation). Each group was subdivided into two subgroups depending upon the manner of administration of the Ampicilline. The first subgroup was injected with 10 mg/kg B.W of Ampicilline at the time of irradiation while the other subgroup was given the Ampicilline in a shape of gelatine capsules, each one containing 10 mg/kg B.W, orally prior to the anaesthesia. Each animal underwent a surgical operation carried out on the medial aspect of the left thigh to expose the femoral vein. Blood of the animals of the treated group was irradiated by introducing the fine needle of the canula into the vein for 5 minutes. Samples of blood were collected from the animals of all groups at 0.5, 1, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours intervals after the injection of the antibiotic and sent for laboratory analysis using HPLC. The results of this study revealed a significant increase in the level of Ampicilline (ng/ml) in the treated group as compared with the control one. The increase in the level was significant as compared with the pretreatment time. The results obtained from this study are said to be attributed to the improvement of reheological properties of blood, and an increase in the capillaries, blood flow, in addition to reduced vascular resistance and vascular tone which lead to increase the motion and out flow of fluids from the interstitial spaces in to the lymphatic improvement of tissue trophic activity.

It is reported here by Mi [1767] that laser irradiation can reduce the Hbm contents in pig's erythrocytes, providing the explanation for the improvement of erythrocyte deformability. The decrease of the Hbm was proportional to the irradiation dose, but the relative change of Hbm was saturated around 35%. The 532 nm laser was more efficient at lowering Hbm than the 632.8 nm laser, consistent with the absorption spectrum of Hbm.

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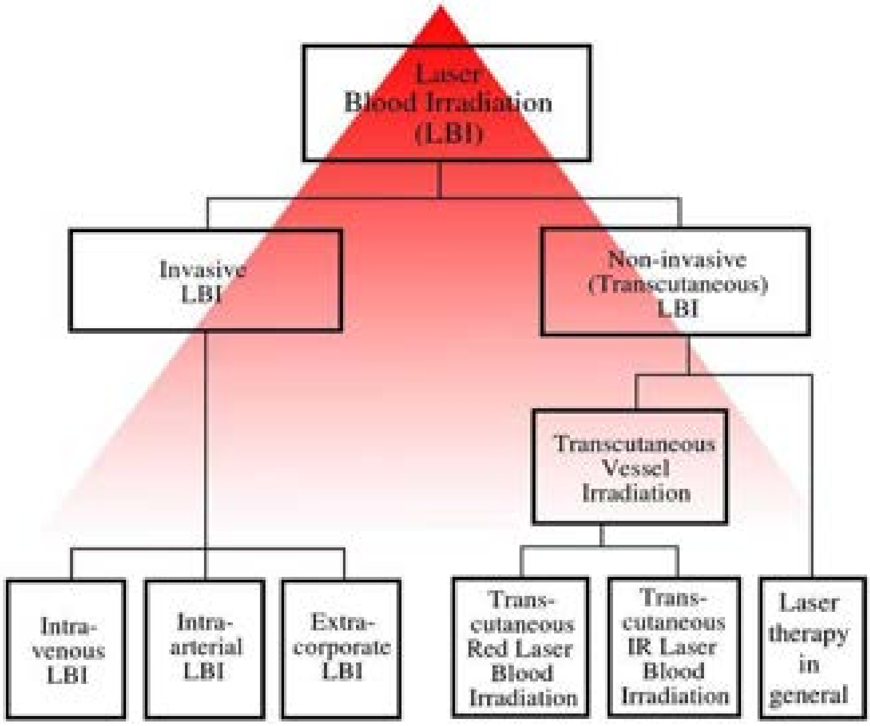


Figure 3.13 Methods of blood irradiation. Modified from Levon Gasparyan.

3.4.23 Irradiation of lymph nodes

Whenever there is a local infection, the recommendation is to irradiate the local lymph nodes to boost the immune system [915]. Recent research by Almeida-Lopes [1470] also suggests that irradiation of lymph nodes in the facial area can reduce pain conditions and oedema. This mode of treatment is especially useful when the focal area is infected, since the laser would partly enhance the local microorganisms as well. In these cases, and in particular for immune depressive patients, a lymph drainage technique can be used. With knowledge of the lymphatic anatomy the lymph nodes involved in the inflammatory process can be irradiated in cases such as periocoronitis, herpes simplex, endodontic abscesses and avleolitis. Almeida-Lopes suggests a dose around 70 J/cm^2 with a two-day interval.

3.4.24 Irradiation of ganglions

Stellate ganglion blocks are reported to be an effective but invasive treatment of upper extremity pain. Irradiation with different light sources offers a non-invasive and safer alternative. Lasers have succesfully been used in several studies [186, 421, 423, 523, 685, 691, 692, 1053, 1054]. Linear polarised light was used in [1574, 1575, 1577, 1578]. In [1576], however, laser, linear polarised light as well as Xenon-ray irradiation were used, but all were ineffective.

Literature:

Takeyoshi [1052] has treated many patients suffering from allergic rhinitis with ganglion blocks. In a comparative study 20 patients had traditional stellate ganglion block (SGB) and 12 patients had laser irradiation over the stellate ganglion (SGL). GaAlAs lasers of 60 mW (10 minutes of irradiation) and 150 mW (7 minutes of irradiation) were used. The number of sessions were maximum 20 over a period of one month. 60% of the patients receiving SGB reported the outcome as "excellent" or "good" while 100% of the patients in the SGL group had this rating.

3.4.25 Combination treatment

In the clinical situation, laser therapy is often used in combination with other therapies. While this is not a good research set-up, it is very often advantageous in the clinic. Laser therapy will enhance the outcome of traditional therapies.

If heat is used in combination with laser therapy, the laser treatment should come first. Heat will increase the blood flow in the tissue, thus increasing the absorption of the light in blood. The opposite then applies to cryogenic therapy.

Ultrasound is very often used in physical therapy. One study [726] has compared the effect of ultrasound, laser therapy and the two modalities in combination. The results suggest that they may counteract one another, since the outcome of the healing was better if they were used alone. This is not the result in the two following studies:

Demir [1490] performed a randomised controlled study investigating the effects of ultrasound and laser treatments on wound healing in rats. The duration of the inflammatory phase decreased with both laser and ultrasound treatments; however, laser was more effective than ultrasound, with more significant results. The proliferation phase showed, for both treatments, an increase in the level of hydroxyproline and the number of fibroblasts, as well as stimulation of the collagen synthesis and the composition. Laser treatment was again more effective than ultrasound. The wound breaking strength was significantly higher with both treatments, and no statistically significant difference emerged between the laser and ultrasound groups, although laser treatment provided a much greater increase in the wound breaking strength than ultrasound. Both treatments had beneficial effects on the inflammatory, proliferation, and maturation phases of wound healing. Both could be used successfully for decubitus ulcers and chronic wounds, in conjunction with conventional therapies such as debridement and daily wound caring. However, laser treatment was more effective than ultrasound in the first two phases of wound healing.

In another study by Demir [1491] 84 healthy male rats were divided into three groups consisting of 28 rats, the left Achilles tendons were used as treatment and the right Achilles tendons as controls. The right and left Achilles tendons of rats were traumatised longitudinally. The treatment was started on post injury day one. The US treatment was applied with a power of 0.5 W/cm^2, a pulse repetition rate of 1 MHz, continuously, 5 minutes daily. A GaAs laser was applied with a 904 nm wavelength, 6 mW average power, 1 J/cm^2 dosage, 16 Hz pulse repetition rate, for 1 minute duration. Although US, L, and combined US + L treatments increased tendon healing biochemically and biomechanically more than the control groups, no statistically significant difference was found between them. Also the researchers did not find significantly more cumulative positive effects of combined treatment.

3.4.26 Interaction with medication

It is demonstrated that laser therapy will interact with pharmaceuticals, such as steroids and NSAIDs. This is still an untapped field of knowledge where much work remains to be done. An interaction with pharmaceuticals could possibly explain why some patients react well to laser therapy whilst others are impervious. One of the first attempts to investigate this problem was done by Meersman [1278]. It was hypothesised a positive and a negative interaction between laser therapy and pharmaceuticals. The pilot research work on Achilles tendinopathy management demonstrated that various chemicals commonly used will interfere positively or negatively with laser therapy and would be a logical explanation for the intermittent and often varied results. The biostimulatory action of laser therapy is countered by the presence of NSAIDs and steroids that are non-acceptors of laser therapy, as the latter block the membrane channels and antennae pigment receptors that laser therapy relies upon. The degree of reduction and total effect is variable and determined by blood levels of the chemical and individual cell receptability. Similar actions on the cell membrane and the receptor site and bonds are caused by beta blockers, calcium channel antagonists and several of the cardiac and neurological medications. These effects have till now not often been considered in research work and are significant when a meta-analysis of the literature is made and such medications is factored in. In this case many of the 'negative studies' on laser therapy are found to not have screened and excluded for the potential of pharmaceutical counter effects. In contrast, specific chemicals are found to be positive agents for laser therapy that will increase the biostimulative effect by preparing the cell receptors and membrane to be capable of a maximal effect. This facilitatory action of laser therapy acceptors is demonstrated by Plenosol, that is photoreceptive at 660 nm, whilst ubiquinon- ferrum- and copper-based local substances that can be subcutaneously infused are 810 nm and 904 nm receptive. Clinically, the total effect is that of a two-stage process that uses a combination of local injection or cutaneously absorbed substances that can be administered or applied and then irradiated with the specific wavelength. It is also demonstrated that the use of Procaine as the local anaesthetic of choice facilitates the passage of specific photo acceptor substances into the affected tissue effectively acting as a 'taxi' whilst serving its primary purpose of local anaesthetic management. The conclusion is that, where possible, medication should be excluded or included if the maximal effect of laser therapy is to be achieved. Where research is initiated to determine the effect of laser therapy, the presence of such chemicals must be considered, then noted and factored into the statistical analysis.

Literature:

Lopes-Martins [1463] writes: Interventions with anti-inflammatory actions such as steroids and nonsteroid anti-inflammatory drugs are frequently used in the treatment of rheumatic and musculoskeletal pain. Recent studies from our and other research groups have shown that low level laser therapy also has an anti-inflammatory effect. Clinical studies have produced less homogeneous results, and non-optimal laser therapy dosage has been identified as a key factor for this. However, poor clinical results may also be caused by pharmacological co-interventions that block the antiinflammatory effect of laser therapy. In the present study, we used the classical experimental mice-model of carrageenan-induced pleurisy, to investigate if the anti-inflammatory effect of low power laser therapy could be blocked by the steroid agent mifepristone. For the intervention group, mifepristone was injected into the pleural cavity an hour prior to the carrageenan injection. Pleurisy was then induced by an intrathoracic injection of carrageenan (0.5mg/cavity), or LPS from E. coli (250 ng/ cavity) in mice. Laser irradiation (650 nm) was then carried out three times with hourly intervals at the skin of the injection site for both groups. Laser therapy was administered with a previously established optimal accumulated dose of 7.5 J/cm^2. While laser therapylaser therapy after 4 hours effectively reduced inflammation almost to pre-injection levels of neutrophil cell counts (1.11_10 (6), [95% CI: 0.41-1.82]), the anti-inflammatory effect was blocked after pre-injection of mifepristone (5.94_10(6), [95% CI: 4.83-7.04]). The implications of these findings are that steroid therapy should be avoided in conjunction with laser therapy, and that clinical studies violating this precaution, should be excluded from reviews and meta-analyses of laser therapy.

The aim of the study by Pessoa [1462] was to evaluate the effect of laser therapy on the wound healing process in the presence of steroids. Forty-eight rats were used, and after execution of a wound on the dorsal region of each animal, they were divided into 4 groups (n=12), receiving the following treatments: G1 (control), wounds and animals received no treatment; G2, wounds were treated with laser therapy; G3, animals received an intraperitoneal injection of steroid dosage (2 mg/kg of body weight); G4, animals received steroid and wounds were treated with laser therapy. The *laser emission device used was a 904 nm unit, in a contact mode, with 2.75 mW, 2.900 Hz, during 120 sec (33 J/cm²). After 3, 7, and 14 days the animals were sacrificed and the parts sent to histological processing. The results have shown that the wounds treated with cortisone had a delay in healing, while laser therapy accelerated the wound healing process. Also, wounds treated with laser in the animals treated with steroid presented a differentiated healing process with a larger collagen deposition and also a decrease in both the inflammatory infiltration and the delay on the wound healing process. laser therapy accelerated healing, caused by the steroid, acting as a biostimulative coadjutant agent, balancing the undesirable effects of cortisone on the tissue healing process.*

Fujihara [1550] irradiated rat calvaria osteoblast cells with 780 nm, 3 J/cm². The cells were grown in nutritional deficit. The anti-inflammatory agent dexamethasone was added to some cultures. The laser irradiated cultures showed faster cell growth, probably by promoting faster cell adhesion. The presence of the steroidal anti-inflammatory agent impaired cell adhesion and growth. This process, however, was reduced by the laser irradiation.

Yang Li [1135] has observed that animals in wound healing studies frequently have reacted with a negative response if anesthetics such as ketamine and ether have been used. It is speculated that there is some reagent competing against laser for the same receptor in the fibroblast.

3.5 Other considerations

3.5.1 What about collimation?

The light from a laser diode is always divergent, usually with a fan shaped beam with an angle of divergence of around 30-90 degrees and perpendicular with an angle of divergence of 5-10 degrees when it is emitted from the semiconductor crystal. If a collimating lens is placed in front of the diode, the light's parallelity can be highly increased, more or less reaching the same parallelity as the beam of a HeNe laser. This is called collimation. The beam from a laser pointer is hence collimated this way. Parallel beams are only advantageous when treating from a distance, since the light is kept together and hits a small surface. This means that we can irradiate from a distance and still achieve a high power density on a small area. If there is no collimation, this can be compensated for by holding the probe closer to the tissue. When light, parallel or not, hits the tissue, it immediately spreads unrestrainedly [429]. Light is spread downwards into the tissue, roughly in the form of a hemisphere like a Ping-Pong ball cut in half, (see Figure 3.14 “Depth of penetration, direct contact” on page 141.) So for treatment involving tissue contact, the parallelity of the beam is of no significance. (See chapter 3.5.4 “Tissue compression” on page 143.)

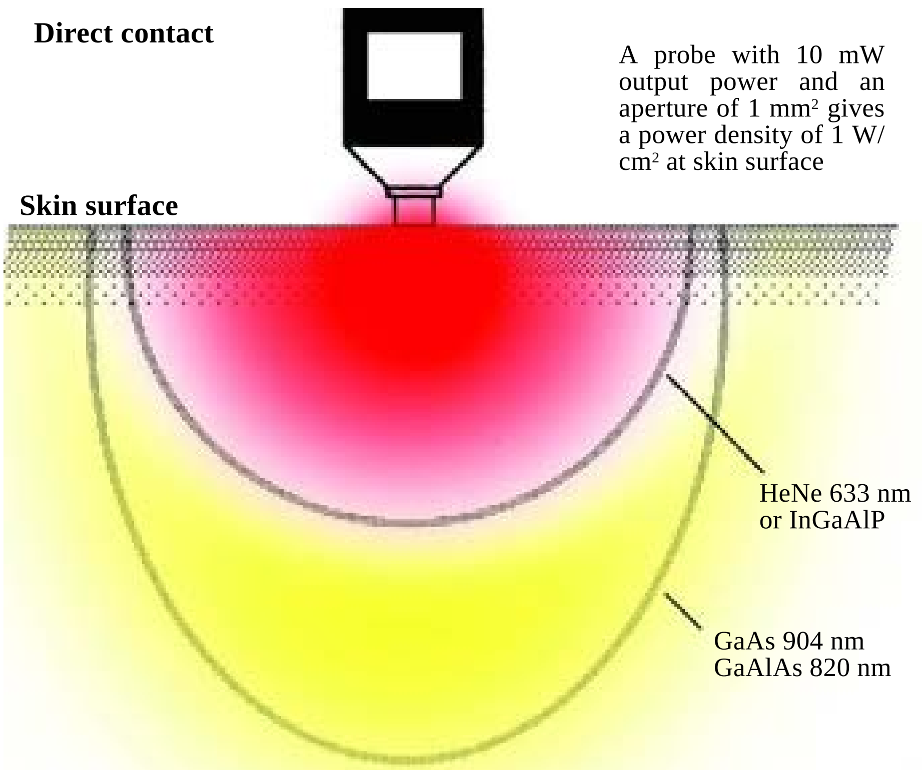
3.5.2 Depth of penetration, greatest active depth

The depth of penetration of laser light depends, as mentioned previously, on the light's wavelength, on whether the laser is superpulsed or not, and on the output power; but also on the treatment technique used. A laser designed for the treatment of humans is rarely suitable for treating animals with fur. There are, in fact, lasers specially made for this purpose. The special design feature here is that the laser diode(s) obtrude from the treatment probe rather like the teeth on a comb. By delving between the animal's hairs, the laser aperture comes into contact with the skin and more light from the laser is "forced" into the tissue.

A rough guide to effective penetration depths of continuous wave & modulated continuous wave lasers (all other parametres being equal) would look roughly like:

Visible Red (630-700 nm): 0.5-1 cm
Near-Infrared (700-800 nm): 2-3 cm
Near Infrared (800-960 nm): 3-5 cm
Near Infrared (970-990 nm): 1-2 cm
Near Infrared (990-1200 nm): 4-5 cm

Further, other factors such as power density, tissue type, tissue temperature, tissue condition, probe/applicator design, operating mode of the laser emitter, treatment technique, and so on, will determine the actual effective depth of penetration for any given laser.



The light from the laser distributes in the tissue like a ball or an egg independently if the incoming beam is parallel or divergent. This is, however, dependent on the wavelengths of the light. Short wavelengths give a smaller but fairly round ball, whilst longer wavelengths give a more egg shaped light distribution.

Figure 3.14 Depth of penetration, direct contact

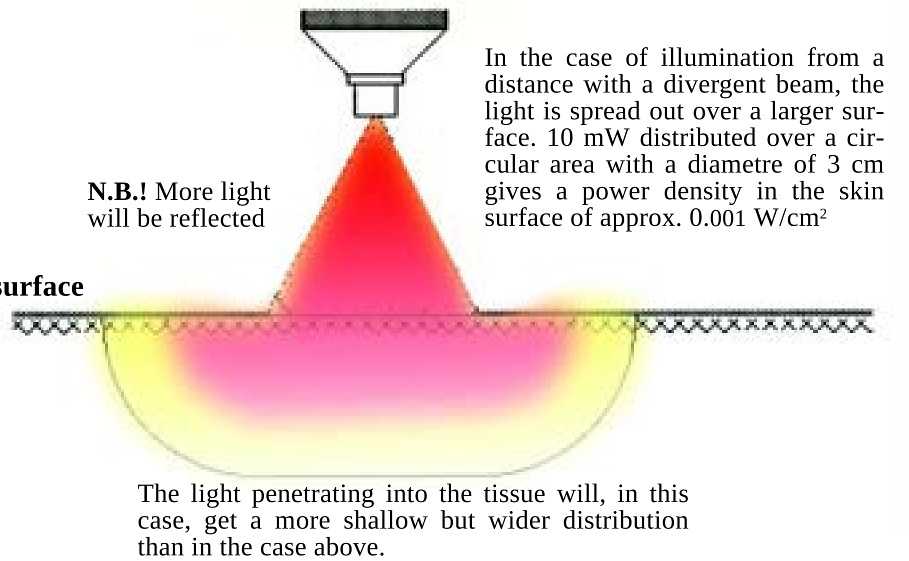


Figure 3.15 Depth of penetration, distance

3.5.3 Factors that reduce penetration

Different tissue types absorb light to different degrees. Dirty skin and dark skin reduce penetration. Unpigmented caucasian skin, absorbs about 5% of the incident energy. Adipose tissue is more transparent [1215] than muscle tissue. Highly vascularised tissue (such as muscle tissue) absorbs more than less vascularised. Haemangiomas tissue contains much haemoglobin and thus needs higher doses.

It is worth noting that laser light also can penetrate bone [26]. Bone absorbs usually not more light than muscles, and there are differences between different types of bone. It is a common misconseption that bone is stopping light as it does ultrasound. But it is not hardness that is important in this case (thick glass!) but a materials' absorption coefficient. If you have a HeNe or InGaAlP laser, let the red laser beam hit one of you teeth - you will see that it penetrates well. It can also be done with common laser pointer.

Oron (Tel Aviv University, 1996) measured the penetration of 660, 780 and 830 nm lasers through flat bone (skull or medial part of tibia of rat, 0.6-0.7 mm) and thick bone (femur of rat, 3 mm). The remaining power measured after penetration was 21%, 23%, and 14% for flat bone and 4.5% for thick bone. Denser bone, such as the bone overlapping the inner ear in humans, would reduce penetration even more. However, it can be estimated that a 100 mW source, 820 nm wavelength, placed in contact with and perpendicular to the surface of the skull delivers $>10^4$ photons per second to the cochlea.

Another factor is reflection. We can here differentiate between surface reflection and backscatter reflection. If treatment is done with a distance between the aperture of the probe and the tissue, the total loss due to reflection is 10-20%. When treating in contact with the tissue the reflection loss can be reduced by 80%.

3.5.4 Tissue compression

A factor of importance here is the compressive removal of blood in the target tissue. When you press lightly with a laser probe against skin, the blood flows to the sides, so that the tissue right in front of the probe (and some distance into the tissue) is fairly empty of blood. As the haemoglobin in the blood is responsible for most of the absorption, this mechanical removal of blood greatly increases the depth of penetration of the laser light. In the case of tissue compression, other types of cells than the blood cells will absorb a larger part of the light energy.

3.5.5 How deep does the light penetrate?

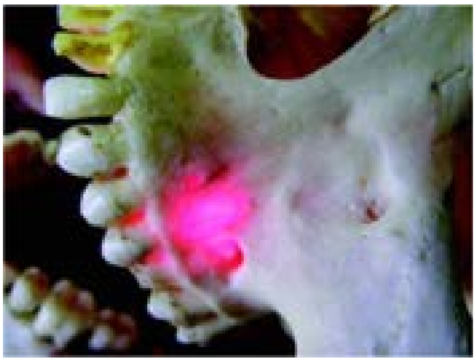


Figure 3.16 30 mW laser through dry bone

There is no exact limit with respect to the penetration of the light. The light gets weaker and weaker the further from the surface it penetrates. There is, however, a limit at which the light intensity is so low that no biological light effect can be registered. This limit, where the effect ceases, is called the greatest active depth.
N.B.: We are now talking about the direct effect of laser light on cells and not biological effects due to systemic effects from laser therapy.

For example: a HeNe laser with an output power of 3.5 mW has a greatest active depth of 6-8 mm depending on the type of tissue involved. A HeNe laser with an output of 7 mW has a greatest active depth of 8-10 mm. A GaAlAs probe of considerable strength has a penetration of 3.5 cm with a 5.4 cm (radius 2.7 cm) lateral spread [429]. A GaAs laser has a greatest active depth of between 20 and 30 mm (sometimes up to 40 mm), depending on its peak pulse output (around a thousand times greater than its average output power). If you are working in direct contact with the skin and press the probe against the skin, then the greatest active depth will be achieved.

Literature:

Byrnes [1527] made ex vivo and in vivo spectrophotometric and power transmission analyses before performing a study on the regeneration and functional recovery after spinal cord injury in rats. Optimum penetration was found between 770 and 850 nm. With 150 mW of 810 nm 6% of the power (9 mW) remained at the area of the ventral side of the spinal cord.

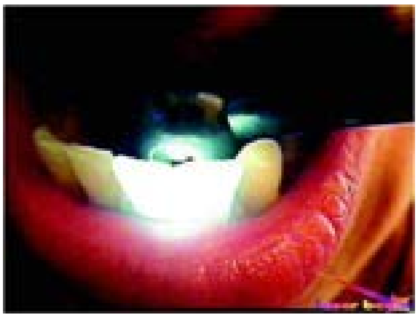


Figure 3.17 830 nm through teeth photographed with IR-camera.
Courtesy: Aldo Brugnera Jr.

Enwemeka [1770] studied the depth of penetration and the magnitude of attenuation of 632.8nm and 904nm light in skin, muscle, tendon, and cartilagenous tissues of live anaesthetised rabbits. Tissue specimens were dissected, prepared, and their thicknesses measured. Then, each wavelength of light was applied. Simultaneously, a power metre was used to detect and measure the amount of light transmitted through each tissue. All measurements were made in the dark to minimise interference from extraneous light sources. To determine the influence of pulse rate on beam attenuation, the 632.8nm light was used at two predetermined settings of the machine; continuous mode and 100 pulses per second (pps), at an on:off ratio of 1:1. Similarly, the 904 nm infrared light was applied using two predetermined machine settings: 292 pps and 2.336 pps. Multiple regression analysis of the data obtained showed significant positive correlations between tissue thickness and light attenuation. Collectively, our findings warrant the conclusions that: (1) The calf muscles of the New Zealand white rabbit attenuates light in direct proportion to its thickness. In this tissue, light attenuation is not significantly affected by the overlying skin, a finding which may be applicable to other muscles. (2) The depth of penetration of a 632.8 nm and 904 nm light is not related to the average power of the light source. The depth of penetration is the same notwithstanding the average power of the light source. (3) Compared to the 904 nm wavelength, 632.8 nm light is attenuated more by muscle tissue, suggesting that is is absorbed more readily than the 904 nm wavelength or conversely that the 904 nm wavelength penetrates more. Thus, wavelength plays a critical role in the depth of penetration of light.

Mathematical simulations and estimates from the literature suggest that the depth of penetration of laser radiation using wavelengths from 630 nm up to 1100 nm may be up to 50 mm. The aim of a study by Esnouf [2093] was to directly measure the penetration depth of a therapeutic laser in human tissue. Human abdominal skin samples up to 0.784 mm thickness were harvested by dermatome following abdominoplasty procedures. These samples were irradiated by an 850 nm, 100 mW, 24 kHz, 0.28 mm diametre *probe and the transmitted radiation measured. The intensity of laser radiation reduced by 66% after being transmitted through a 0.784 mm sample of human abdominal tissue. In this study most laser radiation was absorbed within the first 1 mm of skin.*

Further literature: [429, 1215, 2094]

3.5.6 Laser light irradiation through clothes

It has been suggested that patients can be treated with their clothes on. Taking the great absorption in skin in mind, this appears to be a bad idea, especially if the therapy is performed from some distance and with red light. A non-published experiement by the authors of this book revealed that 20 mW 660 nm laser light was reduced 100% by a thin black T-shirt, while 3 mW remained after passing a white cotton shirt. See: http://www.youtube.com/watch?v=MkGJvvWD1vw

3.5.7 The importance of the tissue and cell condition

Clinical and experimental experience shows that laser therapy has its greatest effects on cells/tissue/organs affected by a generally deteriorated condition, such as in patients suffering from some type of functional disorder, infection or injury to tissue. The light energy seems to produce the greatest benefit where it is most needed. On the other hand, experimentally induced inflammation in otherwise healthy people seems not to react quite as strongly to laser therapy [42]. One can assume that these individuals have good immune systems.

It is reasonable to conclude that some of the contradictory results reported in the literature actually stem from the fact that the above parametres have not been considered.

Literature:

Steinlechner [4] used HeNe and GaAs lasers to stimulate keratinocyte cultures. The conclusion was that laser therapy indeed stimulates keratinocyte proliferation. However, it was found that the cultures growing in a "poor" environment - 1% fetal calf serum (FCS) - were stimulated more by laser therapy than the cultures growing in a better environment - 5% FCS.

Yamamoto [604] made a similar observation. Human fibroblasts were irradiated, using two cultures. One culture was kept in a serum-starved medium and one in an FCS-containing medium. Enhanced laser effect was consistently observed in the serum-starved medium (50%) but not in the FCS medium.

Karu [180] has made an interesting observation with respect to the effects of different laser wavelengths on the chemiluminescence of human blood. Chemiluminescence (CL) is a sensitive tool used within clinical differential diagnostics to measure changes in oxidative cell metabolism. Spontaneous CL of blood from a healthy young woman was tested during a period when she happened to suffer from a cold virus on two occasions. It was evi-

dent that the effects of laser light were dependent on both the wavelength and the pulse repetition rate of the light and were mainly measurable during the growth phase of the infection, i.e. during a certain immunological status of the organism. All the wavelengths tested were effective, but 660 nm was the most effective. A pulse repetition rate of 5000 Hz was most effective. 16 Hz was ineffective.

Karu [512] summarises an experiment on the effect of monochromatic visible light sources on cells: "One can draw two conclusions from experiments with the combined action of light and redox chemicals. First, there is a strong dependence of the irradiation effect on the cell redox state at the moment of irradiation. The cellular response is weak or absent when the redox potential is optimal or near optimal and stronger when shifted. This explains why the magnitudes of cellular responses can differ markedly and sometimes be non-existent. The second conclusion is that an alteration of the redox state toward oxidation is correlated with stimulation, whereas reduction correlates with inhibition. Cells with lower than normal pH, where the redox state is shifted in the reduced direction, are considered to be more sensitive to the stimulative action of light than those with the respective parametres being optimal or near optimal. This circumstance explains the possible variations in observed magnitudes of low-power laser effects. Light action on the redox state of a cell via the respiratory chain also explains the diversity of low-power laser effects."

Ryabykh and Karu [448] went on to measure the CL in a number of healthy donors. 820 nm irradiation had no effect. However, CL was influenced by laser irradiation in patients with acute respiratory illness, blast cells in patients with haemoblastoses (820 nm) and patients with colon cancer (pulsed HeNe laser had effect - CW had no effect).

Severtsev [457] studied whether or not HeNe laser light could improve the ability of the lymphocytes to change their immunogenicity. In three blood donors out of five there was a threefold stimulation and in two cases there was no change. It is very likely that the immunological statuses of the five donors were different.

Brill [417] summarises an experiment involving HeNe irradiation of giant chromosomes: "Biologic effects of low power laser radiation depend both on the irradiation dose and on the temporal presentation of the dose. In prolonged continuous low power laser irradiation a peculiar adaptation of the biosystem is observed manifested by the disappearance of changes typical to the action of lower doses. Response of the genetic apparatus to the photo action depends on the initial functional state of chromosomes' loci. Resulting photoeffects may be manifested both by activation and inhibition of definite genome regions. There are chromosome regions particularly sensitive to HeNe laser action."

Kotani [501] irradiated experimental wounds in three groups of rats: 1) animals with induced diabetes mellitus, 2) animals treated with the fibroblast and collagen inhibitor Doxorubicin, and 3) healthy animals. Group 3 *did not heal significantly better than non-irradiated controls. However, groups 1 and 2 showed significant improvement when compared to non-irradiated animals of the same group.*

van den Brande [508] used laser doppler flowmetry to study the microcirculatory flow at the anteromedial surface of the lower leg during and after a 10-minute HeNe + GaAs application. In healthy volunteers, no change in microcirculatory flow was noted, although there was a marked increase in vasomotor activity. In vascular patients, the skin flux increased by a factor of 2.3.

Yamada [510] exposed osteoblastic cells to HeNe irradiation. No significant change was observed in the lines where the cells were in the confluent state. However, in the lines of cells in the sparse state, DNA incorporation increased 32% compared to control.

In a study by Lubart [592], it was found that the effect of a 780 nm laser on Ca^{2+} uptake by plasma membrane vesicles in the absence of ATP was much greater than in the presence of ATP.

3.5.8 The importance of ambient light

In the clinic the ambient light is not very important but when LPT is performed, the ambient light should be reasonably reduced, not to interfere with the therapeutic light. For the *in vitro* situation, the importance of regulating the ambient light is indeed important and may be more complex than first suggested.

Literature:

The effect of laser light may be partly or completely reduced by broad-spectrum light. There are few studies that investigate the benefit or detriment of combining laser irradiation with broad-spectrum or IR light. In a study by Hawkins [2087] wounded human skin fibroblasts were irradiated with a dose of 5 J/cm² using a HeNe laser, a diode laser, or a Nd:YAG laser in the dark, in the light, or in IR. Changes in cell proliferation were evaluated using optical density at 540 nm, alkaline phosphatase (ALP) enzyme activity, cytokine expression, and basic fibroblast growth factor (bFGF) expression. The optical density and ALP enzyme activity indicate that 5 J/cm² using 1064 nm in the light is more effective in increasing cell proliferation or cell growth than 830 nm in the light, but not as effective as 632.8 nm in the light. bFGF expression shows that the response of wounded cells exposed to 5 J/cm² in IR light is far less than the biological response of wounded cells exposed to 5 J/cm² in the dark or light. The results indicate that wounded cells exposed to 5 J/cm² using 632.8 nm in the dark results in a greater increase in IL-6 when compared to cells exposed to 5 J/cm² in the light or in IR. Results indicate that 5 J/cm² (using 632.8 nm in the dark or 830 nm in the light) is the most effective dose to stimulate cell proliferation, which may ultimately accelerate or improve the rate of wound healing.

In the literature, it is accepted that the first step following visible light irradiation is the formation of ROS by endogenous cellular photosensitisers. In the study by Zan-Bar [2092] sperm of ram and tilapia were irradiated with various light sources (400-800 nm white light, 660 nm red light, 360 nm blue light, 294 nm UV), and their motility and fertility rates were measured. The amount of ROS generated by irradiation was estimated using electron paramagnetic resonance (EPR) technique. Sperm taken from tilapia showed higher motility and fertility following red and white light irradiation. In contrast, the motility and fertility of ram sperm were slightly increased only by red light. A negative effect on motility and fertility of sperm of both species was obtained following irradiation with UV and blue light. The amount of ROS produced in irradiated tilapia sperm was much higher than that of ram sperm. The results show that different wavelengths differentially affect tilapia and ram sperm motility and fertilisation. The difference in response to the various light sources might be explained by the different amounts of ROS formation by ram and tilapia, which are in agreement with the physiology of fertilisation appropriate to each of these species. Based on these results, it is suggested that in vitro fertilisation in mammals should be performed in darkness or at least under red light.

3.5.9 In vitro/in vivo

Many experiments have been performed *in vitro*. As always, the interpretation of these experiments must be made with caution. We have already discussed the consequences of the “nakedness” of cells in the *in vitro* situation. Therefore, doses used in such studies are difficult to extrapolate into a clinical situation. Furthermore, we must remember that a reaction seen or not seen in an *in vitro* experiment reflects the effect of laser therapy on a single isolated cell. In the clinic, there is no single cell effect. Every cell in the body is influenced by a very complex and multipath cascade of processes at each particular moment.

3.6 Laser Therapy with high output lasers

3.6.1 Laser therapy with carbon dioxide lasers

Laser therapy is a relatively new area for carbon dioxide lasers, although papers on the subject were published as early as the mid-eighties. There are several examples of researchers using a carbon dioxide laser without realising the biostimulative effect. Some Swedish studies during the 90's illustrate this fact:

At Malmö General Hospital 506 women were treated for cellular changes in the cervix of the uterus. The tissue was removed by means of a carbon dioxide laser. Before surgery 69% of the patients had papilloma virus. After surgery only 16% of these women had any detectable papilloma viruses. This is a clear example of biostimulation with a CO_2-laser.

At the University Hospital in Lund a carbon dioxide laser was tested on psoriasis. After superficial burning, the lesion disappeared and after complete healing the skin was normal, with no recurrence *in situ* after three years. Interestingly enough, lesions not irradiated but close to the treated site also disappeared.

At Uppsala Academic Hospital, a CO_2-laser has been tested successfully for biostimulative treatment of epicondylitis. This method is also called EDL (Emitted Defocused Laser-light). It should be noted, however, that carbon dioxide lasers are not used as surgical lasers in this context; their incident energy and power density are set within the laser therapy range by spreading out the beam over such a large surface that the laser does not cause burning.

Another surprising effect of the CO_2-laser that has been demonstrated is "laser peeling", a skin treatment for wrinkles. To our knowledge, this was first presented by Abergel [51] in 1989 and in a follow-up [62] in 1992. Some years later, Chernoff [294, 295] performed over 50 exfoliations to smooth out perioral, lip, and periorbital wrinkles and scars. The thermal damage depth was between 75 and 150 µm. The result is surprisingly good and much better than what can be achieved with chemical peeling and mechanical dermabrasion. The mechanism is in part biostimulation.

Kaplan [422], one of the pioneers of CO_2-laser surgery, attributes the excellent healing and lower postoperative pain experienced with CO_2-laser surgery compared to conventional surgery to the simultaneous laser therapy effect. Laser surgery and laser therapy, Kaplan argues, should be regarded as two sides of the same coin.

The CO_2-laser can also be used as an acupuncture tool. Stimulation of acupuncture points has been carried out both with biostimulating power densities (e.g. 100 mW/cm^2) and burning/coagulating/evapourating power densities. Some clinics maintain that carbon dioxide lasers give better results on acupuncture points than HeNe lasers. As the carbon dioxide laser's beam cannot penetrate more than around 0.5 mm into tissue [296], (See chapter 11.1.8 “How deep does light penetrate into tissue?” on page 709), the effects must be due to the influence of the laser energy on the cells encountered, so that signal substances are released and then circulate in the organism. This indirectly confirms the hypothesis that conventional laser therapy has both a local effect in the area treated by laser light, and a systemic effect through the release of metabolites. It is well known that these kinds of secondary effects also occur at the traditional wavelengths of 633, 830, and 904 nm.

One advantage of the carbon dioxide laser is its high power density, which can be achieved over wide areas, thus leading to shorter treatment periods. Another advantage is that the patients also feel the heat (can even be painful) which influences the placeboeffect. The disadvantage, for the foreseeable future, will be the cost of the apparatus. Prices vary between US$ 15.000 and US$ 30.000 for equipment with similar qualities.

The fact that this form of laser therapy has, despite the cost, become popular with some doctors and veterinary surgeons is probably due to the belief of some individuals that the depth of penetration is high because of the high output power of the laser, or because it is a Class 4 instrument (i.e. only for doctors, dentists and veterinarians).

Literature:

Longo [174] compared a CO_2-laser with a GaAs laser in the treatment of acute lumbago in a double-blind study. 3 J/cm^2 was administered to both experimental groups, while a third group received sham irradiation. The two experimental groups had similar results, but the GaAs group was slightly more improved.

Galletti [307] compared the effect of a CO_2-laser and a GaAlAs laser (830 nm) on the healing of surgical wounds in the external femoral condylus of the right hind-limb knee of 12 pigs. The CO_2-laser dose was 1.5 J/cm^2 and the GaAlAs laser dose was 0.5 J/cm^2. The result was approximately the same for both laser types, but significantly better than the controls. Effects were noted down to 4 cm.

Tsai [579] irradiated a radial defect in the avascular zone of rabbit menisci. Energy densities of 50 and 100 J/cm^2 of CO_2 laser were used. A marked increase in fibrochondrocytic proliferation and regeneration of collagen fibres was demonstrated in the 100 J group.

Giavelli [638] found similar results from CO_2- and GaAs-laser when treating gonarthrosis.

Gao [823] has cured 367 persons with facial acne by using direct high-power CO_2-laser irradiation combined with low-power CO_2-laser additional therapy. The cure rate is close to 100%. It was shown that this therapeutic approach is simple. There are no scars after healing.

Nicola [824] presents the results of five years' experience in the application of CO_2 low power laser therapy treating chronic pharyngitis. 85 patients with non-specific chronic pharyngitis were elected to be treated: Group I, 40 patients, predominance of hyperaemic aspect; and Group II, 45 patients, predominance of hypertrophied aspect. Both groups were treated for eight to ten sessions. It was concluded that this method is very suitable for the treatment of chronic pharyngitis, a very common and disturbing symptom for a great number of ear, nose, and throat patients, which still lacks an effective form of therapy.

Further literature: [94, 142, 166, 173, 196, 197, 200, 236, 237, 258, 280, 296, 747, 974, 1772]

3.6.2 Laser therapy with Nd:YAG lasers

The Nd:YAG laser can also have a biostimulating effect if the dose and power density is chosen within the limits of the lasers's therapeutic window. Positive influences on bone regeneration and secondary dentine formation are just two of the effects documented [106, 202]. However, vendors of

Nd:YAG systems are often unwilling to discuss the biostimulating functions of this laser because of the controversial nature of laser therapy. Owners of Nd:YAG lasers should be aware that there is more to this type of laser than the instruction manual would have us believe.

Aphtous ulcers can be successfully treated with Nd:YAG. The energy suggested in the literature is much higher than when therapeutic lasers are used but the treatment can generally be performed without anaesthesia.

Literature:

Abergel [8] has shown that collagen can not only be stimulated by means of different doses, but that it can also be regulated, that is, both inhibited (keloids) and promoted (healing). Abergel [150] has also demonstrated a stimulating effect on human skin fibroblasts as a result of the use of Nd:YAG laser therapy.

Goldman [152] conducted a controlled study of 30 patients with rheumatoid arthritis. He found significant effects of Nd:YAG laser therapy on pain and stiffness.

Kaneko [218] has reported effects of 50 mW Nd:YAG treatment on pain relief from dry socket, paraesthesia of the lower jaw, trigeminal neuralgia, wounds on the tongue and mucous membrane, as well as pain related to TMJ disorders.

Kawamura [202] used Nd:YAG to study the effects of laser therapy on periodontal wound healing. Epithelial down-growth after a flap operation was reduced by laser therapy.

Basford [1062] performed a double-blind, placebo-controlled, randomised clinical trial on patients with low back pain. Sixty-three ambulatory men and women between the ages of 18 and 70 years with symptomatic non-radiating low back pain of more than 30 days' duration and normal neurologic examination results. Subjects were bloc randomised into two groups with a computer-generated schedule. All underwent irradiation for 90 seconds at eight symmetric points along the lumbosacral spine three times a week for 4 weeks by a masked therapist. The Nd:YAG laser emitted 542 mW/cm^2. Subject's perception of benefit, level of function, as assessed by the Oswestry Disability Questionnaire, and lumbar mobility were evaluated. The treated group had a time-dependent improvement in two of the three outcome measures: perception of benefit and level of function. These results were most marked at the midpoint evaluation and end of treatment but tended to lessen at the 1-month follow-up Lumbar mobility did not differ between the groups at any time.

Further literature: [63, 150, 151, 160, 219, 220, 243, 248, 312, 402, 610, 656, 830, 831].

3.6.3 Laser therapy with ruby lasers

The first laser of them all - the ruby laser - had almost disappeared from the world laser market when it was found that strong ruby laser pulses could be used to remove hair growth permanently. Now, more and more ruby lasers are sold worldwide.

We wish to remind readers that it was with the ruby laser that the biostimulative effects were discovered by Mester's group in Hungary. The ruby laser is quite a good laser for laser therapy, but very expensive. However, if you already have one - use it for herpes, zoster, ulcers, scars, sinuitis etc! Penetration is better than light from a HeNe-laser. If you test it, you can see that in a dark room the light pulse goes through your hand.

But before starting, it is important to set the energy density at a setting which will not burn the patient. For example, if the pulse energy (the ruby laser is always pulsed) is 5 joules, we recommend that you use a surface of at least 5 cm^2, giving an energy density of 1 J/cm^2 when the pulse hits the surface to be treated. This means that for each laser pulse fired, each cm^2 will receive a dose of 1 J/cm^2 and 3 shots on the same surface will give a total treatment dose of 3 J/cm^2.

3.6.4 Laser therapy with Er:YAG lasers

Although these lasers have been introduced into biostimulation only recently, there is evidence of the pain relieving effect of Er:YAG lasers. This was first demonstrated in the treatment of hypersensitive dentine. Most researchers have looked at the morphological changes of the dentinal tubuli and overlooked the actualy pain relieving effect.

Literature:

In the study by Zeredo [1588] the researchers tested the possible antinociceptive effect of laser irradiation when applied to a normal tissue before the onset of a painful stimulus. Male rats were used. A 1.5% formalin solution was injected into the right upper lip of the test animals (n=9) immediately after 10 min of low-power Er:YAG laser irradiation (energy: 0.1 J/cm^2 per pulse at 10 Hz). Control animals (n=9) were restrained for 10 min without laser application. The nociceptive response, i.e., the amount of time the rats spent rubbing the formalin injected area, was measured by an investigator blind to whether the animals had been laser irradiated or not. On laser irradiated rats, significantly less nociceptive behavior was observed only during the late phase (12-39 min) of the test. This result is similar to that reported for nonsteroid antiinflammatory drugs (NSAIDs) and other peripherally acting antiinflammatory agents.

Further literature: [1311, 1606, 1646]

3.6.5 Laser therapy with surgical diode lasers

High powered GaAlAs lasers are increasingly popular in dental "surgery" due to their rather small size and comparatively low price. A typical output is 3 W. Indications are minor surgery such as pocket debridement, incisions, gingival contouring, clearing of implants, perimiplantitis, removal of vascular lesions. 980 nm is a common wavelength and could probably be preferred to lower wavelengths used. The less transparent the tissue, the better the coagulating effect and the control of injuries in the surrounding tissue. A "surgical" diode laser in this range is an excllent biostimulator and some manufacturers have added a control switch, lowering the output into a traditional power output of therapeutic lasers.

Literature:
[1788-1792]

3.7 Risks and side effects

There are, of course, two sides to every story. What risks and side effects are associated with laser therapy? (We are naturally inclined to think along those lines.) We must first make it clear that the radiation we are dealing with here is visible light or infrared radiation and nothing more. The purity of the light does not in itself entail any risk - it is as dangerous as the pure tone of a flute compared with any pandemonium of the same volume.

3.7.1 The importance of a correct diagnose

Let us assume that a young person has got a pain in his knee. The knee is treated a number of times over a couple of months. Finally he is investigated by a specialist who finds a tumour in his knee. The doctor's question is: "Why haven't you come here before?"

This is not an actual case. But we give the example to illustrate the importance of obtaining a proper diagnosis before assuming that the pain is not due to cancer. It is important that the laser treatment does not cause a delay in the treatment of cancer and other serious diseases!

3.7.2 Cancer

Can laser therapy cause cancer? The answer is no. (See chapter 1.7.3 "Can electromagnetic radiation cause cancer?" on page 9.) No mutational effects have been observed resulting from light with wavelengths in the red or infrared range in doses used within laser therapy.

But what happens if I treat someone who has cancer and is unaware of it? Can the cancer's growth be stimulated? Well, the effects of laser therapy on cancer cells *in vitro* have been studied, and it was observed that they could be stimulated by laser light. However, with respect to a cancer *in vivo*, the situation is rather different. Experiments on rats have shown that small tumours treated with laser therapy may recede and completely disappear, although laser treatment had no effect on tumours over a certain size [9]. The local immune system is probably stimulated more than the tumour. See also [1, 2, 3].

The situation is the same for bacteria and virus in culture. Laser light in certain doses stimulates these, while a bacterial or viral infection *in vivo* is cured much faster after the right treatment with laser therapy.

In spite of the low risk associated with the irradiation of cancerous areas, any such area should be avoided when performing laser therapy. Only specialists should treat cancer, regardless of the type of therapy.

LPT has been shown to be effective in promoting cell proliferation. There is speculation that the biostimulatory effect of LPT causes undesirable enhancement of tumor growth in neoplastic diseases since malignant cells are more susceptible to proliferative stimuli. The study by Gomes Henriques [2514] evaluated the effects of LPT on proliferation, invasion, and expression of cyclin D1, E-cadherin, beta-catenin, and MMP-9 in a tongue squamous carcinoma cell line (SCC25). Cells were irradiated with a 660 nm using two energy densities (0.5 and 1.0 J/cm^2). The proliferative potential was assessed by cell growth curves and cell cycle analysis, whereas the invasion of cells was evaluated using a Matrigel cell invasion assay. Expression of cyclin D1, E-cadherin, beta-catenin, and MMP-9 was analyzed by immunofluorescence and flow cytometry and associated with the biological activities studied. LPT induced significantly the proliferation of SCC25 cells at 1.0 J/cm^2, which was accomplished by an increase in the expression of cyclin D1 and nuclear beta-catenin. At 1.0 J/cm^2, LPT significantly reduced E-cadherin and induced MMP-9 expression, promoting SCC25 invasion. The results of this study demonstrated that LPT exerts a stimulatory effect on proliferation and invasion of SCC25 cells, which was associated with alterations on expression of proteins studied.

This study confirms the fact that LPT can increase tumour cells in vitro, which is as expected. However, the situation in vivo is quite different and no in vivo studies have reported an increase of tumour cell proliferation when LPT has been used. The stimulation of the immune system seems to be greater than the stimulation of the tumour cells.

3.7.3 Cytogenetic effects?

In a study by Chio [456], human lymphocytes were irradiated by argon laser, HeNe laser or GaAlAs laser light in various doses. With an argon laser, there was a dose-related cytostatic effect between 30 and 300 J/cm^2. Mitosis was inhibited above 240 J/cm^2, and there was an increase in chromosome and chromatid breaks above 180 J/cm^2. As for the other two lasers, there was no significant increase in the frequency of chromosome aberrations. Doses of 0.5-1.5 J/cm^2 (GaAlAs) and 1-4 J/cm^2 (HeNe) increased mitotic activity.

3.7.4 A false picture of health

It is sometimes the case that pain disappears very quickly after a treatment session. It is then essential for the damaged tissue (e.g. an inflamed tendon) that caused the pain not to be overloaded. It is vital to inform the patient that such a false picture of health may emerge, and that the patient himself or herself is responsible for avoiding any stress to the injury. Even if the pain disappears and laser therapy shortens the healing time, the tissue must be given proper time to recover.

3.7.5 Tiredness

One "risk" associated with laser therapy is that the patient may experience extreme tiredness. This is probably due to release of metobolites, but sometimes also to the fact that the treatment eases long-standing pain. This relief allows the patient to catch up on the rest that the pain prevented him or her from getting. There are examples of trotting horses that were completely knocked out for two days after laser therapy treatment but then went back to competing as usual.

3.7.6 Pain reaction

A patient may sometimes experience pain the day after treatment. This is particularly common after the treatment of chronic complaints. It occurs because an injury is "made acute" when the process of healing starts. It is usually not a matter of an overdose. The patient should be informed of the risk of a pain reaction, that it is of a short-term nature and a positive sign. The patient may otherwise think it is some kind of "laser damage".

Except for the treatment of open wounds the risk of overdose on an individual level is actually low. Individual sensitivity should be taken into account.

3.7.7 Do high doses of laser therapy damage tissue?

Reasonable doses given in the course of laser therapy have proved to cause no macroscopic or microscopic damage to tissues. However, there has been concern about the new "high-power" laser therapy systems capable of emitting 100 – 1000 mW and more from a point source. Could GaAlAs applied to a single small spot for 3 minutes cause macroscopic damage? If not, what about 30 minutes? And what about elevation of tissue temperature? Let us have a look at some interesting experiments.

Literature:

Sasaki's [232] study was designed to evaluate concerns about possible damage to tissue following high doses of laser therapy. A 60 mW 830 nm laser was used (spot size 0.3 cm^2, power density 0.2 W/cm^2) on rat skin and subcutaneous tissue. One group received 3 minutes on one single spot per animal (36 J/cm^2), one group 30 minutes on one single spot (360 J/cm^2), and one untreated group served as control. Macroscopic and microscopic evaluations were carried out and photographic records taken. Tissue temperature was also recorded using digitised thermography. Skin temperature in the irradiated areas rose by 1.1 °C over the first 4 minutes of irradiation and then remained constant during the remainder of the 30-minute irradiation period. Macroscopically, there were no visible signs of alteration of skin *colour or texture. Histology revealed no difference in the epidermal, dermal or subdermal tissue architecture in the control specimens or in those irradiated for 3-minute or 30-minute periods.*

Calderhead [245] conducted a similar experiment, evaluating possible photothermal damage to articular membranous tissue following extended exposure to a 830 nm 60 mW laser. Two groups of rats received an incident energy of 108 J on a single joint, one group through the capsule and the other group with the capsule dissected away to allow direct exposure. A third group of animals served as control. No damage was visible microscopically, and no difference was found in the histology of the control specimens or in the indirectly or directly irradiated synovial membrane specimens.

Yoshida [1600] used GaAlAs at powers ranging from 300 to 700 mW, irradiating the stellate ganglion in rats. Exposure times ranged from 10 to 20 minutes. A slight oedema appeared 24 hours after the fifth irradiation at 700 mW. In other groups no pathological changes in the ganglion or in the immediately surrounding tissues were seen.

These three reports indicate that laser therapy does not cause damage to tissue, even when very high doses are given. Bear in mind, however, that these doses were given to healthy tissues and that only structural components in the tissues were studied.

Shefer [181] subjected rate skeletal muscle cells in vitro to HeNe laser at 180 mW/cm² (dose not stated). At four days post irradiation there were no histopathological changes as compared to non irradiated control cells. The same dose had previously been demonstrated to enhance satellite cell proliferation twofold [355]. It may be concluded that stimulative dose ranges do not seem to lead to any histopathological cell changes.

The aim of th study by Fontana [1716] was to evaluate temperature variation induced by a diode laser in periodontal repair. The temperature variation induced by a 810 nm diode laser was investigated in an in vitro study, varying the soft tissue thickness, and in an in vivo study for soft periodontal and bone tissues. The laser powers used were 600 mW, 800 mW, 1.0 W, and 1.2 W, and the light was delivered by a 300-microm fibre. The laser parametres and irradiation time used did not induce a temperature variation high enough to cause thermal irreversible damage to the periodontal tissues investigated.

The aim of a study by Ilic [1590] was to investigate the possible short- and long-term adverse neurological effects of LPT given at different power densities, frequencies, and modalities on the intact rat brain. One hundred and eighteen rats were used in the study. Diode laser (808 nm) was used to deliver power densities of 7.5, 75, and 750 mW/cm² transcranially to the brain cortex of mature rats, in either continuous wave (CW) or pulse (Pu) modes. Multiple doses of 7.5 mW/cm² were also applied. Standard neurological examination of the rats was performed during the follow-up periods after laser irradiation. Histology was performed at light and electron microscopy levels. Both the scores from standard neurological tests and the histopatho-

logical examination indicated that there was no long-term difference between lasertreated and control groups up to 70 days post-treatment. The only rats showing an adverse neurological effect were those in the 750 mW/cm² (about 100-fold optimal dose), CW mode group. In Pu mode, there was much less heating, and no tissue damage was noted. Long-term safety tests lasting 30 and 70 days at optimal 10× and 100× doses, as well as at multiple doses at the same power densities, indicate that the tested laser energy doses are safe under this treatment regime. Neurological deficits and histopathological damage to 750 mW/cm² CW laser irradiation are attributed to thermal damage and not due to tissue-photon interactions.

3.7.8 Is it only an effect of temperature?

Heating pads and lights are used a lot and the beneficial effect is uncontroversial. It has been claimed that the effects of LPT are just an effect of the increased tissue temperature. With the very low outputs used in the 80s and 90s this explanation appears to be rather amateurish. Modern therapeutic lasers can be considerably more potent and indeed an increase of 1 or 2 centigrades in the superficial areas can be measured. This may be beneficial or not, but the small elevation of the temperature is not the basis of the medical effects.

Literature:

A study by Benedicenti [1955] investigated whether diode pulsed laser irradiation enhances ATP production in lymphocytes. Aliquots of an extract of cultured lymphocytes of the Molt-4 cell line were irradiated with 904 nm, pulsed mode, 6 kHz PRR, with an average emission power of 10 mW for 60 min. A Spectra Physics M404 power metre was used to measure light intensity. Controls were treated similarly but not irradiated. The amount of ATP was measured by the luciferin-luciferase bioluminescent assay. The amount of ATP in irradiated cell cultures was 10.79 +/- 0.15 microg/L and in non-irradiated cell cultures it was 8.81 +/- 0.13 microg/L. The average percentage increase of irradiated versus control cell cultures was about 22.4% +/- 0.56% SD. This significant increase is probably due to laser irradiation; it cannot be attributed to any thermal effect, as the temperature during irradiation was maintained at 37.0 degrees +/- 0.5 degrees C. Thus the therapeutic effects of the biostimulating power of this type of laser are identified and its indications may be expanded.

A study by Stadler [2090] investigated the change in local skin temperature in black and white mice during irradiation at 830 nm. Groups of mice (n=12 in each group) were lightly anesthetised. The dorsum was shaved and a 1.0 x 0.5 cm spot was marked in the same location on each subject. Animals wereirradiated with a diode laser (CW, 830 nm, 36 mW output at 5 cm distance). Fluences of 0.0-5.0 J/cm² were delivered. Skin surface temperature was monitored by a thermal camera. Two thermocouples were placed 1 mm below the skin surface at the site of light exposure. Temperature *increased with increasing fluences of exposure. CW irradiation at 830 nm and 5.0 J/cm² fluence thus induces a small temperature increase at the surface and at 1 mm in depth. The smaller effects seen in white mice might be due in part to reflection. This suggests that the thermal effects of irradiation at 830 nm are unlikely to explain the LPT effect. However skin colour should be considered, particularly at higher fluences.*

In a study by Lanzafame [2089] pressure ulcers were created in mice by placing the dorsal skin between two round ceramic magnetic plates for three 12-h cycles. Animals were divided into three groups (n=9) for daily light therapy (830 nm, CW, 5.0 J/cm²) on days 3-13 post ulceration in both groups A and B. A special heat-exchange device was applied in Group B to maintain a constant temperature at the skin surface (30 degrees C). Group C served as controls, with irradiation at 5.0 J/cm² using an incandescent light source. Temperature of the skin surface, and temperature alterations during treatment were monitored. The wound area was measured and the rate and time to complete healing were noted. The maximum temperature change during therapy was 2.0 +/- 0.64 degrees C in Group A, 0.2 +/- 0.2 degrees C in Group B and 3.54 degrees C +/- 0.72 in Group C. Complete wound closure occurred at 18 +/- 4 days in Groups A and B and 25 +/- 6 days in Group C. The percentage of the wound closure at 14 days was 75. 4 +/- 7.2% and 77.7 +/- 5.6% for Groups A and B, respectively (NS differences). However, animals in Group C demonstrated a wound closure of 36.3 +/- 4.8%. These results demonstrate that the salutary effects of LPT on wound healing are temperature independent in this model.

To investigate the cellular mechanisms by near-infrared laser on the nervous system, Mochizuki-Oda [2020] examined the effect of 830 nm laser irradiation on the energy metabolism of the rat brain. The laser was applied for 15 min with an irradiance of 4.8 W/cm². Tissue adenosine triphosphate (ATP) content of the irradiated area in the cerebral cortex was 19% higher than that of the non-treated area, whereas the adenosine diphosphate (ADP) content showed no significant difference. Laser irradiation at another wavelength (652 nm) had no effect on either ATP or ADP contents. The temperature of the tissue was increased by 4.4 - 4.7 degrees C during the irradiation of both wavelengths. These results suggest that the increase in tissue ATP content did not result from the thermal effect, but from a specific effect of the laser operated at the 830 nm wavelength.

3.7.9 Protection against radiation injury

The radio-protective effect of LPT was actually one of the observations made by McGuff already in 1964 [1853-1859].

Literature:

Podolskaya [366] has used HeNe laser on post-radiation reactions and injuries in lip skin and mucous membranes (post-radiation heilitis). The method has been more successful than previously used medical treatments.

There were no complications in the laser group, while the traditionally treated group had several allergic reactions and re-operations. The pace of epithelialisation was 7 mm/week in the HeNe group, as compared to 4.1 mm/ week in the control group.

Popova [147] studied the effects of HeNe laser light on the healing of muscle tissue after irradiation with 10 Gy roentgen. The muscle tissue of rats was removed, irradiated with X-rays and re-transplanted. Improved healing compared with the control group was observed whether laser light was administered before or after the transplant.

The effect of HeNe laser pre-irradiation on UVA (343 nm)-induced DNA damage in the human B-lymphoblast cell line NC37 was investigated by Dube [1773], using the comet assay. HeNe laser pre-irradiation was observed to result in a dose-dependent decrease in UVA-induced DNA damage. This effect was also found to be dependent on the incubation period between HeNe laser pre-irradiation and the UVA exposure. Whereas the control cells with a higher DNA damage point to an initial ability of faster repair, both the control and the HeNe laser pre-irradiated cells subsequently show the same rate of DNA repair. The results suggest that HeNe laser irradiation protect the cells from UVA-induced DNA damage primarily through an influence on processes that prevent an initial DNA damage.

HeNe laser pre-irradiation-induced protection against UVC damage was investigated in wild-type E. coli K12 strain AB1157 and its isogenic DNA repair mutant strains. At a dose of 7 kJ/m^2, pre-irradiation was observed by Kohli [1774] to induce protection in recA proficient strains at both the irradiances investigated (2 and 100 W/m^2). However, at the same dose (7 kJ/m^2), while no protection was observed at 100 W/m^2 in the recA- strain, some protection appeared to be there at 2 W/m^2. Mechanistic studies carried out on these strains at the two irradiances suggest that, whereas the protection observed at 100 W/m^2 is mediated by singlet oxygen that observed at 2 W/m^2 is not. Further, the fact that protection at 100 W/m^2 was observed only in recA proficient strains suggests that it may arise due to the induction of DNA repair processes controlled by the recA gene. The latter may arise due to the oxidative stress produced by singlet oxygen generated by He-Ne laser irradiation. In contrast, the protection observed at 2 W/m^2 appears to be independent of the DNA repair proficiency of the strain.

Kohli [1775] observed that pre-irradiation with a helium-neon laser induces protection against UVC radiation in wild-type E. coli strain K12AB1157. The magnitude of protection was found to depend on the helium-neon laser irradiance, exposure time, and period of incubation between helium-neon laser exposure and subsequent UVC irradiation. The optimum values for dose, irradiance and interval between the two exposures were found to be 7 kJ/m^2, 100 W/m^2 and 1 h, respectively. The possible involvement of singlet oxygen in the helium-neon laser-induced protection is also discussed.

A study was made by Voskanian [1776] of the combined effect of laser radiation (helium-neon laser) and X-rays on bacteriae of different genotypes. The sensitivity of cells to X-rays was decreased by pre- and post-irradiation with laser. In the latter case, the radio-modifying effect of laser was more pronounced.

The combined effect of 532 nm laser radiation and alpha-particles on survival of Escherichia coli (AB 1157) was investigated by Voskanian [1777]. The sensitivity of cells to alpha-particles was decreased by pre- and post-irradiation with laser.

In an experiment by Karu [1778] monolayer of HeLa cells, at the stationary phase of growth, exposed to He-Ne laser radiation (632.8 nm; 100 J/m^2*) either 5 min or 60 min prior to gamma irradiation (0.1-10 Gy; 6.75 Gy/min), or 5 min after irradiation has been investigated. With a 5-min interval between irradiation sessions (both sequences) the survival curves are virtually the same as those for gamma-irradiated cells only. With He-Ne laser radiation delivered 60 min before gamma irradiation with doses exceeding 5 Gy, a fraction of radioresistant cells is identified whose D0 is almost twice as high as D0 of basic cell mass (3.6 and 1.7 Gy respectively. The survival curve becomes a two-component one. A hypothesis is proposed that HeNe laser radiation activates, in some cells, the processes that promote the repair of radiation*

Further literature: [1081, 1812, 1824]

3.8 How to measure effects of laser therapy

In many "alternative medical therapies", the effects are measured by asking the patient before and after "How do you feel?", and if, after therapy, the patient says "Much better!", the therapy is considered effective. In the case of laser therapy, several biological treatment effects can be studied by means of objective detection methods rather than subjective evaluations.

3.8.1 Thermography

One such method is thermography. With this technique, the temperature distribution on a surface is presented as a picture in which the different temperatures are shown in different colours (a "colour-coded" image). Thus, a change in blood flow can be detected second-by-second and minute-by-minute after a laser exposure.(See thermograpy pictures on page 282-283.)

Literature:

Kamikawa [319] used three different types of laser in a group of pain patients. Apart from irradiating the painful area, distant acupuncture points were used. The three lasers were: Nd:YAG of maximum 200 mW, GaAlAs 10 mW, and GaAs 10 mW. The laser beam focus was 1 mm^2*. The thermographs showed a remarkable circulatory increment, extending in a wide area around the irradiated spots. Heat production in the irradiated spots disappeared* *soon after therapy, but the circulatory increment lasted for a while and pain was relieved. In a patient with Raynaud's disease, recordings were made at different room temperatures. At a room temperature of about 18 degrees, vascular response was easily evoked by laser therapy. At a room temperature of around 14 degrees, peripheral vasodilatation reluctantly appeared under prolonged irradiation. Fingers were used to illustrate the effect. Stimulatory effects could only be seen in the irradiated fingers. When a 150 mW Nd:YAG was used for three minutes on a spot, the temperature elevation was 3 degrees. The effect lasted for a few hours. This patient was given forty treatments, and his symptoms were reduced the following winter without further treatment.*

Bradley [117] used thermography to examine the difference between the effect of needles and a GaAs laser on acupuncture points. Both needle and laser acupuncture produced an area of raised thermal emission at the site of stimulation. The effect was somewhat slower when initiated by a laser (2-4 minutes) than with needles (immediate).

Obata [185] studied the effect of 30 mW GaAlAs on a group of patients with diagnosed rheumatoid arthritis. Thermography was used on the irradiated hand to check the possible correlation between pain relief and thermographic response. A VAS scale was used to assess the degree of pain relief. Patients reacting with an immediate decrease in temperature had the best pain relief.

Makihara [1769] reports that his results suggested that low-level laser irradiation had a long-lasting effect on facial cutaneous tissues. Nine healthy subjects underwent irradiation using the continuous wave setting of a CO_2 laser with a power output of 1.0 W. The laser tip was positioned 10 cm above the skin over the right TMJ area for 10 min. The actual fluence on the facial surface was 7.64 J/cm^2. Variation of the facial temperature was evaluated by using thermography. The facial temperature 10 min after stopping irradiation was higher than that after 10 min of irradiation applied to the opposite side. The warmer area was found not only over the TMJ area but also over the temporal area, forehead area, and eyelid area on both sides.

Further literature: [126, 232, 189, 478, 495, 1208, 1246, 1249, 1659, 2065].

3.8.2 Magnetic resonance imaging

This is another objective method of quantifying the effect of laser therapy tissue repair.

Schaffer [904] explored the effect of a diode laser (780 nm) on normal skin tissue. Time-dependent contrast enhancement was determined by magnetic resonance imaging (MRI). In the examinations, six healthy volunteers were irradiated on their right planta pedis (sole of foot) with 5 J/cm^2 at a power density of 100 mW/cm^2. T1-weighted magnetic resonance imaging was used to quantify the time-dependent local accumulation of Gadolinium-DPTA, its actual content in the local current blood volume as well as its dis-

tribution to the extracellular space. Images were obtained before and after the application of laser light. When laser light was applied, the signal to noise ratio increased by an average of 0.35 (range 0.23-0.63) after irradiation according to contrast-enhanced MRT. According to the authors, it can be observed that, after biomodulation with light of low energy and low power, wound healing improves and pain is reduced. This effect might be explained by an increased blood flow in this area. Therefore, the use of this kind of laser treatment might improve the outcome of other therapeutic modalities such as tumour ionising radiation therapy and local chemotherapy.

3.8.3 High resolution digitised ultrasound B-scan

This is yet another method of objectively measuring the effect of laser therapy in wound healing, described by Dyson [923].

3.8.4 Tensile strength

Asencio-Arana [148] examined the strength and collagen concentration of high-risk anastomosis in the colons of rats after endoscopic irradiation with HeNe laser. The results showed that repeated irradiation (1.9 J/cm^2) with HeNe laser light increased the tensile strength of the anastomosis by almost 100% by the fourth day after the operation. An equivalent experiment with 6.4 J/cm^2 brought about significantly increased strength. The difference in collagen concentration, however, did not reach a significant level.

There are several positive studies on tensile strength. Braverman [50], Lyons [462], and Riendeau [68] used HeNe, while Enwemeka [463] used GaAs and Stadler [954] GaAlAs.

3.8.5 Other objective methods

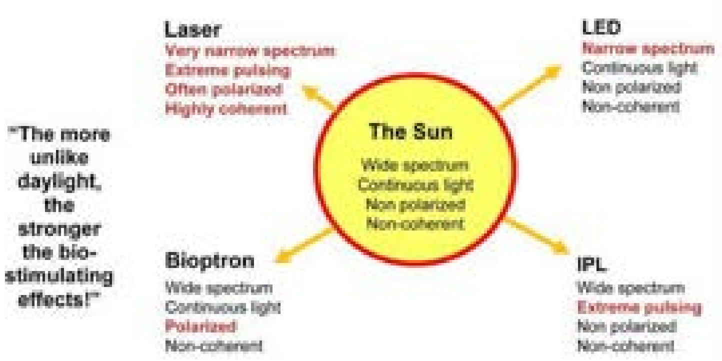
Other examples of objective methods are measurements of nerve conduction velocity, nerve action potential, chemiluminescence of blood, the study of vascularisation by means of a microscope [35], and the secretion of metabolites. Grip strength measurement is yet another method [2110].

3.8.6 Does it have to be a laser?

A good point - does it have to be a laser? Could we use a normal torchlight instead? Of course we could, but we would not achieve the same biological effects as with a laser. It is known, see chapter 11.1 “Are the biostimulative effects laser specific?” on page 698, that all light affects the living organism, but in a number of studies in which the effects of light from various sources have been compared, the laser light is shown to give the strongest effect.

Polarised wide band light (i.e. incoherent but polarised light) will indeed have a fair effect on "naked" tissues such as open wounds and mucous membranes, and, of course, on tissue *in vitro*. This has been demonstrated in early studies by Mester [23], Kana [204] and Marín [498]. However, polarisation is lost very soon after the light enters the tissue [1192]. Thus, only superficial structures will react to polarised light. If you are interested in the details and more literature, you can read more in Chapter 11.

Different light sources compared to the sun. They all create biostimulative effects under certain circumstances, but the lasers give the strongest biostimulation. Combining different lasers in one plume or combining lasers with LEDs means that you have taken a step towards daylight (broader spectrum).



"The more unlike daylight, the stronger the biostimulating effects!"

Figure 3.18 The sun

Literature:

The effect of HeNe and monochromatic red incoherent light on the protein and glycose metabolism in hamsters was studied by Onac [447]. Both light sources had a stimulative effect but the effect of incoherent light (peak at 618 nm) was lower.

More reading obout LEDs in Chapter 6.

3.8.7 FDA (Food and Drug Administration)

The status of laser therapy in the United States is formulated on the web site of the FDA:

Biostimulation lasers, also called low level laser therapy (LLLT), cold lasers, soft lasers, or laser acupuncture devices, were cleared for marketing by FDA through the Premarket Notification/510(k) process as adjunctive devices for the temporary relief of pain. These clearances were based on the presentation of clinical data to support such claims. FDA will consider similar applications for these and other claims with the decision to require clinical data being made on an individual basis, taking into consideration both the device and the claim. Please note that FDA law and regulations contain provisions that permit limited distribution of unapproved devices for use in clinical investigations. There are numerous clinical investigations being conducted in this and other countries to determine safety and efficacy with these devices for the intended uses that are proposed.

Certain unapproved, nonsignificant risk Class III medical devices, including biostimulation lasers, may only be distributed in the U.S. to individual practitioners who have approval from an Institutional Review Board (IRB) for the investigational clinical use of the device, or to investigators participating in a study under an Investigational Device Exemption (IDE) approved by the Center for Devices and Radiological Health (CDRH), as *specified in the Code of Federal Regulations (CFR), 21 CFR 812. Even with IRB approval, a sponsor must comply with IDE requirements such as monitoring investigations, maintaining records, making reports, and complying with prohibitions on promotion and commercialisation of investigational devices. The investigators would have similar responsibilities, also covered in 21 CFR 812.*

A few lasers have received FDA clearance, each one for a specific indication. Other laser manufacturers have used the old approach of several LED manufacturers, i.e. to have the laser approved for "heat therapy". The use of heat in the treatment of musculo-skeletal conditions is non-controversial and therefore manufacturers of LEDs and lasers can apply for clearance from the FDA, not for biostimulation but for topical heat therapy. The clearance makes it possible for the manufacturers to sell their equipment, but not to make any medical claims of biostimulation. Thus, an "FDA approval" is a rather vague description of the scientific base of the equipment.

3.8.8 How well documented?

A substantial body of scientific documentation is required for a new treatment method to be accepted by the medical community, which is of course positive. However, more than 30 years' clinical experience without any reports of significant side effects or injury should suffice for laser therapy not to inspire fears of unknown side effects. Over 3.500 research reports are not that many in this context, but neither are they negligible. However, do we need to know everything before we begin to use a method, if we know for sure that it is not dangerous?

Let us make a comparison with the world's most widely used medicine: acetylsalicylic acid. It has been used for generations, as its pain-relieving and antipyretic properties could be easily observed. However, the theory that acetylsalicylic acid works by alleviating pain centres in the brain has been abandoned in recent years. It is now believed that it inhibits the production of some prostaglandins. It has also been discovered recently that the substance has a positive effect on vascular illnesses. In any event, empiricism has held sway here. We do not know exactly how laser therapy works either, but whoever decides to put it to the test in a clinical environment will soon see that it works.

We can compare laser therapy with a description of NSAID (non-steroidal anti-inflammatory drugs) in a medical book. This group of pharmaceuticals for the treatment of osteoarthritis is described as follows:

"*NSAID has a beneficial effect on inflammation and reduces morning stiffness, and alleviates swelling and pain in the joints. In spite of this, there is no proof that the substances affect the course of the illness, or that they can prevent erosion of the cartilage and joints. The clinical effects of NSAID are usually obtained within a week. If no effect is noted, it can be worthwhile to* *try another substance within the NSAID group, as patients show individual sensitivity to closely related substances.*"

If we substitute "laser therapy" for "NSAID" and "laser" for "substance", those who work with biostimulation will recognise the situation.

"*Laser therapy has a beneficial effect on inflammation and reduces morning stiffness, and alleviates swelling and pain in the joints. In spite of this, there is no proof that the laser therapy affects the course of the illness, or that it can prevent erosion of the cartilage and joints. The clinical effects of laser therapy are usually obtained within a week. If no effect is noted, it can be worthwhile to try another laser within the laser therapy group, as patients show individual sensitivity to different laser wavelengths.*"

Both the statements above are true and documented, but only one is generally accepted. It is interesting to quote the foreword of the Master Thesis by Bjordal [732]: "First I was surprised by the scant evidence in favour of NSAID or steroid injections in shoulder tendinitis/bursitis and lateral epicondylalgia. Next I was surprised to find that the evidence in favour of laser therapy was at the same level both in clinical effect and statistical power."

It is interesting to note that Bjordal [1456] has published a meta analysis on the effect of non-steroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors in osteoarthritic knee pain in 2004. The negative outcome of this analysis had great media coverage. However, there was hardly any media coverage when the same group of evaluators presented scientific evidence enough to make laser treatment of osteoarthritic knee pain reimbursable and accepted as one out of three recommended therapies in Norway.

3.8.9 Confused?

Anyone who studies the literature carefully can become confused. Some wavelengths achieve the best effects on this and that, while others have poorer effects or none at all. Some doses lead to beneficial effects, but when the dose is increased, the effects wear off. If we treat a condition, some of the parametres we want to influence may be affected, but perhaps not all. If we administer treatment from a distance, we do not get the same effect as if we treat in contact or with pressure. Some frequencies are said to produce effects on pain, others on oedema. What are we to believe? And what do we do to find the best dose, wavelength, etc.?

There is still much to learn in the field of laser therapy, and for the time being we must be satisfied with the knowledge that we have. This is often a combination of clinical experience with a degree of scientific foundation. The biological effects we produce can, in any case, be seen as an empirical mean value effect, and as long as this entails concrete and positive results we can be satisfied with this rather rigid treatment model. In the future, people are likely to think that we used laser light in a primitive fashion - but for the time being, we must content ourselves with the fact that laser therapy really works and has no harmful effects.

Is the use of laser therapy, then, only a job for trained scientists? Hardly! As usual, reality is rather more difficult than the producers of glossy brochures would have us believe, but in practice it is a lot easier than this book sometimes implies. Anyone with medical knowledge can successfully use laser therapy after an introductory course. You do not need to know everything to be a good therapist, but the more you learn the greater the success you will encounter in your day-to-day work.

3.8.10 The funding of research

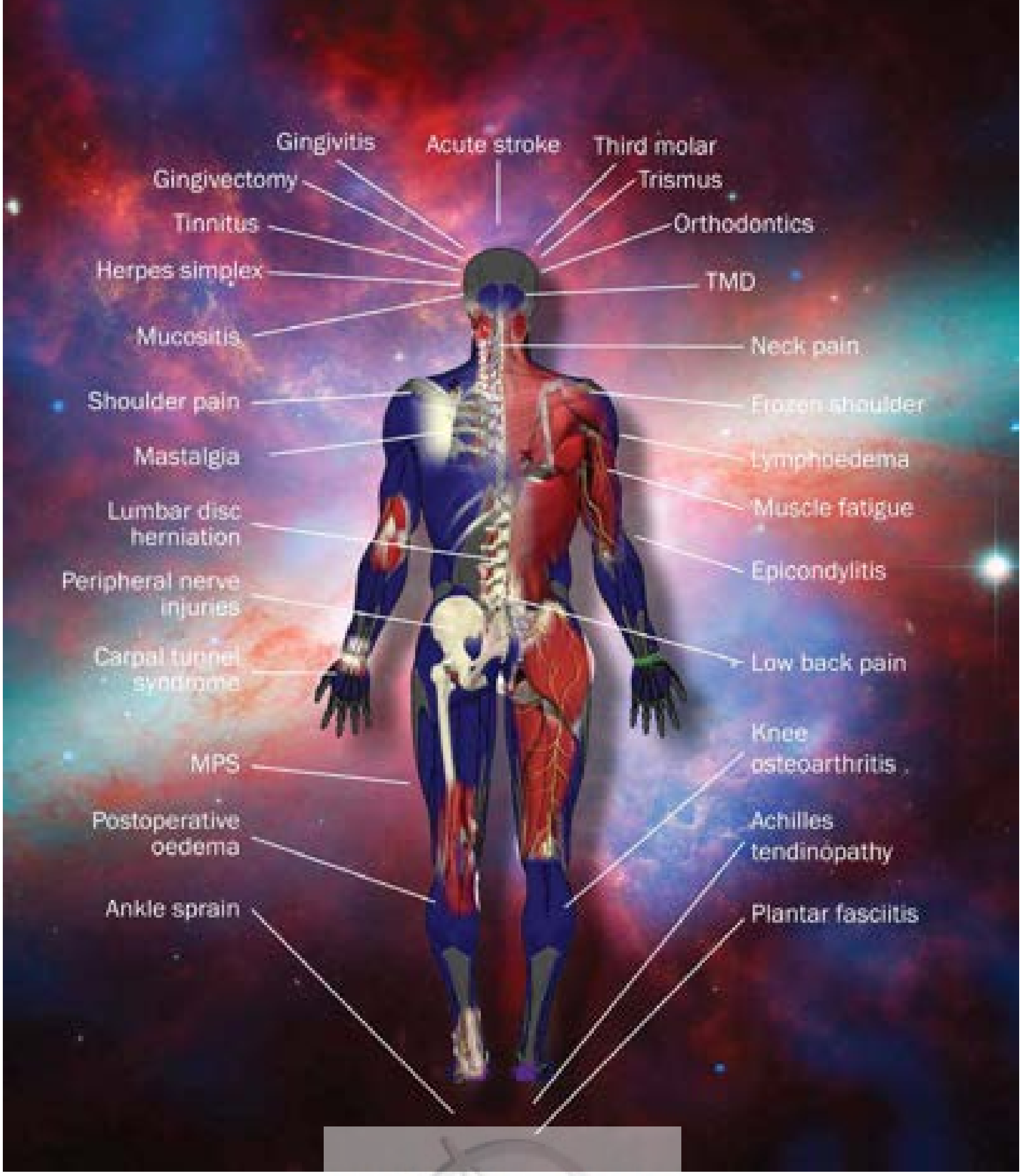
It is now and then suggested that manufacturers of laser therapy equipment should prove their claims by financing research. While quite a few of the manufacturers actually have used their scarce resources to do precisely that, it is not reasonable to expect much such funding. There is no patent on laser therapy equipment, so any valuable information found in research will be available to every manufacturer on the market. Funding pharmaceutical research is quite a different matter. Pills can be patented.

3.8.11 As time goes by

It must be stated again that time in itself is an important parameter in LPT. The cells need low energies over long time to accelerate. The World Association for Laser Therapy recommends a minimum time of 20 seconds for each point. To achieve wound healing and reduction of the inflammatory process, low output power and long time is more effective than high output power and short time. Long time is not only optimal for the local reaction but also allows systemic effects to work. From a clinical point of view it is tempting to take a short-cut to save time, but the clinical outcome will be different. Holding a laser pen can be rather boring. But treatment time can be shortened if initially a proper diagnosis is made, if the pathological location is identified and if the laser is used with pressure, as described elsewhere in this book.

Therapists should have in mind that the energy needed to reach the intended target is related to the depth of the target and the tissue between the skin and the target. This is obvious for open wounds and small joints where the target is superficial. Large joints need much more energy and targets located under muscles require a lot before the target is saturated with the intended energy. For the latter indication powerful Class 3B lasers are very useful, whereas laser below 100 mW can achieve better results for more superficial conditions, provided time and patience allow. There are situations when higher energies can be used initially in order to inhibit pain to facilitate walking and training. Once the patient has become more mobile, lower energies should be used to stimulate the healing process.

Chapter 4 - Medical indications



Medical and dental indications are often interrelated. In the following section, we have provided cross-references where the indication is applicable to both. Relatively little commentary is provided on the various indications. Instead we have selected some studies, letting their contents speak for themselves. We have included some indications for which the documentation is weak, in hopes of inspiring future research.

When doses in quoted *in vitro* studies are to be extrapolated for clinical use, several things must be remembered. Therefore, we have limited the text to quoting whatever is stated in the report. Indeed, we have the feeling that some authors have not understood the difference between “Joule” and "J/cm^2". And keep in mind that a high value for J/cm^2 does not necessarily mean that the energy applied was high, maybe only that the fibre was thin. The best way of gaining information about suitable dosages for musculoskeletal conditions is to check the recommendations of the *World Association for Laser Therapy* found on http://waltza.co.za. With more than 2500 studies quoted, we have not always been able to go to the original papers and extract all the parameters (if at all documented). Care should therefore be taken in the interpretation of abstracts. Positive as well as negative outcome depend on the parameters - “it is all in the parameters”.

In the following text, we have included some personal comments in the scientific abstracts. These are marked in **bold** text.

4.1 Who and what can be treated?

It is not unusual for therapists to ask: “Can I treat this with LPT?” As soon as we hear the question “Can I treat ...”, we can answer: “Yes”! LPT is a completely safe treatment as long as it is done with lasers up to a few hundred milliwatts. But we always point out the importance of having a reliable diagnosis - a diffuse pain can be due to cancer, ilius or ...

However, the correct question is not “Can I treat that?” but “Can that be treated?” It is not true that anyone successfully can treat anything; a combined knowledge of medicine and LPT is mandatory for good clinical results. With few exceptions, the worst thing that can happen is that nothing happens. In the following text, evaluations of the application of LPT for various indications will be given. These recommendations are mainly based upon the available scientific literature, but also upon our own experience and the experience of our broad network of therapists. Many indications for LPT are not yet “invented”. Still, some of them are being used with success, even though no studies have been published. However, in this book we have restricted ourselves to those indications actually found in the literature, even though the scientific quality in some cases is low.

Since LPT works by stimulating the natural cellular processes, it is easy to imagine many new indications documented in the near future.

4.1.1 Acne

Acne is one of the oldest indications for LPT. HeNe laser has been used by beauticians for more than 25 years and has been reported to be effective in combination with traditional therapies such as dermabrasion. Recent studies using expensive dye lasers have had great media exposure, but do not really generate any new knowledge. In these studies, the possible effects on the microbes are discussed; however, the important biostimulatory effect is not recognised by some of these authors. There is a lot of anecdotal reports on acne and therapeutic lasers but hardly anything published. Although the scientific evidence is poor, LPT for acne can be recommended. Not only because it reduces the acute symptoms, but also because it reduces the risk of permanent scarring.

Literature:

Webb [615] wanted to test the claim that LPT could prevent or improve previously created hypertrophic scar tissue. A 17 mW 660 nm laser diode was used at dosages of 2.4 or 4 J/cm². Two cell lines derived from hypertrophic scar tissue (HST) and normal dermal tissue explants (NDT) were irradiated and a cell count was taken. The irradiated hypertrophic cells exhibited significantly higher cell counts than control on days one to four for HST and days one to three for NDT.

Seaton [1328] treated acne vulgaris using a low level pulsed dye laser. One single irradiation was given to 31 patients and sham irradiation to 10 patients. After 12 weeks, acne severity (measured by Leeds revised grading system) was reduced from 3.8 to 1.9 in the laser group and 3.6 to 3.5 in the sham group. Total lesion counts fell by 53% in laser patients and 9% in controls, and inflammatory lesion counts reduced by 49% in laser patients and 10% in controls. The most rapid improvements were seen in the first four weeks after treatment.

In a study by Hou [2041], 186 patients with severe acne were selected from the out-patient department in the hospital. The sex ratio was 1:1.5 (male:female), age ranging from 17-58 years old. Before treatment, all cases were scored according to a 4-point assessment schedule, and those with serious heart problems, chronic infectious disorders and long-term use of corticosterone drug were ruled out of the trial. A sham placebo and single antibiotic groups were carried out throughout the trial. The laser treatment parameters were 810 nm, power adjustable 5-1200 mW, 4-8 J/cm². Every treatment included pointing around loci for 5 minutes per point and locally lesion lighting 10 minutes per area, and a course consisted of at least six treatments with the programme once a day. Then, the therapeutic trial was assessed after two courses of the aforementioned schedule were completed. The mixed remedy of both LPT with antibiotic formula produced better response, total effective rate 96.45 %, better than the sham placebo and single antibiotic control groups. Meanwhile, it also showed less scar formation *and hypopigmentation or even less skin whitening than both control groups did.*

In a study by Aziz-Jalali [2449], two different wavelengths (630 and 890 nm) were evaluated in treatment of acne vulgaris. This study was a single-blind randomised clinical trial. Patients with mild to moderate acne vulgaris and age above 18 years and included were treated with red (630 nm) and infrared (890 nm) on the right and left sides of the face respectively, twice in a week for 12 sessions, and clinically assessed at baseline and weeks 2, 4, 6, and 8. Twenty-eight patients participated in this study. Ten weeks after treatment acne lesion were significantly decreased in the side treated by 630 nm but this decrease was not significant in the site treated by 890 nm.

Further literature: [62, 833, 958, 2230]

4.1.2 Allergy

Allergy is yet another example of an indication with poor scientific backing. We still dare to recommend the use of LPT. Not only because it is safe, but because we have seen it work well. Allergy is an increasing problem worldwide and prolonged intake of pharmaceuticals is yet another problem to tackle. Temporary relief from seasonal pollinosis is an excellent indication, especially if the patient can use a home care laser.

Literature:

Takeyoshi [1052] has treated patients suffering from allergic rhinitis with ganglion blocks. In a comparative study 20 patients had traditional stellate ganglion block (SGB) and 12 patients had laser irradiation over the stellate ganglion (SGL). GaAlAs lasers of 60 mW (10 minutes of irradiation) and 150 mW (7 minutes of irradiation) were used. The number of sessions was maximum 20 over a period of one month. 60% of the patients receiving SGB reported the outcome as "excellent" or "good" while 100% of the patients in the SGL group had this rating.

Ailioaie [981] and Tulebaev [555] report positive effects on allergic rhinitis using LPT.

Ailioaie [1204] reports promising results in the laser treatment of children's allergic purpura. This condition, of unknown aetiology, is characterised by migratory polyarthralgia or polyarthritis, abdominal pain, vasculitis of the small vessels and in the kidney. Conventional therapy consists of NSAIDs to control subjective problems, antibiotics when indicated and corticosteroids in acute phases. The prognosis for recovery is generally good, though symptoms frequently (25-50%) return over a period of several months. In the Ailioaie study, 31 children aged 2-16 years were divided into two groups (15/16) after clinical and laboratory tests. One group was given conventional therapy whereas the other was treated with a laser scanner of 670 nm (50 mW) and 830 nm (300 mW) nm in combination, 4-10 J/cm^2. Scanning was performed daily for 21 days. The clinical outcome was good in both groups but in the laser group the improvement was spectacular during *the first 10 days and all final scores measured were better in the laser group. Hematuria, indicating renal involvement, was noted in 18.75% of the non-laser treated children.*

Seventy seven patients suffering from rhinoconjunctivitis were randomly assigned by Albu [2283] to the two treatment groups: Group A (phototherapy) and Group B (azelastine). Subjective and objective outcomes were represented by changes in Total Nasal Symptom Score (TNSS), Quality of life scores (Rhinoconjunctivitis Quality of Life Questionnaire - RQLQ), and nasal resistance. The study demonstrated that both azelastine and intranasal phototherapy are able to significantly improve TNSS, including individual nasal symptoms. Nevertheless, LPT reduced nasal obstruction better than azelastine. Both treatments were highly effective in improving RQLQ scores overall and in seven separate domains.

A study by Lee [2284] was intended to evaluate the safety and efficacy of LPT of a 650 nm laser irradiation system in perennial allergic rhinitis patients. This clinical trial was an open-label, single-center study with 42 perennial allergic rhinitis subjects. Following laser irradiation in the nasal cavity with a laser irradiation system, the efficacy at weeks 1 through 4 was determined. The symptoms were scored with four parameters (nasal obstruction, rhinorrhea, sneezing and itching) before and after illumination of the laser, and the total score was recorded. A survey of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was conducted by patients before and after treatment. Following treatment, significant improvement in the clinical symptoms of nasal obstruction, rhinorrhea, sneezing and itching was reported by 68% of perennial allergic rhinitis patients. The overall RQLQ scores significantly improved by 45% from the baseline with the treatment after 4 weeks. These results indicate that phototherapy is an effective modality for treating perennial allergic rhinitis and is another option in the steroid-free management of immune-mediated mucosal diseases.

The study by Choi [2442] was designed to investigate the effects of LPT on experimental allergic rhinitis (AR) models induced by ovalbumin. Twenty-four mice were divided into 4 groups: normal, control, low, and high dose irradiation. Low and high dose LPT (30 mW, 658 nm) were irradiated once a day for 7 days. Total IgE, cytokines concentrations (IL-4 and IFN-alpha), and thymus and activation regulated chemokine (TARC) were measured. Histological changes in the nasal mucosal tissue by laser irradiation were examined. LPT significantly inhibited total IgE, IL-4, and TARC expression in ovalbumin-induced mice at low dose irradiation. The protein expression level of IL-4 in spleen was inhibited in low dose irradiation significantly. IL-4 expression in EL-4 cells was inhibited in a dose dependent manner. Histological damages of the epithelium in the nasal septum were improved by laser irradiation with marked improvement at low dose irradiation. These results suggest that LPT might serve as a new therapeutic tool in the treatment of AR with more effectiveness at low dose irradiation.

Further literature: [350, 1052, 1205]

4.1.3 Antibiotic resistance

Some of the readers of this book would probably not be alive if penicillin had not accidentally been discovered in 1928. Or at least they would have had fewer children and relatives alive. The use of antibiotics on a large scale did not start until the mid 40ies. You and me, then, have lived with it and taken it for granted. But no longer! The bacteria are fighting back and we are now practically defenceless against a growing number of bacterial resistance. New thinking is needed, and maybe also old thinking, from the days with no antibiotics. According to a Swedish newspaper report, 100.000 US citizens and 25.000 Europeans die prematurely due to lack of effect of antibiotics. Not going to get lower.

Among the possible new weapons in the war against antibiotic resistance is laser phototherapy (LPT). Shouldn't surprise anyone. After all, the first Nobel Prize in medicine was rewarded for light therapy. Light is a potent ally in the war and deserves more focus very soon. The use of blue and ultraviolet light is already well known, but less used, probably because using a pill is more convenient.

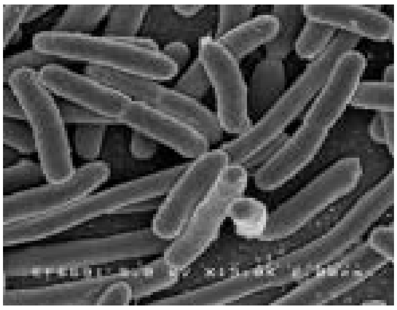


Figure 4.1 Scanning electron micrograph of Escherichia coli bacilli. (Wikipedia)

LPT will probably not harm any microorganism in itself. The immune system will, and has evolved over billions of years to handle that situation. And LPT enhances the immune system. QED? There is an urgent need to pinpoint the situations where the single or additional use of LPT can substitute or reduce the need for antibiotics. One obvious such situation is the diabetic wound. Proper use of LPT will in the first place eliminate the wound and in the second place reduce the amount of antibiotics used during the healing process. But while we clinically know LPT as an excellent method to treat diabetic ulcers, the literature is scant, to say the least. LPT here does not kill bacteria; it simply reduces the attack areas. Fair enough.

It is known that LPT increases microcirculation. Increased microcirculation means enhanced immunological activity in an area - a hard situation for bacteria. Studies also suggest that intravenous LPT increases microcirculation in organs, making the uptake of pharmaceuticals such as antibiotics more effective, and thus requiring lower dosage [2468].

The pharmaceutical companies have largely failed in finding new antibiotics and no longer keen on spending their money in this field of research. The situation is getting urgent and all small avenues have to be investigated. It is time to focus on what LPT can do in this field and to initiate new studies.

Literature:

The aim of the study by Silva [2273] was to assess the effect of LPT on the rate of bacterial contamination in infected wounds in the skin of rats. His was an experimental study using 56 male Wistar rats. The animals were randomly divided into eight groups of seven each. Those in the "infected" groups were infected by Staphylococcus aureus MRSA in the dorsal region. A 658 nm laser, 5 J/cm^2 was used to treat the animals in the "treated" groups in scan for 3 consecutive days. Samples were drawn before inoculating bacteria and following laser treatment. The statistical analysis of median values showed that the groups submitted to laser treatment had low bacterial proliferation. The laser with a dose of 5J/cm^2 in both intact skin and in wounds of rats infected with Staphylococcus aureus MRSA, was shown to reduce bacterial proliferation. **One theory is that laser light reacts with endogenous prophyrines and creates a PAD effect.**

The work by Mehdi [2468] was designed to evaluate the effect of LPT administered intravenously on the level of antibiotic in the blood. A GaAs laser of (200 nsec pulse width, average power 1 mW at 1 kHz pulse repetition frequency) with an optical package which contained a connector and optical fibre with fine cannula fixed in its end was constructed locally for this purpose. 28 male adult New Zealand white rabbits were used in this study. They were divided into two groups (control & laser), each group was subdivided into two subgroups depending upon the manner of administration of the Ampicilline. The first one was injected with 10 mg/kg B.W of the Ampicilline at the time of irradiation while the other subgroup given the Ampicilline in a shape of gelatine capsules, each one containing 10 mg/kg B.W orally prior to the anaesthesia. Each animal underwent a surgical operation carried out on the medial aspect of the left thigh to expose the femoral vein. Blood of the animals of the treated group was irradiated by introducing the fine needle of the cannula into the vein for (5 minutes). Samples of blood were collected from the animals of all groups at the times (0.5, 1, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours) intervals after the injection of the antibiotic and sent for laboratory analysis using HPLC. The results of this study revealed a significant increase in the level of the Ampicilline (ng/ml) in the treated group as compared with the with the control groups. The increase in the level was significant as compared with the pre-treatment time.

4.1.4 Arteriosclerosis

Arteriosclerosis refers to a thickening and hardening of arteries. Two small studies are not an impressive foundation for a recommendation. But again, with no side effects reported, and traditional therapies not very successful, what is there to loose?

Literature:

Laser treatment of arteriosclerosis (claudicatio intermittens) of the lower limbs has been described by Attia [964]. In the study, 20 patients with arteriosclerosis in the lower limbs were treated with HeNe 20 mW, 830 nm, 250 mW, applied transcutaneously to the lumbar region by a scanner for 30 minutes, six days a week for two months. The duration of the condition varied from one to eight months. Pain was relieved in 16 patients after three to seven applications of treatment. At the end of the therapy, 8 patients were able to walk 1500 metres without experiencing pain in the calf muscles. Three patients discontinued therapy for reasons not related to the therapy and one patient showed no improvement.

Similar results are reported by Klimenko [1306].

4.1.5 Arthritis

Arthritis is a wide indication, including diagnoses such as rheumatic arthritis (RA), osteoarthritis (OA), morbus Bechterew and psoriatic arthritis. It is unlikely that laser treatment will cure any of these conditions, as with any other medication, but the symptoms and the quality of life of the patients can often be improved considerably. In addition to pain relief, increased range of movement and reduced swelling can be achieved to some extent. A suitable dosage for a small joint such as a finger is from the lateral side 1-2 J, with GaAs always at a lower dose. For larger joints, a considerably higher dosage is needed. A knee, for instance, may need 15-25 J per session. Hip and shoulder arthritis require a high laser output, and a probe applied with strong pressure on suitable anatomical points, to achieve a sufficient dose to the target area. Only infrared will work on deep structures, while all wavelengths will work on small joints.

Conditions of chronic pain may react with an increase in pain, which is why it is best to begin with a low dosage. This should be explained to the patient, so that the initial occurrence of pain is not used as a reason to discontinue the treatment. The pain reaction in itself is unpleasant, but is actually an indication of a positive reaction to the treatment.

Prolonged treatment schedules are necessary with a total accumulated (all sessions) dose of no less than 25 J for a small joint such as a finger. Three to five sessions per week are recommended in the initial phase. Patients in the early stages are more likely to experience prolonged benefits from LPT [1100], whereas patients in the later stages will obtain a better quality of life but with more or less transient effects of LPT [1023]. However, in sharp contrast to pharmaceuticals [1059], there will be no other side effects than the potential initial pain reaction. About 90% of the prescribed NSAIDs in Canada are attributed to the treatment of arthritis [1140]. It has also been postulated that about one third of the arthritis budget has been used to handle side effects of NSAIDs. These figures support the use of a side-effect free method such as LPT. It would be ideal for an elderly chronic patient to have a suitable laser of his own, or one leased from the hospital.

The British Medical Journal [2203] reported that the US Centers for Disease Control and Prevention had declared there was a national epidemic of prescription drug overdoses which led to 14,800 deaths in 2008. This is more than cocaine and heroin combined for the same period.
The authors highlight the following key points:

"Death from opioid pain relievers (OPR) is an epidemic in the United States.

"Sales of OPR quadrupled between 1999 and 2010.

"Enough OPRs were prescribed last year to medicate every American adult for a month

Abuse of OPRs costs health insurers approximately $72.5 billion annually in health-care costs.

NSAIDs were the 15th biggest cause of death in the USA according to the New England Journal of Medicine 1999 [2204].

With the above in mind, LPT appears to be an attractive alternative.

LPT influences the synovial fluid and its membranes [63, 639,718,751,1018,1022] and the articular cartilage [151,550,898,1021]. The PGE_2 activity is also modified [243,1008] as well as interleukin 1-ß [188,370].

Since the whole organism is involved, irradiating one or several joints will only give temporary relief [293,1023]. To obtain true improvement of quality of life, all the reachable joints involved should be treated in many consecutive sessions [397] and comparatively high energies must be used [585]. It is essential that the large and deep-lying joints be given a sufficient dosage. Such treatment is certainly time-consuming but the alternatives, on the other hand, are rather bleak. It is possible for the patients to treat themselves according to instructions, as suggested by Stelian [617].

Although all wavelengths will have some effect, there is a difference in the total outcome, with some wavelengths more effective than others, due to better penetration of infrared light in large joints. In a study by Giavelli [638], 406 patients with osteoarticular diseases were treated with various wavelengths. The results were as follows: In gonarthrosis patients, statistical analysis of the results showed no significant differences between CO_2 laser and GaAs laser treatments, but there were significant differences between CO_2 laser and HeNe laser treatments, and between GaAs laser and HeNe laser treatments. In lumbar arthrosis patients treated with a GaAs or HeNe laser, significant differences were found between the two laser treatments, and the combined sweeping plus point techniques appeared to have a positive trend relative to the sweeping method alone, especially in sciatic suffering. In the algodystrophy syndrome in hemiplegic patients, significant differences were found between CO_2 and HeNe laser treatments, between high and low CO_2 laser doses, and between a low CO_2 laser dose and a high HeNe laser dose. The differences above do not indicate that HeNe is less useful in LPT, only that the deep lying structures treated could not be sufficiently saturated by HeNe laser light alone.

GaAs appears to have the best effect on osteoarthritis, and the majority of the positive studies for this indication have used GaAs [588]. GaAs also has the deepest penetration rate and is therefore the best option for large joints.

The importance of high energy per point is illustrated in the study by Tascioglu [1505]. This study design was randomised, placebo-controlled and single blinded. Sixty patients with knee OA, according to the American College of Rheumatology criteria, were included and randomly assigned to three treatment groups: active laser with a dosage of 3 J per painful point (15 J per session), active laser with a dosage of 1.5 J per painful point (7.5 J per session) and placebo laser treatment groups. A GaAlAs laser with a power output of 50 mW, 830 nm was used. The patients were treated 5 times weekly with 10 treatments in all. Compared to baseline, at week three and at month six, no significant improvement was observed within the groups. Similarly, no significant differences were found among the treatment groups at any time. Only painful points were irradiated whereas cartilage and synovia remained untreated. Irradiation of painful points is only of secondary importance in LPT, irradiation at the target area is more important.

A Meta analysis by Bjordal [1421,1798] on the effect of NSAIDs on knee osteoarthritis pain appears to become important for the recognition and future development of LPT. A research group summarises that nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors (coxibs), reduce short-term pain associated with knee osteoarthritis only slightly better than placebo, and long-term use of these agents should be avoided. Up for analysis were 23 placebo-controlled trials involving 10,845 patients, 7767 of whom received NSAID therapy and 3078 placebo therapy. All in all 21 of the NSAID-studies were funded by the pharmaceutical industry, and the results of 13 of these studies were inflated by patient selection bias as previous NSAID-users were excluded if they had not previously responded favourably to NSAID. Such an exclusion criterion for non-responders has never been seen in any controlled trial of LPT or other non-pharmacological therapies of osteoarthritis. In the remaining 10 unbiased NSAID-trials, the difference from placebo was only 5.9 mm on a 100 mm pain scale. This is far less than established data on differences that are considered minimally perceptible (9 mm) or clinically relevant (12 mm) for knee osteoarthritis patients. In addition, none of the trials found any effects beyond 13 weeks. This bleak support for long term use of NSAIDs is an excellent support for non-pharmaceutical methods, such as LPT.

Adverse effects of long term medication with NSAIDs, and particularly coxibs, have received much attention in the "Vioxx-scandal". Consequently, coxibs like Vioxx have been withdrawn, Prexige has been withheld from the market, and the whole group of coxibs are now under special observation by drug agencies in both Europe and the United States. In contrast to the virtually non-existent side effects of LPT, NSAID side effects cause an estimated 2000 deaths annually in Great Britain alone, due to the fact that half of the 8.5 million osteoarthritis patients in Britain take these drugs on a regular basis. The considerable international interest in the findings of the Norwegian research group has been highlighted by articles in several major newspapers across Europe and North America, and with more than 60 unique website-listings within two weeks after publication. The recent development is further moving the balance in disfavour of NSAIDs and coxibs, and may well be the end of the era where they served as reference treatment for osteoarthritis.

The current situation may pave the road for other risk-free alternatives such as LPT, which has appeared to provide clinically relevant changes in several randomised placebo-controlled trials. From the findings of a Norwegian Health Technology Assessment Report, LPT could potentially be at least twice as effective as NSAIDs, if applied with optimal dose and energy. Even though the number of laser trials is still smaller than for NSAIDs, the unequivocal scientific findings so far have earned LPT a top spot in levels of evidence and treatment recommendations for knee osteoarthritis issued by the Norwegian Drug Agency. LPT is also reimbursed in the physiotherapy programme by the National Health Insurance Agency, and is one of the standard therapies for knee osteoarthritis pain in Norway. As with all laser applications, it is necessary to use the laser and dosimetry parameters within the therapeutic window.

In conclusion, LPT for arthritis is an excellent indication. Being a chronic condition, there are no methods that can cure OA or RA, treatment will have to be lifelong. The problem is that some medications will shorten the life of the patient it is supposed to help. LPT is safe and without the serious side effects of pharmaceuticals. Being a life-long therapy, it would ideally mean initial therapy by a trained therapist three to four times per year, and a suitable low powered home laser unit for maintaining the effect.

	820, 830, 1060 nm		904 nm		632 nm	
Loca-tion	Lowest power density in mW/cm^2	Dose per point in joules	Lowest power density in mW/cm^2	Dose per point in joules	Lowest power density in mW/cm^2	Dose per point in joules
Finger/ toe	10	1– 5	3	0.5-5	10	2 – 5
Knee	10	5 – 20	3	0.5-5	10	6 – 30
Lum-bar spine	100	40 – 200	15	7.5 - 37.5	Not investi-gated	> 30
TMJ	10	1 – 5	3	0.5-5	10 – 400	2-4

Table 4.1 Arthritis

The table shows suggested optimal range of power density in mW/cm^2 and dose in $joule/cm^2$ for the most common joints for infrared GaAlAs (continuous) lasers with wavelength 820, 830 and Nd:YAG lasers with wavelength 1064 nm, infrared GaAs lasers with wavelength 904 nm, and HeNe lasers, respectively. The number of points will have to be adjusted acc. to the size of the joint in question.

Modified after Bjordal [588].

Literature:

In vitro studies

Palma has previously showed that HeNe laser light blocks the increment of Prostaglandin E1 (PGE_1) and Bradykinine (B) in the Plasma Fibrinogen Level (PFL). In a new study [357], another substance related to the inflammatory process, Tromboxane (Tx), was studied. The experiment confirmed the total block of PGE_1/B when HeNe was administered. However, the complex PGE_1/B/Tx was only partially blocked.

The study by Gavish [1579] was designed to determine the influence of LPT on the kinetics of MMP stimulation and decay, specific cytokine gene expression, and subcellular localisation of promyelocytic leukemia (PML) protein on HaCaT human keratinocytes: The cells were irradiated by a 780 nm titanium-sapphire (Ti-Sa) laser with 2 J/cm^2 energy density. MMP was monitored with Mitotracker, a mitochondrial voltage-sensitive fluorescent dye. Cytokine gene expression was carried out using semi-quantitative-reverse transcription polymerase chain reaction. Subcellular localisation of PML protein, a cell-cycle checkpoint protein, was determined using immunofluorescent staining. The fluorescence intensity of MMP was increased *immediately after the end of laser by 148 +/- 6% over control. Subsequently it decayed, reaching 51 +/- 14% of the control level within 200 minutes. This decay was characterised by an exponential curve with a lifetime of 79 +/- 36 minutes. Following irradiation, the expression of interleukin-1alpha, interleukin-6, and keratinocyte growth factor (KGF) genes were transiently upregulated; but the expression of the proinflammatory gene interleukin-1ß, was suppressed. The subnuclear distribution of PML was altered from discrete domains to its dispersed form within less than 1 hour after laser irradiation. These changes reflect a biostimulative boost that causes a shift of the cell from a quiescent to an activated stage in the cell cycle heralding proliferation and suppression of inflammation. Further characterisation of MMP kinetics may provide a quantitative basis for assessment of the effect of laser irradiation in the clinical setting.*

Indications of an effect on the metabolism of cartilage are found in studies by Akai [466], Ruiz Calatrava [1057] and van der Veen [1058]. These studies used dosages similar to those in fibroblast studies. Researchers using higher dosages failed to demonstrate a stimulative effect [1191].

The aim of a study by Morrone [898] was to verify the effects of LPT performed with 780 nm, 2500 mW on human cartilage cells in vitro. The cartilage sample used for the biostimulation treatment was taken from the right knee of a 19-year-old patient. After the chondrocytes were isolated and suspended for cultivation, the cultures were incubated for 10 days. The culture was divided into four groups. Groups I, II, III were subject to biostimulation with the following laser parameters: 300 J, 1 W, 100 Hz pulse repetition rate, 10 min. exposure, 300 J, 1 W, 300 Hz pulse repetition rate, 10 min. exposure; and 300 J, 1 W, 500 Hz pulse repetition rate, 10 min. exposure, respectively. Group IV did not receive any treatment. The laser biostimulation was conducted for five consecutive days. The data showed good results in terms of cell viability and levels of Ca and Alkaline Phosphate in the groups treated with laser by comparison with the untreated group. The results obtained confirm previous positive in vitro results from the same authors, that the GaAlAs laser provides biostimulation without cell damage. The very high doses used complicate the conclusions from earlier studies.

Herman [151] used Nd:YAG in vitro on bovine articular cartilage. Irradiation could be shown to consistently up-regulate cartilage proteoglycan, collagen, noncollagen protein and DNA synthesis in the absence of histological or biochemical evidence of enhanced matrix catabolism. Laser-induced repair could be shown biochemically in an in vitro model system of enzymatically mediated cartilage matrix deposition.

In a study by Wong [1605] condrocyte proliferation following in vitro heating through different methods, including Nd:YAG laser, was demonstrated. The stimulation observed is attributed to the heat effect only. However, no evidence of chondrocyte DNA replication was observed in tissues heated by non-laser methods. Since the laser source of heating was the only *one showing DNA replication, it is likely that the biostimulatory effect in the peripheral part of the laser beam contributed to this effect.*

Yamura [1896] studied the effect of 810 nm radiation on synoviocytes from rheumatoid arthritis (RA) joints. Cells were pre-exposed to TNF-alpha to mimic the inflammatory environment of a RA joint. The mRNA and protein levels of multiple cytokines were measured as a function of time after LPT. The production of IL-1ß and TNF-alpha were reduced by 810 nm after treatment.

In a study by Taniguchi [2068] rabbit synovial fibroblasts were cultured, and laser irradiation (660 nm) was applied at the power density of 40 mW/cm² for 2 minutes, corresponding to laser fluence of 4.8 J/cm². The effect of laser irradiation on cell proliferation, cell cycle progression, and expression of cyclin-dependent kinase inhibitors (CKIs) were investigated. The researchers also examined whether the effects of laser irradiation on HIG-82 cell proliferation were affected by cAMP content, which is known to influence the cell cycle via inducing CKIs. LPT promoted synovial fibroblast proliferation and induced cytoplasmic localisation of cyclin-dependent kinase inhibitor p15. Moreover, the proliferation of synovial fibroblasts was reduced by cAMP, while cAMP inhibitor, SQ22536, induced p15 cytoplasmic localisation and as a result, elevated synovial fibroblast proliferation was observed. In addition, the promotive effect of laser-induced HIG-82 synovial fibroblast proliferation was abolished by cAMP treatment. These findings suggest that cAMP may be involved in the effect of laser on synovial fibroblast proliferation. The researchers revealed the effect and molecular link involved in synovial fibroblast proliferation induced by 660 nm irradiation.

In a study by Yamura [2066] synoviocytes from RA patients were treated with 810 nm radiation before or after addition of tumour necrosis factor-alpha (TNF-alpha). mRNA for TNF-alpha, interleukin IL-1ß, IL-6, and IL-8 was measured after 30, 60, and 180 minutes using RT-PCR. Intracellular and extracellular protein levels for 12 cytokines/chemokines were measured at 4, 8, and 24 hours using multiplexed ELISA. Radiation at 810 nm (5 J/cm²) given before or after TNF-alpha decreases the mRNA level of TNF-alpha and IL-1ß in RA synoviocytes. This treatment using 25 J/cm² also decreases the intracellular levels of TNF-alpha, IL-1ß, and IL-8 protein but did not affect the levels of seven other cytokines/chemokines. TNF-alpha-induced activation of NF-kappaB is not altered by 810 nm radiation using 25 J/cm². The authors conclude that the mechanism for relieving joint pain in RA by LPT may involve reducing the level of pro-inflammatory cytokines/chemokines produced by synoviocytes. This mechanism may be more general and underlie the beneficial effects of LPT on other inflammatory conditions.

Skinner [754] stimulated cultured human embryonic fibroblast cells with GaAs. Fibroblast procollagen production was monitored by the synthesis of {3H} hydroxyproline, and DNA replication was assessed by {3H} thymidine incorporation. Following laser treatment, controlled pepsin digestion measured the increase in cell biostimulation. Maximum increase of collagen *production and cell biostimulation occurred after four episodes of LPT at 24-hour intervals.*

An extended explanation of the fundamental effect of LPT in general is presented by Hamblin [1897]. Red and near-IR light is thought to be primarily absorbed by cytochrome c oxidase, which is unit four in the mitochondrial respiratory chain. Since the recent discovery of mitochondrial nitric oxide synthase, it has been realised that nitric oxide produced in the mitochondria can inhibit respiration by binding to cytochrome c oxidase and competitively displacing oxygen, especially in stressed or hypoxic cells. Light absorption displaces or photodissociates the nitric oxide and thus allowed the cytochrome c oxidase to recover and cellular respiration to resume.

Animal studies

The anti-inflammatory effect of HeNe laser was observed by Campaña [1133]. Calcium pyrophosphate was injected into both joints of the lower limbs in rats, to mimic microcrystalline arthropaty (gout). The untreated group showed a strong diffuse inflammatory reaction for mono and polymorphonuclears with fibro and angioblastic proliferation, with ematous lax stroma. No inflammation was observed in the laser group. The experience of this research group is reviewed in [1680].

In an experiment in rats, Campaña [582] found that laser induced a similar reduction of PGE_2 levels as NSAID in experimentally induced synovitis.

The influence of 632.8 nm, 13 J/cm^2, three times a week on 13-week immobilised articular cartilages was examined by using a rabbit knee model in a study by Bayat [1640]. The number of chondrocytes and the depth of articular cartilage of the experimental group were significantly higher than those of the sham irradiated group. Surface morphology of the sham-irradiated group had rough prominences, fibrillation and lacunae but the surface morphology of the experimental group had more similarities to the control group than to the sham irradiated group. There were marked differences between ultrastructure features of the control group and the experimental group in comparison with the sham irradiated group. Thus, laser irradiation on 13-week immobilised knee joints of rabbits neutralised the adverse effects of immobilisation on articular cartilage.

The influence of laser radiation on human osteoarthrotically changed chondrocytes was investigated by Bauman [1846] using various wavelengths, power densities and dependences on the exposure time in order to confirm the positive results obtained in an animal experiment. It was manifested that, if there was a specific parameter constellation (2 W, 16 W/cm^2; 60 s; 120 J), an enhanced matrix synthesis (cartilage material from 36 patients) could be achieved. The proof succeeded by applying the radioisotope marking method (3H-proline). Interestingly enough, it turned out that *the application of too high a power density but constant energy density resulted in a reduced matrix synthesis rate (reduction of 28%).*

Akai [466] studied the influence of 810 nm laser on bone and cartilage during joint immobilisation of rats' knee models. The hind limbs of 42 young rats were operated on in order to immobilise the knee joint. They were assigned to three groups one week after operation; irradiance 3.9 W/cm^2, 5.8 W/cm^2, and sham treatment. After six sessions of treatment for another two weeks both hind legs were prepared for 1) indentation of the articular surface of the knee (stiffness and loss tangent), and for 2) dual energy X-ray absorptiometry (bone mineral density) of the focused regions. The indentation test revealed preservation of articular cartilage stiffness with 3.9 and 5.8 W/cm^2 therapy. LPT may possibly prevent biomechanical changes by immobilisation.

In the study by Lievens [1324] cartilage tissue of the ear of mice was used as an experimental set-up. It is clear that the elastic cartilage tissue of the ear is not totally comparable with the hyaline cartilage of articulations. For technical reasons, however, and because of the fact that the chondrocytes are comparable, it was decided to use mice ears in this experiment. A 0,4 mm hole was drilled in both ears on 30 mice. The right ear remained untreated, while the left ear was treated daily with GaAs laser for three minutes. Macroscopical as well as histological evaluations were performed on the cartilage regeneration of both ears. The results show that after one day post-surgery no differences were found between the irradiated and the non-irradiated group. After the second day, only in the irradiated group was there a clear activation of the perichondrium. After four days, there was a significant ingrowth of the perichondrium into the drill hole in the experimental group and there was only an active perichondrium zone in our control group.

The purpose of a study by Aimbire [1560] was to investigate the effect of LPT on rat trachea hyperreactivity (RTHR), bronchoalveolar lavage (BAL) and lung neutrophils influx after Gram-negative bacterial lipopolyssacharide (LPS) intravenous injection. The RTHR, BAL and lung neutrophils influx were measured over different intervals of time (90 min, 6 h, 24 h and 48 h). The energy density (ED) that produced an anti-inflammatory effect was 2.5 J/cm^2, reducing the maximal contractile response and the sensibility of trachea rings to methacholine after LPS. The same ED produced an anti-inflammatory effect on BAL and lung neutrophils influx. The Celecoxib COX-2 inhibitor reduced RTHR and the number of cells in BAL and lung neutrophils influx of rats treated with LPS. Celecoxib and laser reduced the PGE_2 and TXA2 levels in the BAL of LPS-treated rats. These results demonstrate that 685 nm LPT produced anti-inflammatory effects on RTHR, BAL and lung neutrophils influx in association with inhibition of COX-2-derived metabolites.

Guerino [1666] investigated the effects of HeNe laser irradiation on the inflammatory process induced in the articular cartilage of the right knee of guinea pigs. Through electron microscopy analysis it was possible to iden-

tify the induced arthritis in the articular cartilage and its modification after the laser treatment. The laser radiation promoted a reduction in the proliferation of the inflammatory cells in the damaged tissue and also induced the formation of cartilage bridges that tied the destroyed parts favouring the formation of a repaired tissue in the injured cartilage.

A study by Moriyama [1694] was designed to demonstrate that bioluminescence imaging (BLI) can be used as a new tool to evaluate the effects of LPT during in vivo inflammatory process. Here, the efficacy of LPT in modulating inducible nitric oxide synthase (iNOS) expression using different therapeutic wavelengths was determined using transgenic animals with the luciferase gene under control of the iNOS gene expression. Thirty transgenic mice were allocated randomly to one of four experimental groups treated with different wavelengths (635, 785, 808 and 905 nm) or a control group (non-treated). Inflammation was induced by intra-articular injection of zymosan A in both knee joints. Laser treatment (25 mW, 200 s, 5 J/cm² was applied to the knees 15 min after inflammation induction. Measurements of iNOS expression were performed at various times (0, 3, 5, 7, 9 and 24 h) by measuring the bioluminescence signal using a highly sensitive charge-coupled device (CCD) camera. The results showed a significant increase in BLI signal after irradiation with 635 nm laser when compared to the non-irradiated animals and the other laser treated groups, indicating wavelength dependence of LPT effects on iNOS expression during the inflammatory process, and thus demonstrating an action spectrum of iNOS gene expression following LPT in vivo that can be detected by BLI. Histological analysis was also performed and demonstrated the presence of fewer inflammatory cells in the synovial joints of mice irradiated with 635 nm compared with non-irradiated knee joints.

The purpose of a study by Sandoval [2067] was to evaluate the effects of LPT on the clinical signs of inflammation and the cellular composition of synovial fluid (SF) in the inflamed knee of the rabbit. Inflammation in the right knee of 36 rabbits was induced by intracapsular injection (0.2 mL) of Terebinthina commun (Tc). The animals were randomly assigned to three groups: acute experimental group (AEG), chronic experimental group (CEG), and control group (CG), which only received Tc. Each group was divided in two subgroups of six animals each. The AEG and CEG groups began to receive laser treatment 2 and 5 d after the induction of inflammation, respectively. Laser irradiation at 830 nm, 77 mW, power density 27.5 W/cm² was applied daily for 7 d for either 0.12 sec or 0.32 sec, resulting in doses of 3.4 J/cm² and 8 J/cm², respectively. Body mass, joint perimeter, joint temperature, and the morphology of the SF were analysed. There were no statistically significant differences between groups in the body mass, joint perimeter, and SF morphology. Laser irradiation with the selected parameters produced only a few subtle differences in the inflammatory signs and the SF. The lack of effects may have been due to the extremely short irradiation time.

The course of arthrosis was investigated by Gottlieb [1701] on an animal-experimental arthrosis model considering macroscopic aspects, and the proteoglycan and the glycosaminoglycan contents. Based on these parameters, the influence of 692.6 nm, 20 mW, on the progress of arthrosis was investigated. Thirty days following joint instability surgery another operation was carried out during which the femoral condyles were irradiated using different energy densities (1 or 4 J/cm^2). Seven days after the second operation, macroscopic findings were made and the proteoglycan content was established. Macroscopically, a progressively increasing severity of cartilage changes during the course of arthrosis was detected, and the proteoglycan content was found to decrease. The changes in the irradiated joints proved to be less severe, with the higher energy density having a greater positive influence of statistical significance.

The aim of a study by Cho [1425] was to determine whether LPT aided the recovery of damaged articular cartilage in joints with artificially induced osteoarthropathy (OA). OA was induced by injecting hydrogen peroxide (H_2O_2) into the articular spaces of both knees in rabbits, twice a week for four weeks. The induction of OA and the effect of LPT were evaluated by biochemical, radiological and histopathological analysis. Superoxide dismutase (SOD) activity increased about 40% in the OA group, as compared to the controls. Although SOD activity in the OA group was not significantly different from the 2-week groups, it was significantly different from the 4-week control and treatment groups. There was also a significant difference between the 4-week control and treatment groups. Simple radiographs and three-dimensional computed tomographs (3D CT) did not show detectable arthropathy in the OA group, nor any particular changes in the 2-week groups. In contrast, distinct erosions were seen in the distal articular cartilage of the femur, with irregularity of the articular surface, in the 4-week control group, while the erosions were reduced and arthropathy improved slightly in the 4-week treatment group. Generally, erosions formed on the articular surface in the OA group. In comparison, severe erosions damaged the articular cartilage in the 4-week control group, but not in the 2-week control and treatment groups. Regeneration of articular cartilage was seen in gross observations in the 4-week treatment group. Histopathologically, there was slight irregularity of the articular surface and necrosis in the OA group, and serious cartilage damage, despite slight chondrocyte regeneration, in the 4-week control group. Conversely, the 4-week treatment group showed chondrocyte replacement, with sometimes close to normal articular cartilage on the articular surface. These results suggest that LPT was effective in the treatment of chemically-induced OA.

In a total of 45 rabbits, knee-joint arthrosis was induced in a study by Pfander [1741]. Depending on the post-operative survival time, the cartilage was investigated macroscopically, histologically and immunohistochemically (within a period of 10 days to 8 months). Thereafter, the influence of laser irradiation at a wavelength of 692.6 nm and energy densities of 1 and 4 J/

cm^2 *on the cartilage morphology seven days following the exposure was examined. After joint instability surgery it was found that the cartilage changes in the main stress area (MSA) and in regions outside the main stress area (ROMSA) progressed differently. Various qualitative and semi-quantitative changes were found for collagens I, II, IV and V, and for the glycoproteins fibronectin and tenascin. Immunohistochemically, there was a growing expression of collagen I in the apical layers, collagen II showed a stronger pericellular expression, and collagen IV showed, after an initial growth of the pericellular expression, a reduced territorial expression and a stronger apical-interterritorial expression in the osteoarthrotic cartilage. For fibronectin, the cellular expression turned out to grow in the ROMSA. In the MSA it decreased, but at the same time the interterritorial expression grew. For Tanascin, there was a decrease of the interterritorial expression in the radial zone while the pericellular and interterritorial expression of the apical layers of the osteoarthrotic cartilage grew. Lasing proved to significantly influence the osteoarthrotically changed cartilage when applied at an energy density of 1 J/*cm^2*, i.e., the morphological changes had not yet progressed to the extent the control group had. Both the chondrocyte density and the glucosaminoglycan content turned out to be higher. When lasing was applied at higher energy densities, no significant difference among the control groups was found. Thus, it could be demonstrated in vivo that an arthrotic process decelerates through the influence of laser light of low-energy densities.*

In a study by Lin [1742], 72 rats with three different degrees of pain-induced OA over right knee joints were collected for helium-neon laser treatment. The severity of induced arthritis was measured by 99mTc bone scan and classified into three groups (I-III) by their radioactivity ratios (right to left knee joints). The rats in each group were further divided into study subgroups (Is, IIs, and IIIs) and control subgroups (Ic, IIc, and IIIc) randomly. The arthritic knees in the study subgroups received HeNe laser treatment, while those in the control groups received sham laser treatment. The changes of arthritic severity after treatment and at the follow-up two months later were measured. The histopathological changes were evaluated through light microscope after disarticulation of sections (H.E. stain), and the changes of mucopolysaccharide density in cartilage matrix were measured by Optimas scanner analyser after Alcian blue (AB) stain. The densities of mucopolysaccharide induced after treatment in arthritic cartilage were compared and correlated with their histopathological changes. The density of mucopolysaccharide rose at the initial stage of induced arthritis, and decreased progressively in later stages. The densities of mucopolysaccharide in treated rats increased upon complete laser treatment more than in those of the controls, which is closely related with the improvement in histopathological findings, but conversely with the changes in arthritic severity. HeNe laser treatment will enhance the biosynthesis of arthritic cartilage and result in the improvement of arthritic histopathological changes.

Castano [1840] tested LPT on rats that had zymosan injected into their knee joints to induce inflammatory arthritis. The author compared illumination regimens consisting of a high and low fluence (3 and 30 J/cm^2), delivered at high and low irradiance (5 and 50 mW/cm^2) using 810 nm daily for five days, with the positive control of conventional corticosteroid (dexamethasone) therapy. Illumination with a 810 nm laser was highly effective (almost as good as dexamethasone) at reducing swelling, ***and a longer illumination time (10 or 100 minutes compared to 1 minute) was more important in determining effectiveness than either the total fluence delivered or the irradiance.*** *LPT induced reduction of joint swelling correlated with reduction in the inflammatory marker serum prostaglandin E_2 (PGE_2).*

The objective of the study by Alves [2377] was to evaluate the effect of LPT operating at 50 mW and 100 mW on joint inflammation in rats induced by papain, through histopathological analysis, differential counts of inflammatory cells (macrophages and neutrophils), as well as gene expression of IL-1SZ and IL-6, and protein expression of TNF-alpha. 60 Wistar rats were randomly divided into 4 groups of 15 animals, namely, a negative control group; an inflammation injury positive control group; a 50 mW LPT group, subjected to injury and treated with 50 mW LPT; and a 100 mW LPT group, subjected to injury and treated with 100 mW LPT. The same energy and dose were used in both groups, but irradiation time was 40s in the 100 mW group and 80s in the 50 mW group. The animals were subject to joint inflammation (papain solution, 4%) and then treated with LPT. On the day of euthanasia, articular lavage was collected and immediately centrifuged; the supernatant was saved for analysis of expression of TNF-alpha protein by ELISA and expression of IL-1SZ and IL-6 mRNA by RT-PCR. A histologic examination of joint tissue was also performed. Both laser treatment modalities were efficient in reducing cellular inflammation, and both decreased the expression of IL-1SZ and IL-6. However, the 100 mW treatment led to a higher reduction of TNF-alpha compared to the 50 mW treatment.

Clinical studies

The Hungarian experience of using LPT in rheumatoid arthritis has been summarised by Mester [894] as follows:

"Barabás [1018] irradiated the joints of rheumatoid arthritis (RA) patients. In the first open study the range of motion and circumference of the treated joints were measured, a Ritchie index was used as a semi-objective parameter, while subjective parameters as joint tenderness and pain on a visual analogous scale (VAS) were registered. Walking time was registered as a functional disability parameter. Laboratory activity parameters and the 99mTechnetium index were measured. The second part of the clinical study was double blind. Infrared (10 mW and 100 mW) lasers were used, versus dummy devices with the same appearance. The third part of the study was in vitro experiments. Synovial membranes of rheumatoid arthritis patients were irradiated. The DNA/RNA ratio of the RA group was compared to the control

group. A significant difference was detected between the two groups. The fourth phase of the clinical studies was to detect the effects of laser irradiation in other rheumatic diseases: psoriatic arthritis, sacroileitis, osteoarthritis, entesopathy, tenosynovitis, bursitis calcarea, fibromyalgia, localised muscle spasm, periarthritis humeroscapularis etc. The different wavelengths (604, 630, 660, 670, 690, 750, 780, 790, 820, 830, 904, 1053, 1219 nm,) were compared (30 - 100 mW) with other physiotherapy modalities, such as ultrasound." The group size in the double blind study was 80 (50 laser, 30 placebo) and each finger joint received 1 J/cm^2 daily for 25 days.

Johannsen [605] treated 22 patients with RA in a double-blind study. The two most painful MCP joints on the most affected hand were chosen for treatment, and 2.9 J of GaAlAs light was applied to four points. Treatment was offered three times a week for a month. None of the five parameters measured showed any effect of LPT.

Amano [578] applied 790 nm 0.8 J to six points for six consecutive days on the lateral side of the knee in a group of 14 RA patients due to undergo arthroplasty. During operation, small samples of the synovial membrane were removed from the lateral and the medial non-irradiated area. Histological findings in the irradiated synovial membrane showed flattening of epithelial cells, decreased villous proliferation, narrowed vascular lumen, and less infiltration of inflammatory cells by comparison with the non-irradiated synovia.

Barberis [718] treated 12 patients with chronic rheumatoid arthritis stages II and III. One knee in each patient was selected and irradiated with HeNe, 8 J/cm^2, 11 points, 15 applications. Synovial tissue analysis showed that LPT reduced pre- and post-treatment levels of PGE_2.

Obata [185] studied the effect of GaAlAs on a group of patients with diagnosed rheumatoid arthritis. Thermography was used on the treated hand to check the possible correlation between pain relief and thermographic response. A VAS scale was used to assess the degree of pain relief. In 10 patients, the HST (highest skin temperature) decreased immediately after irradiation. Nine of these patients experienced significant pain relief. Eight patients had an increase of HST following irradiation and five of these experienced non-significant pain relief.

Palmgren [97] conducted a controlled double-blind study of the effects of GaAlAs on 35 patients with rheumatoid arthritis. Eight joints on the worst affected hand were treated with a laser 3.58 J/cm^2 or placebo laser. In the experimental group, grip strength and movement were improved and swelling decreased; pain and morning stiffness were reduced. Pain was also reduced in the placebo group, although less than in the experimental group, while other parameters stayed unchanged.

Antipa [775] has tried to establish the efficiency of LPT in various inflammatory and non-inflammatory rheumatic diseases over a five-year period. In the study, 514 patients with osteoarthrosis, 326 patients with non-articular rheumatism and 82 patients with inflammatory rheumatism were *treated. Four different treatment procedures were used: 1) only GaAs; 2) both GaAs and HeNe; 3) placebo laser; and 4) classic anti-inflammatory therapy. The results were analysed using local objective improvements and the score obtained from a pain scale before and after treatment. It was concluded that LPT (especially HeNe with GaAs) is more efficient than placebo LPT and also yielded better, or at least similar, results in most of the cases compared to classical anti-inflammatory therapy.*

In the study by Rogvi-Hansen [1138] the outcome was negative, but the actual area of the articular capsule was not irradiated, although the indication studied was condromalacia patellae. This study used the treatment method implemented by Walker [38], irradiating the patella, the ipsilateral femoral nerve in the groin and the proximal part of the peroneal muscle. Walker used 1 mW HeNe, whereas this latter study used GaAs 17 mW. A 1 mW HeNe is unlikely to produce any results in a large joint such as the knee. ***And, as suggested by the Latin name of the condition, the cartilage itself has to be irradiated, not only the secondary complications. Although one of these studies is positive, the protocol of both is questioned.***

In a clinical study comprising 224 patients, Glazewski [1079] found that "application of low-intensity laser irradiation enables us to shorten NSAIDs treatment duration, reduce dose size and obtain better therapeutic effects." Indications treated were i.a. rheumatoid arthritis, coxarthrosis, gonarthrosis and spondylosis. The lasers used were GaAs 890 nm in the range 3.6 - 7.4 mW, dose range 0.75 - 3.0 J/cm^2.

In the double blind study by Taghawinjad [335] the outcome in the verum group was no better than that of the placebo group. However, the laser used was a combined HeNe (4.4 mW) + GaAs (5 × 0.3 mW) held at a distance of 160 mm from the skin, and covering an area of 40 mm^2. ***The power density in this set-up is very low and the penetration insufficient.***

Molina [334] compared two groups where one received ASA (acetylsalicylic acid) and the other ASA (four gram daily) plus LPT. During the initial double-blind phase, GaAs 6-8 J/cm^2 was applied to a total of 21 points in the hand. In an additional open phase, HeNe 6-10 J/cm^2 was administered. The ASA/LPT group responded more favourably to the therapy. GaAs appeared to be more successful than HeNe.

Soriano [331] reports good results in treating a group of 938 patients with osteoarthritis, using 904 nm, 6-10 J/cm^2. Acute conditions responded better than chronic conditions. The subgroups were: NSAID + LPT, massage/physiotherapy + LPT, and LPT only. The results in the three subgroups were practically identical. Chronic knee and hip pain had low scores (38%), others ranged from 84% to 100%.

Stelian [617] divided 50 patients with knee OA into three groups: one received 830 nm, one HeNe and one placebo laser. The infrared group was double blind whereas the HeNe group had to be an open study. The patients treated their knees twice daily for 10 days, a total of 22 J per day. GaAlAs and HeNe had approximately the same effect. The laser groups had signifi-

cantly less pain at the end of the therapy and at check-ups at 2-12 months. Their general well-being was measured with a Disability Index Questionnaire. This index was reduced by half in the laser groups but remained unchanged in the placebo group.

Similar parameters but a different treatment schedule was used by Bülow [1025]. Each patient received 22.5 J per session in nine sessions over three weeks. Laser source was a GaAlAs laser of 25 mW. ***Although reported as negative, a closer analysis of the data submitted reveals a significant short-term effect, which is masked in the text. When these masked facts are revealed, this study presents a significant but short-term effect of LPT for these parameters.***

Haimovici [82] studied osteoarthritis in finger joints and found that both HeNe and GaAlAs improved all the parameters measured. In the same study, the effects of anti-inflammatory medication and laser were compared. The medication gave slightly better results than the laser, but the best effects of all were achieved when the two were used in combination. ***This underlines the fact that laser should not be seen as a single form of therapy but as a valuable means of assistance.***

Obata [397] performed "Total Laser Irradiation" on 89 patients. This means that all active inflammatory joints were treated each session until pain relief was observed in all joints. The laser used was a 10 mW 780 nm unit. The erythrocyte sedimentation rate improved by more than 10 mm in 55% of the patients in the 20-session group. Lansbury's index improved by 10% in 47% of the cases. The serum immune-complex tended to decrease and the findings of synovial scintigraphy correlated well with the clinical effects.

Lerner [826] used a HeNe laser on a group of 33 patients suffering from Mb Bechterew. Irradiation was given over the spine and joints for 20 sessions. A total of 20 patients received LPT in combination with 75-100 mg of indomethacin per day, while 13 patients received LPT alone due to indomethacin intolerance. Therapeutic efficacy was assessed according to a number of clinico-laboratory indices. The most marked effect was observed in the combination group. The use of LPT alone was comparable with using indomethacin at a daily dose of 75 mg.

Mb Bechterev (Wikipedia)

The double blind study by Gladkova [1078] has a rather negative outcome. ***However, since doses between 0.004-0.02 J/cm² were used, a negative outcome is to be expected.***

In a double-blind crossover study, Gärtner [199, 568] used GaAs and HeNe lasers to treat stage III-IV ankylosing spondylarthritis. Treatment was given for 20 to 30 minutes daily for five consecutive days each week for three weeks. Spinal ROM and *laboratory tests including CRP and ESP showed no significant changes. However, pain score, morning stiffness and frequency of nocturnal awakening were significantly reduced.* ***With today's more powerful lasers, the results are likely to improve.***

In two Meta analyses of osteoarthritis and rheumatoid arthritis, Brosseau [1023, 1024, 1154] found a moderate but short term effect for rheumatoid arthritis, enough for recommending the method for clinical purposes. ***These two studies, however, lack a proper analysis of the dosages used, and the result of using a very low dosage in some studies confuses the true outcome of LPT studies. Further, the different wavelengths are "put into the same basket" although it is obvious that they have different effects.***

Brosseau [1528] examined efficacy of active 860 nm versus sham-laser on finger joints and three superficial nerves. Randomly assigned OA-patients received three treatments per week for six weeks of laser (n=42) or sham (n=46). Pain relief, morning stiffness, and functional status did not significantly improve for laser versus placebo. No significant differences were found in finger range of motion, except carpometacarpal opposition, grip strength and patient global assessment, which improved for active LPT participants.The author concludes: "LPT is no better than placebo at reducing pain, morning stiffness, or improving functional status for OA-hand patients". ***We believe this is a questionable conclusion since the study used only 0.12 J per finger joint, and random pulsing. The discussion also fails to discuss the great differences in dosage and treatment techniques in the references [1683].***

In another Meta analysis of the effect of LPT on osteoarthritis pain, Bjordal [588] summarises: "A literature search identified 88 randomised-controlled trials, of which 20 trials included patients with osteoarthritis and chronic joint disorders. Five trials were excluded for not irradiating the affected joint capsule. Two trials that reported significant results in favour of active laser were excluded from statistical pooling due to insufficient data presentation and lack of repeated laser irradiation. Of the remaining thirteen trials, five trials reported non-significant results. These five trials used treatment parameters outside our predefined optimal dose range, and their results were significantly poorer (p<0.001) than the results from eight trials giving treatment within the optimal dose range. For the 398 patients included in these eight trials, a pooled mean weighted difference of 42.9% (range 23-62) was registered in favour of active treatment. Adverse effects were few and mild, and unblinded follow-up observations suggested that pain reduction could last for more than one month. With the reservation of possible heterogeneity in the limited patient sample, location-specific doses of LPT appear to be effective in reducing pain from mild osteoarthritis."

This study underlines the importance of a proper dosage and subgroup analysis, an issue that has been largely overlooked by previous reviewers of LPT.

In the study by Basirnia [1323], treatment was performed on 20 patients, ageing from 42 to 60 years. All patients had received conservative treatment with poor results. Laser device used for this treatment was a pulsed diode laser; 810 nm, once a day for five consecutive days, followed by a 2-day interval. There was a total of 12 sessions of laser application. Irradiation was performed on five periarticular tender points, each for two minutes. The treatment outcome (pain relief and functional ability) was observed and measured according to the following methods: 1) Numerical rating scales, 2) Self-assessment by the patient, 3) Index of severity for osteoarthritis of the knee, 4) Analgesic requirements. Significant improvement in pain relief and quality of life was achieved in 70% of patients, compared to their previous status. There was no significant change in range of motion of the knee.

In a double-blind study by Ortutay [609] on the effect of LPT on psoriatic arthritis using 820 nm light, seven out of eight patients in the treatment group showed improved clinical activity: increased range of movement, decreased joint stiffness and tenderness. In the placebo group, only two out of eight patients improved.

Figure 4.2 Psoriatic arthritis (Wikipedia)

Treatment efficacy of physical agents in osteoarthritis of the knee (OAK) pain has been largely unknown, and a systematic review by Bjordal [1279] was aimed at assessing their short-term efficacies for pain relief. The authors performed a systematic review with meta-analysis of efficacy within 1-4 weeks and at follow-ups 1-12 weeks after the end of treatment. A total of 36 randomised placebo-controlled trials (RCTs) were identified with 2434 patients where 1391 patients received active treatment. Three or more out of five methodological criteria (Jadad scale) were satisfied by 33 trials. The patient sample had a mean age of 65.1 years and a mean baseline pain of 62.9 mm on a 100 mm Visual Analogue Scale (VAS). Within 4 weeks of the commencement of treatment manual acupuncture, static magnets and ultrasound therapies did not offer statistically significant short-term pain relief over placebo. Pulsed electromagnetic fields offered a small reduction in pain of 6.9 mm (n=487). Transcutaneous electrical nerve stimulation (TENS, including interferential currents), electro-acupuncture (EA) and LPT offered clinically relevant pain relieving effects of 18.8 mm (n=414), 21.9 mm (n=73) and 17.7 mm (n=343) on VAS respectively versus placebo control. In a subgroup analysis of trials with assumed optimal doses, short-term efficacy increased to 22.2 mm for TENS, and 24.2 mm for LPT on VAS. Follow-up data up to 12 weeks were sparse, but positive effects seemed to persist for at least 4 weeks after the course of LPT, EA and TENS treatment was stopped. In conclusion, TENS, EA and LPT administered with opti-

mal doses in an intensive 2-4 week treatment regimen, seem to offer clinically relevant short-term pain relief for OAK.

The aim of a study by Montes-Molina [2064] was to evaluate the effectiveness of an interferential pattern generated by two identical and independent lasers in the relief of knee pain. A double-blind controlled clinical trial was performed on 152 patients with knee pain who were randomly assigned into two different groups. Group I patients (n=76) received interferential laser therapy generated by two identical laser probes located opposite each other on the knee joint. Group II patients (n=76) received one live probe in conventional laser therapy and one dummy probe. The device used in both groups was 810 nm laser, 100 mW, in continuous mode. Fifteen laser sessions were applied transcutaneously on 5 knee points (6 J/point) per session. In addition, patients in both groups received a quadriceps strength programme based on isometric exercises. A Visual Analogue Scale (VAS) was used for pain evaluation in different situations, such as in standing, in knee flexion/extension, and when going up and down stairs. VAS pain scores were evaluated before, in the middle of, and after treatment. Results showed no significant differences between groups for all VAS scores or in the interaction with the sessions. The VAS score results showed a statistically significant pain reduction throughout all sessions. Interferential laser therapy is safe and effective in reducing knee pain. However, the results of the study indicate that it is not superior to the use of a single conventional laser.

In a study by Hegedus [2065] patients with mild or moderate KOA were randomised to receive either LPT or placebo LPT. Treatments were delivered twice a week over a period of 4 wk wth 830 nm, CW, 50 mW) in skin contact at a dose of 6 J/point. The placebo control group was treated with an ineffective probe (power 0.5 mW) of the same appearance. Before examinations and immediately, 2 wk, and 2 mo after completing the therapy, thermography was performed: joint flexion, circumference, and pressure sensitivity were measured; and the Visual Analogue Scale was recorded. In the group treated with active LPT, a significant improvement was found in pain (before treatment [BT]: 5.75; 2 mo after treatment : 1.18); circumference (BT: 40.45; AT: 39.86); pressure sensitivity (BT: 2.33; AT: 0.77); and flexion (BT: 105.83; AT: 122.94). In the placebo group, changes in joint flexion and pain were not significant. Thermographic measurements showed at least a 0.5 degrees C increase in temperature - and thus an improvement in circulation compared to the initial values. In the placebo group, these changes did not occur.

Malliaropoulos [2190] performed a randomised, double-blinded, placebo-controlled study to assess the effectiveness of LPT in patients with meniscal pathology, including only symptomatic patients with tiny focus of grade 3 attenuation (seen only on 0.7 thickness sequences) or, intrasubstance tears with spot of grade 3 signal intensity approaching the articular surface. None of the patients in the study group underwent arthroscopy or new magnetic resonance imaging investigation. Pain was significantly improved for *the LPT group than for the placebo group. Pain scores were significantly better after LPT. Four (12.5 %) patients did not respond to LPT. At baseline, the average Lysholm score was 77±4.6 for the LPT group and 77.2±2.6 for the placebo group. Four weeks after LPT or placebo therapy, the laser group reported an average Lysholm score of 82.5±4.6, and the placebo group scored 79.0±1.9. At 6 months, the laser group had an average Lysholm score of 82.2±5.7, and after 1 year, they scored 81.6±6.6. Treatment with LPT was associated with a significant decrease of symptoms compared to the placebo group: it should be considered in patients with meniscal tears who do not wish to undergo surgery.*

The purpose of a study by Zati [2282] was to evaluate the effect of a Nd:YAG on the regeneration of cartilage tissue in patients with traumatic lesions. Clinical, histological and immunohistochemical evaluations were performed. Ten patients affected by chondral lesions scheduled for ACI procedure, were enrolled into the study. During the chondrocyte expansion for ACI procedure, cartilage from five patients was treated by Nd:YAG High Intensity Laser Therapy (HILT group). No laser treatment was performed in the remaining patients, who were used as controls. Cartilage repair was assessed by clinicians using two different scores: Cartilage Repair Assessment (CRA) and Overall Repair Assessment (ORA). Cartilage biopsy specimens were harvested to perform histological and immunohistochemical analyses at T0 (before laser treatment) and T1 (at the end of the treatment). A significant decrease in cartilage depth was noticed in the HILT group at T1. Histological and immunohistochemical evaluations showed some regenerative processes in cartilaginous tissue in terms of high amount of proteoglycans, integration with adjacent articular cartilage and good cellular arrangement in the HILT group. By contrast, a not well organised cartilaginous tissue with various fibrous features in the control group at T0 and T1 was observed.

The aim of a study by Alghadir [2404] was to investigate the effect of LPT on pain relief and functional performance in patients with chronic knee osteoarthritis (OA). Forty patients with knee OA were randomly assigned into active laser group (n=20) and placebo laser group (n=20). The LPT device used had 50 mW, 850 nm, diameter beam of 1 mm. Eight points were irradiated and received dosage of 6 J/point for 60 s, with a total dosage of 48 J/cm² in each session. The placebo group was identical but treated without emission of energy. LPT was applied two times per week over the period of 4 weeks. Outcome measurements included pain intensity at rest and at movement on Visual Analogue Scale, knee function using Western Ontario McMaster Universities Osteoarthritis Index scale, and ambulation duration. These measurements were collected at baseline and post-intervention. The results showed significant improvements in all assessment parameters in both groups compared to baseline. Active laser group showed significant differences in pain intensity at rest and movement, knee function, and ambulation duration when compared with the placebo group.

The dose per point is 3 J (50 x 60) and total energy applied 24 J (3 x 8). The fluence is also obviously incorrect in the abstract. In the full paper, 100 mW is reported. Also the 0.008 cm² beam from a 100 mW laser = 12.7 W/cm² when applied for 60 seconds = 762 J/cm² per point not the 48 J/cm² reported. The authors probably meant 8 points x 6 joules = 48 joules, not 48 J/cm²

Alfredo [2425] selected forty participants with knee osteoarthritis, 2-4 osteoarthritis degree, aged between 50 and 75 years and both genders. Participants were randomised into one of two groups: the laser group (LPT, 3 J and exercises) or placebo group (placebo laser and exercises). Pain was assessed using VAS, functionality using the Lequesne questionnaire, range of motion with a universal goniometer, muscular strength using a dynamometer, and activity using the WOMAC questionnaire at three time points: (T1) baseline, (T2) after the end of laser therapy (three weeks) and (T3) the end of the exercises (11 weeks). When comparing groups, significant differences in the activity were also found. No other significant differences were observed in other variables. In intragroup analysis, participants in the laser group had significant improvement, relative to baseline, on pain, range of motion, functionality and activity. No significant improvement was seen in the placebo group.

The aim of a randomised controlled study by Kheshie [2524] was to compare the effects of LPT and high-intensity laser therapy (HILT) on pain relief and functional improvement in patients with knee osteoarthritis (KOA). A total of 53 male patients participated in this study, with a mean (SD) age of 54.6 (8.49) years. Patients were randomly assigned into three groups and treated with HILT and exercise (HILT + Exercise), LLLT and exercise (LLLT + Exercise), and placebo laser plus exercise (PL + Exercise) in groups 1, 2, and 3, respectively. The result showed that HILT and LLLT combined with exercise were effective treatment modalities in decreasing the VAS and WOMAC scores after 6 weeks of treatment. HILT combined with exercises was more effective than LPTT combined with exercises, and both treatment modalities were better than exercises alone in the treatment of patients with KOA.

Looking at the parameters used, this study gives conflicting and confusing results. The high intensity laser was applied over an area of about 100 cm², delivering some 13 mW/cm². This is under recommended LPT energies. The "low level laser", on the other hand, used 4 x 200 mW stationary over the patella for over 30 minutes. This is higher than recommended LPT energies. Both approaches seem to be substandard and an evaluation of the "high" or "low" energies is impossible. This is a typical example where manufacturers of "high" energy lasers do their best to convert their expensive lasers into "low level" lasers.

After the literature search by Jang [2329], 22 LPT trials related to joint pain were selected. The average methodological quality score of the 22 trials consisting of 1014 patients was 7.96 on the PEDro scale; 11 trials *reported positive effects and 11 trials reported negative effects. The mean weighted difference in change of pain on VAS was 13.96 mm in favour of the active LPT groups. When only considering the clinical trials in which the energy dose was within the dose range suggested in the review by Bjordal et al. in 2003 and in World Association for Laser Therapy (WALT) dose recommendation, the mean effect sizes were 19.88 and 21.05 mm in favour of the true LPT groups, respectively. The review shows that laser therapy on the joint reduces pain in patients. Moreover, when restricting the energy doses of LPT into the dose window suggested in the previous study, more reliable pain relief treatments can be expected.*

Further literature: [98, 99, 100, 152, 193, 210, 325, 343, 434, 453, 518, 605, 617, 738, 955, 1019, 1020, 1026, 1027, 1055, 1060, 1133, 1139, 1150, 1166, 1172, 1308, 1313, 1419, 1449, 1532, 1680, 1799, 2290, 2533]

4.1.6 Asthma

Inflammation, increase of cytokine production and decreased relaxation capacity of airway smooth muscles are characteristic of asthma. LPT seems to have an ameliorating relaxing response of trachea smooth muscles exposed to TNF-alpha. The research literature available for treating asthma is thin on the clinical side, but we have here yet another example of an indication where there are only benefits to be gained by trying.

Literature:

The purpose of a study by Aimbire [1668] was to investigate the effect of LPT on the mechanism of TNF-alpha-induced alteration of adrenoceptor responsiveness in trachea smooth muscle (TSM) in male rats. Inflammation, increase of cytokine production and decreased relaxation capacity of airway smooth muscles are characteristic of asthma. A controlled animal study with rats randomly divided into groups was performed. The responsiveness of TSM and the cAMP accumulation were measured 24 h after incubation with TNF-alpha. Five minutes after incubation, the TSM were irradiated by a 655 nm laser with laser-doses of 2.6 J/cm^2 and mounted in an organ bath apparatus. Laser irradiation was able to restore the relaxing response of TSM to isoproterenol but not to forskolin after TNF-alpha incubation. Laser also restored the cAMP induced by isoproterenol. These results demonstrate that the laser irradiation increased the responsiveness of TSM and the accumulation of cAMP to isoproterenol, probably due to the inhibition of the TNF-alpha.

It has not been known if the decreased ability to relax airway smooth muscles in asthma and other inflammatory airway disorders can be influenced by therapeutic laser irradiation. To investigate if this modality could reduce impairment in inflamed trachea smooth muscles (TSM) in rats, Aimbire [1668] performed a controlled rat study, where trachea was dissected and mounted in an organ bath apparatus with or without a TNF-alpha solution. LPT was administered perpendicularly to a point in the middle of the *dissected trachea with a wavelength of 655 nm and a dose of 2.6 J/cm². This irradiation partially restored TSM relaxation response to isoproterenol. Tension reduction was 47.0 % in the laser-irradiated group compared to 22.0% in the control group. Accumulation of cAMP was almost normalised after LPT at 22.3 pmol/mg compared to 17.6 pmol/mg in the non-irradiated control group.*

The aim of another study by Aimbire [1560] was to investigate the effect of LPT on male rat trachea hyperreactivity (RTHR), bronchoalveolar lavage (BAL) and lung neutrophils influx after Gram-negative bacterial lipopolysacharide (LPS) intravenous injections. The RTHR, BAL and lung neutrophils influx were measured over different intervals of time (90 min, 6 h, 24 h and 48 h). The energy density (ED) that produced an anti-inflammatory effect was 2.5 J/cm², reducing the maximal contractile response and the sensibility of trachea rings to methacholine after LPS. The same ED produced an anti-inflammatory effect on BAL and lung neutrophils influx. The Celecoxib COX-2 inhibitor reduced RTHR and the number of cells in BAL and lung neutrophils influx of rats treated with LPS. Celecoxib and laser reduced the PGE_2 and TXA2 levels in the BAL of LPS-treated rats. These results demonstrate that 685 nm LPT produced anti-inflammatory effects on RTHR, BAL and lung neutrophils influx in association with inhibition of COX-2-derived metabolites.

It is unknown if the decreased ability to relax airways smooth muscles in asthma and other inflammatory disorders, such as acute respiratory distress syndrome (ARDS), can be influenced LPT. In this context, the work by de Lima [2102] was developed in order to investigate if LPT could reduce dysfunction in inflamed bronchi smooth muscles (BSM) in rats. A controlled ex vivo study was developed where bronchi from Wistar rat were dissected and mounted in an organ bath apparatus with or without a TNF-alpha. LPT administered perpendicularly to a point in the middle of the dissected bronchi with a wavelength of 655 nm and a dose of 2.6 J/cm², partially decreased BSM hyperreactivity to cholinergic agonist, restored BSM relaxation to isoproterenol and reduced the TNF-alpha mRNA expression. An NF-kappaB antagonist (BMS205820) blocked the LPT effect on dysfunction in inflamed BSM. The results obtained in this work indicate that the LPT effect on alterations in responsiveness of airway smooth muscles observed in TNF-alpha-induced experimental acute lung inflammation seems to be dependent of NF-kappaB activation.

Wang [2431] investigated the effect of LPT on allergic asthma in rats and compared its effect with that of the glucocorticoid budesonide. Asthma was induced by challenge and repeated exposure to ovalbumin. Asthmatic rats were then treated with LPT or budesonide suspension. LPT at 8 J/cm² once daily for 21 days could relieve pathological damage and airway inflammation in asthmatic rats. LPT could decrease the total numbers of cells and eosinophils in bronchoalveolar lavage fluid. LPT could reduce levels of IL-4 and increase IFN-gamma levels in bronchoalveolar lavage fluid and serum, *meanwhile reduce serum IgE levels. Flow cytometry assay showed that LPT can regulate the Th1/Th2 imbalance of asthmatic rats. LPT had a similar effect to that of budesonide. These findings suggest that the mechanism of LPT treatment of asthma is by adjustment of Th1/Th2 imbalance. Thus, LPT could take over some of the effects of budesonide for the treatment of asthma, thereby reducing some of the side effects of budesonide.*

LPT controls bronchial hyperresponsiveness (BHR) associated with increased RhoA expression as well as pro-inflammatory mediators associated with NF-kB in acute lung inflammation. Herein, Silva [2498] explored if LPT can reduce both BHR and Th2 cytokines in allergic asthma. Mice were studied for bronchial reactivity and lung inflammation after antigen challenge. BHR was measured through dose-response curves to acetylcholine. Some animals were pretreated with a RhoA inhibitor before the antigen. LPT (660 nm, 30 mW and 5.4 J) was applied on the skin over the right upper bronchus and two irradiation protocols were used. Reduction of BHR post LPT coincided with lower RhoA expression in bronchial muscle as well as reduction in eosinophils and eotaxin. LPT also diminished ICAM expression and Th2 cytokines as well as signal transducer and activator of transduction 6 (STAT6) levels in lungs from challenged mice.

Intravenous HeNe laser irradiation has been used to reduce symptoms in asthmatic patients [1032, 1033, 1035].

Laser acupuncture is reported to be successful in treating this condition. [118, 878, 879, 883]. One example is the investigation by Milojevic [1546] which was aimed at defining therapeutic effects of LPT by stimulating acupuncture points or local treatment of asthma. A prospective analysis included 50 patients treated during 2000, 2001 and 2002. Together with conservative treatment of present disease, these patients were treated with laser stimulation of acupuncture points for 10 days. During treatment changes of functional respiratory parameters were recorded. Results were compared with those in the control group. The control group consisted of the same number of patients and differed from the examination group only by not using laser stimulation. Patients with bronchial asthma showed a significant improvement of all estimated lung function parameters just 30 minutes after laser stimulation. Improvement achieved on the third and the tenth day of treatment was significantly higher in the examination group in comparison with the control group. Further investigation confirmed that improvement of measured lung function parameters was significantly higher in younger patients, in patients whose disease lasted shorter, as well as in women. Patients with asthma, who were treated every three months for a one-year period, displayed a significantly lower frequency and intensity of attacks. A 10-day course of laser stimulation of acupuncture points in patients with bronchial asthma improves both the lung function and gas exchange parameters. Positive effects of laser treatment in patients with bronchial asthma are achieved in a short time and they last long, for several weeks, even *months. Successive laser stimulation in asthmatics prolongs periods of remission and decreases the severity of asthmatic attacks.*

Further literature: [340, 710, 840, 1315, 1318, 1667, 1668]

4.1.7 Blood preservation

Donor blood is usually stored in a blood bank as separate components, and some of these have short shelf lives. There are no storage solutions to keep platelets for extended periods of time. The longest shelf life used for platelets is seven days. Red blood cells, the most frequently used component, have a shelf life of 35-42 days at refrigerated temperatures. Plasma can be stored frozen for an extended period of time and is typically given an expiration date of one year. Treating donor blood with LPT seems to have a preservative effect and could increase the shelf life.

Literature:

The studies by Siposan [987, 1129] have shown that LPT, even though used at low doses and low power densities, produced some changes of the rheological factors of the blood, as follows: a revitalising and regenerating effect on mitosis stimulation and a non-damaging and biostimulating effect on the cell membrane.

The aim of a study by do Nascimento [1738] was to investigate the effects of LPT at different energy densities (0.1-2.0 J/cm^2) on the capacity of long-term cryopreserved peripheral blood progenitor cell (PBPC) for growth of colony-forming units (CFU) in vitro. Cryopreserved PBPC samples were thawed after 3 years in order to demonstrate the positive effect of LPT and after 5 years in order to confirm the LPT proliferative effect. A 685 nm laser with 25 mW power was used as the source of irradiation. Cultures were exposed to energy densities of 0.1, 0.5, 1.0, 1.5, and 2.0 J/cm^2 before incubation (10 irradiated and 10 controls at each energy density group). A higher number of CFU was observed at the dose of 1.0 J/cm^2 (control 21.3 ± 8.5 × 105 cells, irradiated 40.1 ± 10.5 × 105 cells). No differences were observed in cultures exposed to doses of 0.1, 0.5, and 1.5 J/cm^2. A decreased number of CFU was demonstrated in samples exposed to the dose of 2.0 J/cm^2 (control 21.4 ± 11.9×105 cells). PBPC samples cryopreserved for 5 years were thawed for CFU assays and exposed to a single dose of 1.0 J/cm^2; once again the exposed group showed a higher number of CFU (control 8.8 ± 7.8 × 105 cells, irradiated 18.1 ± 13.1 × 105 cells). Dependent upon the energy density, LPT elevates (1.0 J/cm^2) or decreases (2.0 J/cm^2) the potential of long-term cryopreserved PBPC for growth of CFU in vitro.

Further literature: [1448]

4.1.8 Blood pressure

The literature here is meagre and no definite conclusions can be made. However, the hints in the literature below are interesting and deserve further attention. Blood pressure medication is one of the most profitable businesses in the pharmaceutical industry and certainly an important contribution to global health. Yet, non-pharmacological methods without side effects are sought after. Light is known to stimulate the release of NO, and this may be the mechanism behind the studies below.

Literature:

Umeda [144] tested the effects of a GaAlAs laser on the control of blood pressure. Radiation was administered via the medulla oblongata. The results from a group of 30 patients suffering from hypertension were excellent in 20% of the cases, good in 37%, fairly good in 23%, and the treatment had no effect in 20%. In a control group of patients with normal blood pressure, no noteworthy results were achieved, except that those bordering on low blood pressure experienced a rise.

Velizhanina [698] used laser irradiation as monotherapy in 42 patients with early essential hypertension. Hypotensive and antioxidant effects of LPT plus its ability to decrease total peripheral resistance were more pronounced in patients with stage I hypertension.

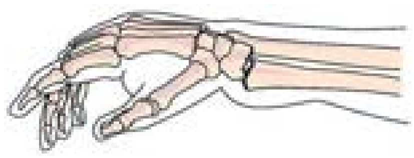
Mokmeli [2046] allocated 125 patients according to their systolic blood pressure in 3 groups: 1. Normotensive (<120 mmHg, n=50), 2. Pre-hypertensive (120-139 mmHg n=50), 3. Hypertensive (stage I =140-159 mmHg, n=25). All the groups were treated for 30 minutes with an intravenous laser with a 630 nm, 2.5 mW power at the end of an intravenous fibre. Pulse rate, systolic, diastolic, and pulse pressures were measured before, after, and 15 minutes after the IVL. There was no statistically significant difference for pulse rate, systolic and diastolic blood pressure in normotensive group, however a significant difference was observed for pulse rate, systolic and diastolic blood pressure in pre-hypertensive group as for systolic and diastolic blood pressure in hypertensive group. In conclusion, IVL is an effective method for modifying factors to result in a reduction of arterial pressure. It can be combined with anti-hypertensive drugs in pre-hypertensive and hypertensive patients as a modality of treatment; the method is also safe to use on normotensive patients.

Superficial light in general may have an effect on blood pressure and not limited to coherent light, since UV light has the same effect acc. to Liu [2485], who reports: The incidence of hypertension and cardiovascular dis-

ease correlates with latitude and rises in winter. The molecular basis for this remains obscure. As nitric oxide (NO) metabolites are abundant in human skin we hypothesised that exposure to UVA may mobilise NO bioactivity into the circulation to exert beneficial cardiovascular effects independently of vitamin D. In 24 healthy volunteers irradiation of the skin with 2 Standard Erythemal Doses of UVA lowered BP, with concomitant decreases in circulating nitrate and rises in nitrite concentrations. Unexpectedly, acute dietary intervention aimed at modulating systemic nitrate availability had no effect on UV-induced hemodynamic changes, indicating that cardiovascular effects were not mediated via direct utilisation of circulating nitrate. UVA irradiation of the forearm caused increased blood flow independently of NO-synthase activity, suggesting involvement of pre-formed cutaneous NO stores. Confocal fluorescence microscopy studies of human skin pre-labelled with the NO-imaging probe DAF2-DA revealed that UVA-induced NO release occurs in a NOS-independent, dose-dependent fashion, with the majority of the light-sensitive NO pool in the upper epidermis. Collectively, our data provide mechanistic insights into an important function of the skin in modulating systemic NO bioavailability which may account for the latitudinal and seasonal variations of BP and cardiovascular disease.

Further literature: [574, 698, 971, 1166, 1215]

4.1.9 Bone regeneration



Bone loss may occur due to trauma, pathologies or following some surgical procedures. The regeneration of bone tissue is of central interest in relation to a great number of interventions. Wound healing is a complex process, which involves both local and systemic responses and bone healing is slower than that observed in soft tissues. Bone healing differs from the healing of soft tissues due to both the morphology and composition being slower than that of soft tissues and consists of consecutive phases, which differ depending upon the type and the intensity of the trauma and of the extension of the damage to the bone.

All laser wavelengths have been shown to influence bone regeneration, but, as always, the penetration of the different wavelengths must be taken into consideration. LPT has been found to accelerate cell proliferation optimally in the growing phase, when cells are considered as undifferentiated osteoprogenitor cells [1908].

The photobiological effect is a response to the absorption of a specific wavelength by a molecular photoreceptor. The magnitude of the biomodulative effect depends on the physiologic status of the cell at the irradiation time, and may explain why the biomodulative effect is not always detectable. A unique parameter in itself able to produce a photobiological response does not exist, but the conjugation of different parameters and its variations does. It still remains uncertain if bone stimulation by laser light is a general effect, or if the isolated stimulation of osteoblasts is possible.

It is known that the stimulant effect of laser light on bone occurs during the initial phase of proliferation of both fibroblasts and osteoblasts, as well as on initial differentiation of mesenchymal cells. Fibroblastic proliferation and its increased activity have been detected previously on irradiated subjects and cell cultures, and these are responsible for the great concentration of collagen fibres seen within irradiated bone.

Another important aspect to be observed is the effects of the laser light on the blood vessels. The vascular response to LPT is one of the possible mechanisms responsible for the positive clinical results observed following LPT. Vascularisation is an important and decisive factor for the healing of wounds and for the relief of the pain. Repeated irradiation is necessary to keep the process going; a single exposure is not enough. Three to four sessions per week for two consecutive weeks is an approximate schedule.

A promising area is the association of the LPT with biomaterials. It has been shown that combining the laser with both organic and inorganic bone grafts results in quicker healing of the bone. The use of BMPs further improve the results and complete harvesian systems can be seen as early as 14 days after wounding. Another promising area is the use of LPT to improve the results of autologous bone grafts. The aims of a report by Pinheiro [1920] were to report the state of the art with respect to photoengineering of bone repair using LPT. LPT has been reported to be an important tool in positive bone stimulation both in vivo and in vitro. These results indicate that photophysical and photochemical properties of some wavelengths are primarily responsible for the tissue responses. The use of correct and appropriate parameters has been shown to be effective in the promotion of a positive biomodulative effect in healing bone. A series of papers reporting the effects of laser therapy on bone cells and tissue, as well as new and promising developed protocols, have been presented. The results indicate that bone irradiated mostly with infrared (IR) wavelengths show increased osteoblastic proliferation, collagen deposition, and bone neoformation when compared to nonirradiated bone. Furthermore, the effect of laser therapy is more effective if the treatment is carried out at early stages when high cellular proliferation occurs. In conclusion, it is possible that the LPT effect on bone regeneration depends not only on the total dose of irradiation, but also on the irradiation time and the irradiation mode. The threshold parameter of energy density and intensity are biologically independent of one another. This independence accounts for the success and the failure of laser therapy achieved at low-energy density levels.

Literature:

In vitro studies

Yamada [414] irradiated cultured osteoblastic cells with a HeNe laser. The cell growth rate and DNA synthesis were increased only in the growing phase of culture. During long-term culture, calcium accumulation was enhanced by laser irradiation at 1 J/cm^2, with four sessions of irradiation resulting in a 46% increase compared to the control group. Alkaline phosphatase activity, however, was unchanged.

Ozawa [369] studied the effect of GaAlAs on bone formation in vitro. Osteoblast-like cells were isolated from rat calvariae of 21d rat fetuses. The cultivated cells were irradiated once only or once a day for 21 days at various energy doses (10.8-108 J/cm^2 per day). The total area of mineralised bone nodules on day 21 was evaluated. DNA content, alkaline phosphatase activity (ALP), and the amount of extracellular collagen were also measured. LPT significantly increased the number and the total area of bone nodules in a dose-dependent manner. Cell proliferation and ALP activity were higher in the early and middle culture periods, while the collagen content was higher in the middle and late periods as compared to controls. Calcium and phosphorus were both higher in the irradiation groups.

Hamajima [1564] investigated the stimulatory effect of laser irradiation on bone formation during the early proliferation stage of cultured osteoblastic cells. A mouse calvaria-derived osteoblastic cell line, MC3T3-E1, was utilised to perform a cDNA microarray hybridisation to identify genes that induced expression by laser at the early stage. Among those genes that showed at least a twofold increased expression, the osteoglycin/mimecan gene was upregulated 2.3-fold at two hours after laser irradiation. Osteoglycin is a small leucine-rich proteoglycan (SLRP) of the extracellular matrix which was previously called the osteoinductive factor. SLRP are abundantly contained in the bone matrix, cartilage cells and connective tissues, and are thought to regulate cell proliferation, differentiation and adhesion in close association with collagen and many other growth factors. The researchers investigated the time-related expression of this gene by laser, using a reverse transcription polymerase chain reaction (RT-PCR) method, and more precisely with a real-time PCR method, and found increases of 1.5-2-fold at two to four hours after laser treatment, compared with the non-irradiated controls. These results suggest that the increased expression of the osteoglycin gene by laser irradiation in the early proliferation stage of cultured osteoblastic cells may play an important role in the stimulation of bone formation in concert with matrix proteins and growth factors.

In the study by Ueda [1181], osteoblastic cells isolated from fetal rat calvariae were irradiated once with 830 nm, 500 mW in two different irradiation modes; continuous irradiation (CI), and 1 Hz pulsed irradiation (PI). The authors then investigated the effects on cellular proliferation, bone nodule formation, alkaline phosphatase (ALP) activity, and ALP gene expression. Laser irradiation in both groups significantly stimulated cellular *proliferation, bone nodule formation, ALP activity, and ALP gene expression, as compared with the non-irradiation group. Notably, PI markedly stimulated these factors when compared with the CI group. Since 1 Hz pulsed laser irradiation significantly stimulated bone formation in vitro, it is most likely that pulse frequency is an important factor affecting biological responses in bone formation.*

In a study by Stein [1763], cultured osteoblast cells were irradiated using HeNe laser irradiation (632.8 nm; 10 mW). On the second and third day after seeding, the osteoblasts were exposed to laser irradiation. The effect of irradiation on osteoblast proliferation was quantified by cell count and colourimetric MTT assay 24 and 48 h after the second irradiation. A significant 31-58% increase in cell survival (MTT assay) and higher cell count in the once-irradiated as compared to non-irradiated cells were monitored. Differentiation and maturation of the cells was followed by osteogenic markers: alkaline phosphatase (ALP), osteopontin (OP), and bone sialoprotein (BSP). A two-fold enhancement of ALP activity and expressions of OP and BSP were much higher in the irradiated cells compared to non-irradiated osteoblasts.

The aim of another in vitro study by Stein [2014] was to investigate the initial effect of LPT on growth and differentiation of human osteoblast-like cells. SaOS-2 cells were irradiated with laser doses of 1 J/cm^2 and 2 J/cm^2 using a laser with 670 nm wavelength and an output power of 400 mW. Untreated cells were used as controls. At 24 h, 48 h and 72 h post-irradiation, cells were collected and assayed for viability of attached cells and specific alkaline phosphatase activity. In addition, mRNA expression levels of osteopontin and collagen type I were assessed using semi-quantitative RT-PCR. Over the observation period, cell viability, alkaline phosphatase activity and the expression of osteopontin and collagen type I mRNA were slightly enhanced in cells irradiated with 1 J/cm^2 compared with untreated control cells. Increasing the laser dose to 2 J/cm^2 reduced cell viability during the first 48 h and resulted in persistently lower alkaline phosphatase activity compared with the other two groups. The expression of osteopontin and collagen type I mRNA slightly decreased with time in untreated controls and cells irradiated with 1 J/cm^2, but their expression was increased by treatment with 2 J/cm^2 after 72 h. These results indicate that LPT has a biostimulatory effect on human osteoblast-like cells during the first 72 h after irradiation.

Pires Oliveira [1908] irradiated osteoblastic cell cultures (OFCOL II) with 830 nm; 50 mW; 3 J/cm ; 600 microm diameter optical fibre, and divided into two groups: group 1: irradiated cells, and group 2: non-irradiated cells. Irradiation occurred at 24-h intervals for a total of three days. After each interval, the cells were marked with Mito Tracker Orange dye to assess the biostimulatory effect on mitochondrial activity and cell proliferation using an MTT assay. Intense grouping of mitochondria in the perinuclear region was observed at 24 h and 48 h following irradiation. Changes from a filamentous to a granular appearance in mitochondrial morphology *and mitochondria distributed throughout the cytoplasm were observed 72 h following proliferation. Such changes led to an in vitro proliferation process, as confirmed by the MTT assay. In conclusion, LPT showed itself capable of altering mitochondrial activity and the population of OFCOL II cells.*

The aim of study by Pacheco [2243] was to evaluate the effects of red and infrared lasers at high energy densities on pre-osteoblast MC3T3 proliferation and differentiation. Cells were irradiated with red (660 nm) and infrared (780 nm) lasers (90 and 150 J/cm², 40 mW). The control group did not receive irradiation. Cell growth was assessed by a colourimetric test (MTT) (24, 48, 72, 96 h) and cell differentiation was evaluated by alkaline phosphatase (ALP) quantification after growth in osteogenic medium (72, 96 h; 7, 14 days). None of the irradiation groups had an enhancement in cell growth. The production of ALP was not influenced by irradiation at any period of time.

The objective of a study by Huertas [2253] was to evaluate the effects on MG-63 cell proliferation of application of a pulsed diode laser of 940 nm at low energy levels. After 24 hrs. of culture, osteoblasts underwent pulsed laser radiation at 0.5, 1, 1.5, and 2 W and fluences of 1-5 J. A control group was not irradiated. After the treatment, cells were incubated for 24 hrs. and cell proliferation was analysed using a spectrophotometric measure of cell respiration (MTT assay). Results were expressed as percentage proliferation versus controls. At 24-hr culture, cell proliferation was increased in laser-treated cells at intensities of 0.5, 1, and 1.5 W/cm² versus controls; the energy density was positively correlated with cell growth, which reached a peak at 3 J and decreased at higher fluences. The use of pulsed low-level laser with low-energy density range thus appears to exert a biostimulatory effect on bone tissue. Although the data on cell proliferation are robust, in-depth investigation is required into the effect of these irradiation doses on other cell parameters. The present findings demonstrate that laser therapy could be highly useful in tissue regeneration in different clinical settings, including nursing, physical therapy, dentistry, and traumatology.

Animal studies

Nagasawa [106] describes two experiments on bone regeneration. In the first experiment, holes of 1 mm diameter were drilled in the femurs of 36 rats. The rats were divided into six groups of six. Before suturing, the holes in the femurs of five of the groups were irradiated with one type of laser light per group (Nd:YAG, GaAlAs, HeNe, CO2, KrF excimer 248 nm). The sixth group was the control and was not treated with a laser. After ten days, the wound area was studied under a microscope. Some osteoclasts were visible in the untreated group, but few samples were spongy and there were few trabeculae. In the Nd:YAG group, active spongy formation could be observed, with visible trabeculae. Similar formations were observed in the GaAlAs and HeNe groups. In the group treated with a carbon dioxide laser, delayed healing was observed, while the excimer laser group showed signs of necrosis.

All rats received a 100 J/cm² dosage, except the excimer group, in which the dosage was 2 J/cm².

The other experiment involved the use of BMP (bone morphogenetic protein). This is a bioactive substance, which participates in bone formation. It exists in osteoblasts and can be stored in an inactive form. Small pellets were made from calf collagen and impregnated with extracted BMP. The dry weight of the pellets was 8 mg. Pellets of this kind were implanted under the skin on the backs of rats. Six rats were treated with 100 J/cm² of GaAlAs laser, and six with 50 J/cm² of HeNe laser, after the implantation, but before the wound was sutured. A control group of six rats was not treated. After three weeks, all the pellets were removed and weighed, measured and analysed with respect to their content of Ca and P. The average dry weight of the control group's pellets was 11.6 mg, while it was 14.24 mg for the GaAlAs group, and 13.98 mg for the HeNe group. The Ca levels were 0.86 mg (control group), 1.28 mg (GaAlAs), and 1.0 mg (HeNe). The P levels were 1.04, 1.24, and 1.22 respectively. Nagasawa suggested the following explanation of the results: in addition to stimulating BMP, LPT also causes undifferentiated mesenchymal cells to change into osteoblasts, by means of which the osteogenetic activity increases.

The study by Márquez Martínez [2016] assessed histologically the effect of LPT on the repair of surgical defects on the femur of rats filled with lyophilised bovine bone. The animals were divided into three groups: group I (control); group II (graft); group III (graft + LPT). The animals in the irradiated groups received 16 J/cm² per session divided into four points around the defect receiving the first irradiation immediately after surgery and repeated every 48 h for two weeks. Animal death occurred 15, 21, and 30 days after surgery. The specimens were routinely processed and stained with H/E and Sirius red and analysed by light microscopy. There was histological evidence of improved collagen fibre deposition at early stages of the healing; an increased amount of well-organised bone trabeculae at the end of the experimental period on irradiated animals.

The aim of a study by Gerbi [1471] was to evaluate the effectiveness of 830 nm, 40 mW, CW, in the repair of bone defects (3 mm²) submitted to organic and inorganic bovine bone graft implantation in the femur of rats (42 animals). The sample was divided into five groups: Group I (control, 6 animals); Group II (Organic Bone graft, 9 animals); Group III (Organic Bone + Laser, 9 animals); Group IV (Anorganic Bone Graft, 9 animals); Group V (Anorganic Bone Graft + Laser, 9 animals). The irradiated groups received seven irradiations every 48 hours, the first immediately after the surgical procedure. The dosimetry was of 16 J/cm² per session, divided in four points of 4 J/cm². The sacrifice periods were of 15, 21 and 30 days. The obtained results demonstrated that an improved and faster bone repair could be observed in the irradiated groups, evidenced by the largest concentration of collagen fibres in the period of 15 and 21 days and for a larger bone formation and a well organised bone trabeculae at the end of the period (day

30), when compared with the control group. Both biomaterials favoured bone neoformation inside the defect

Another paper by Gerbi [1620] is part of an ongoing series of works in which biomaterials (bone morphogenetic proteins) are used in association with LPT. Forty-eight adult male Wistar rats were divided into four randomised groups: group I (control, n=12); group II (LPT, n=12); group III (BMPs + organic bovine bone graft, n=12); and group IV (BMPs + organic bovine bone graft + LPT, n=12). The irradiated groups received seven irradiations every 48 h, beginning immediately after the surgical procedure. The laser therapy (830 nm, 40 mW CW, spot size = 0.6 mm) consisted of 16 J/cm^2 per session divided equally over four points (4 J/cm^2 each) around the defect. The subjects were sacrificed after 15, 21, and 30 days, and the specimens were routinely embedded in wax, stained with hematoxylin and eosin and sirius red, and analysed under light microscopy. The results showed histological evidence of increased deposition of collagen fibres (on days 15 and 21), as well as an increased amount of well-organised bone trabeculae at the end of the experimental period (30 days) in the irradiated animals versus the non-irradiated controls. .

The aim of a study by Weber [1615] was to histologically assess the effect of 830 nm laser on the healing of bone defects associated with autologous bone graft. Sixty male rats were divided into four groups: G1 (control); G2 (laser on the surgical bed); G3 (laser on the graft) and G4 (laser on both the graft and the surgical bed). The dose per session was that of 10 J/cm^2, and it was applied to the surgical bed (G2/G4) and on the bone graft (G3/G4). Irradiation was carried out at every other day for 15 days (830 nm, 50 mW, 10 J/cm^2). The dose was fractioned into four points. The animals were sacrificed 15, 21 and 30 days after surgery; specimens were taken and routinely processed. The light microscopic analysis was performed by an experienced pathologist. In the groups where the laser was used during surgery on the surgical bed (G2/G4), bone remodelling was both quantitatively and qualitatively more evident when compared to subjects of groups G1 and G3.

Nagasawa [107] has also studied the effects of an argon laser (514 nm) used at an output level appropriate for LPT. Periapical lesions, which despite conventional endodontics had shown no sign of starting to heal two months after the start of root treatment, were treated with an argon laser (100-400 mW) directly in the root canal. In some cases, the healing process began after a single treatment.

Lomnitski [179] studied reparative osteogenesis in 105 rabbits. The healing of drilled cavity defects in the mandibles stimulated with HeNe laser light of various powers was monitored using a histological method, and the distinctive reparative effects of the laser light were evaluated.

Yaakobi [87] made holes in the tibias of rats. HeNe laser irradiation on days 5 and 6 post-injury increased calcium accumulation twofold compared to control. Osteoblastic activity increased, too, as reflected by alkaline phosphatase activity.

Horowitz [473] performed calvarial trepanations in 18 rats. HeNe laser light was applied every day for two weeks. Through infrared spectroscopy the following parameters were found to have improved compared with the control group: 1) amount of mineralisation, 2) factor of conformation, 3) protein to lipid ratio, 4) structural stage.

Saito [569] expanded the midpalatal suture in rats. A 100 mW GaAlAs laser was used to influence bone regeneration. Irradiation during the two first postoperative days was effective, accelerating regeneration by a factor of 1.2 to 1.4 compared to the control group. Irradiation in the later period (days four to six) was not effective, neither was a single irradiation.

Pyczek [832] studied the effect of LPT on the haematopoietic system of rats and also on the basic haematological parameters. A 5 mW HeNe and an 80 mW GaAs laser were used. Intact skin on the hind legs of rats was exposed over a section of the femur. Peripheral blood analysis was carried out before and after the experiments. These indicated that GaAs laser light induced a decrease in bone marrow mastocytes and peripheral blood basophils with an increase in the number of eosinophils. An increase in mitotic activity in the bone marrow was observed in the exposed groups of animals. No significant changes in Hb, Ht, erythrocyte or reticulocyte levels in the peripheral blood were noted, nor was there an increase in megakaryocyte emperipolesis.

The results of a rat study by Ozawa [1011] suggest that laser irradiation may play two principal roles in stimulating bone formation. One is stimulation of cellular proliferation, especially proliferation of nodule-forming cells of osteoblast lineage, and the other is stimulation of cellular differentiation, especially to committed precursors, resulting in an increase in the number of more differentiated osteoblastic cells and an increase in bone formation. The two processes can only be stimulated through laser irradiation of immature cells.

Atomic Force Microscopy (AFM) and Scanning Electron Microscopy (SEM) were used in the study by Cruz-Höfling [1326] to quantify bone morphology during post-injury ossification in rat tibiae and characterise the differences induced by laser compared with the naturally occurring regenerative process. A 1.5 diameter hole was made surgically in the tibia and two different doses of laser were applied for 7 or 14 consecutive days, starting 24 hrs after lesion. The collagen fibre lamellar organisation in the matrix, typical of mature bone, was promoted by the HeNe laser at doses of either 31.5 J/cm^2 or *94.5 J/cm^2*

Gordjestani [1271] failed to find any stimulatory effect of bone regeneration in a rat experiment. Even though this study was well designed, the dose was high. The artificially created bony defects in the parietal bone were irradiated through the rat fur every day for 28 consecutive days with a dose of 20 J/cm^2 and a power density of 33.3 mW/cm^2. The laser used was a GaAs laser and it is generally recognised that dosages with this type of laser should be kept lower than for GaAlAs.

The influence of HeNe laser radiation on the formation of new blood vessels in the bone marrow compartment of a regenerating area of the mid-cortical diaphysis of the tibiae of young adult rats was studied by Garavello [1544]. A small hole was surgically made with a dentistry burr in the tibia and the injured area received a daily LPT over 7 or 14 days transcutaneously starting 24 h after surgery. Incident energy density dosages of 31.5 and 94.5 J/cm^2 were applied during the period of the tibia wound healing investigated. Light microscopic examination of histological sections of the injured area and quantification of the newly-formed blood vessels were undertaken. LPT accelerated the deposition of bone matrix and histological characteristics compatible with an active recovery of the injured tissue. HeNe LPT significantly increased the number of blood vessels after 7 days of irradiation at an energy density of 94.5 J/cm^2 , but significantly decreased the number of vessels in the 14- day irradiated tibiae, independent of the dosage. These effects were attributed to laser treatment, since no significant increase in blood vessel number was detected between 8 and 15 non-irradiated control tibiae.

The aim of the work by Lizarelli [914] was to evaluate histometrically the effect of irradiation with 790 nm laser in the chronology of alveolar repair of rats. Groups of five animals had their upper right incisors extracted under anaesthesia and the mucous sutured; three groups received 1.5 J/cm^2 of irradiation immediately after the extraction with laser sweeping over the operated area. After that, the animals were sacrificed 7, 14 and 21 days after the dental extraction. The material was decalcified and processed for inclusion in paraffin. Longitudinal sections of seven micrometers in the alveolus were made and stained with HE and the percentage of the bone tissue was assessed. The results show that LPT produced acceleration in osseous formation (10%) in some periods. The influence of laser irradiation on the healing process is more significant when the laser light can be applied just after the tissue trauma. Cells with a lower than normal pH, where the redox state is shifted in the reduced direction, are considered to be more sensitive to the stimulative effect of light than those in which the respective parameters are optimal or near optimal. The proposed redox-regulation mechanism may present a fundamental explanation of some of the clinical effects of irradiation. A consequence of this is that the difference between the groups after 7 days is more significant than between the other groups.

Pinheiro [1128] evaluated morphometrically the amount of newly formed bone after 830 nm laser irradiation of surgical wounds created in the femur of rats. A total of 48 rats were divided into four groups with 12 animals in each group. Group A received 4.8 J/cm^2 transcutaneously, three times a week, and sacrificed after 28 days. Group C received only three sessions and was sacrificed after 7 days. Group B and D served as control. There was a significant difference between group C and control but not between A and control.

The aim of the study by Pinheiro [2242] was to assess, by light microscopy and histomorphometry, the repair of surgical fractures fixed with internal rigid fixation (IRF) treated or not with IR laser (780 nm, 50 mW, 4 x 4 J/cm^2 = 16 J/cm^2) associated or not to the use of hydroxyapatite and guided bone regeneration. Surgical tibial fractures were created under general anesthesia on 15 rabbits that were divided into 5 groups, maintained on individual cages, at day/night cycle, fed with solid laboratory pelted diet, and had water ad libidum. The fractures in groups II, III, IV, and V were fixed with miniplates. Animals in groups III and V were grafted with hydroxyapatite and GBR technique used. Animals in groups IV and V were irradiated at every other day during two weeks (4 x 4 J/cm^2, 16 J/cm^2 = 112 J/cm^2). Observation time was that of 30 days. After animal death, specimens were taken, routinely processed to wax, cut and stained with HA and Sirius red, and used for histological assessment. The results of both analyses showed a better bone repair on all irradiated subjects especially when the biomaterial and GBR were used. In conclusion, the results suggest that the association of hydroxyapatite and laser light results in a positive and significant repair of complete tibial fractures treated with miniplates.

Nicola [1262][1566] studied the activity in bone cells after 660 nm laser irradiation, close to the site of the bone injury. The femurs of 48 rats were perforated (24 in the irradiated group and 24 in the control group) and the irradiated group was treated with 660 nm, 10 J/cm^2 of radiant exposure on the 2nd, 4th, 6th and 8th day after surgery (DAS). The researchers carried out histomorphometry analysis of the bone. It was found that activity was higher in the irradiated group than in the control group: (a) bone volume at 5 DAS; (b) osteoblast surface at 15 DAS; (c) mineral apposition rate at 15 and 25 DAS; (d) osteoclast surface at 5 DAS and 25 DAS; and (e) eroded surface. It is concluded that this type of irradiation increases the activity in bone cells (resorption and formation) around the site of the repair without changing the bone structure.

The aim of a study by Matsumoto [1922] was to analyse the role of cyclo-oxygenase-2 following bone repair in rats submitted to LPT. A total of 48 rats underwent surgery to inflict bone defects in their tibias after being randomly distributed into two groups: negative control, and a laser exposed group, i.e., the animals were treated with LPT by means of gallium arsenide laser at 16 J/cm^2. The animals were killed after 48 h, 7 days, 14 days, or 21 days. The tibias were removed for morphological, morphometric, and immunohistochemistry analysis for cyclo-oxygenase-2. Statistical significant differences were observed in the quality of bone repair and quantity of formed bone between groups 14 days after surgery. In the same way, cyclo-oxygenase-2 immunoreactivity was more intense in bone cells for intermediate periods evaluated in the laser exposed group. Taken together, such results suggest that LPT is able to improve bone repair in the tibia of rats 14 days after surgery as a result of an up-regulation for cyclo-oxygenase-2 expression in bone cells.

A study by Liriani-Galvao [1645] aimed to compare the consequences of LPT and low-intensity pulsed ultrasound (LIPUS) on bone repair. Many studies have assessed the effects of LPT and LIPUS on bone repair, but a comparison of them is rare. Male Wistar rats (n=8) with tibial bone osteotomy were used. One group had the osteotomised limb treated with LPT (780 nm, 30 mW, 112.5 J/cm^2) and the second group with LIPUS (1.5 MHz, 30 mW/cm^2), both for 12 sessions (five times per week); a third group was the control. After 20 days, rats were sacrificed and had their tibias submitted to a bending test or histomorphometric analysis. In the bending test, maximum load at failure of the LPT group was significantly higher. Bone histomorphometry revealed a significant increase in osteoblast number and surface, and osteoid volume in the LPT group, and a significant increase in eroded and osteoclast surfaces in the LIPUS group. In conclusion LIPUS enhanced bone repair by promoting bone resorption in the osteotomy area, while LPT accelerated this process through bone formation.

The aim of a study by Rabelo [1887] was to compare the effect of LPT on the wound healing process in non-diabetic and diabetic rats. Among the clinical symptoms caused by diabetes mellitus, a delay in wound healing is a potential risk for patients. It is suggested that LPT can improve wound healing. The tissue used for this study was extracted from animals suffering from diabetes, which was induced by Streptozotocin, and from non-diabetic rats. Animals were divided into two groups of 25 rats each (treated and control) and further subdivided into two groups: diabetic (n=15) and non-diabetic (n=10). A full-thickness skin wound was made on the dorsum area, with a round 8 mm holepunch. The treated group was irradiated by a HeNe laser with the following parameters: 15 mW, exposition time of 17 sec, 0.025 cm^2 irradiated area, and energy density of 10 J/cm^2. Square full-thickness skin samples (18 mm each side, including both injured and non-injured tissues) were obtained 4, 7, and 15 days after surgery and analysed by qualitative and quantitative histological methods. Quantitative histopathological analysis confirmed the results of the qualitative analysis through histological microscope slides. When comparing tissue components (inflammatory cells, vessels and fibroblast/area), the authors found that treated animals had a less intense inflammatory process than controls.

A study by Pinheiro [1881] assessed histologically the effect of laser on the repair of surgical defects created in the femurs of treated and non-treated Wistar rats with bone morphogenetic proteins (BMPs) and organic bovine bone graft. A total of 48 adult male Wistar rats were divided into four randomised groups: group 1 (controls, n=12); group 2 (laser, n=12); group 3 (BMPs + organic bovine bone graft + GBR, n=12); and group 4 (BMPs + organic bovine bone graft + GBR + laser, n=12). The irradiated groups received seven irradiations every 48 h, the first immediately after the surgical procedure. Laser (830 nm, 40 mW, CW, 0.6 mm) consisted of a total of 16 J/cm^2 per session at four points (4 J/cm^2 each) equally spaced around the periphery of the defect. The animals were sacrificed after 15, 21, and 30 *days, and the specimens were routinely embedded in wax and stained with hematoxylin and eosin and Sirius red stains and analysed under light microscopy. The results showed histological evidence of increased deposition of collagen fibres (on days 15 and 21), as well as an increased amount of well-organised bone trabeculi at the end of the experimental period (day 30) in irradiated animals compared to non-irradiated controls.*

The aim of the paper by Almeida-Lopes [2036] was to search for the best application fluency and emission mode, using an infrared laser in the repair of bone defects in the rat tibia. Thus, the histological quality of the neoformed bone was evaluated by analysis using common optic microscopy and polarised light. Application parameters: 100 mW, 830 nm, laser beam diameter = 0.06 nm, CW and 10 Hz, three sessions with 72 h intervals, energies and respective fluencies: 2 J=70 J/cm^2 , 4 J=140 J/cm^2, 6 J=210 J/cm^2, 8 J=160 J/cm^2, 10 J=200 J/cm^2. Laser therapy has increased and sped up the time bone repairing process (in the initial period of 10 days). This laser effect showed to be dose-dependent with the presence of an effective therapeutic window presenting biostimulation of the bone tissue between a total energy of 4 J and 8 J for both emission modes. The use of the laser with 10 J of energy generated, characterised by the bioinhibition of the tissues (in the initial period of 10 days). This inhibition took place at the exact irradiation spot.

Murine bone marrow cells, which contain both osteoblast and osteoclast progenitors, were cultured and induced to differentiate in the absence or in the presence of LPT in a study by Bouvet-Gerbettaz [2055]. Laser exposition parameters were determined using a power meter and consisted in an 808 nm light in CW mode, with an energy density of 4 J/cm^2 administered three times a week. Cell proliferation and differentiation were assessed after specific staining and microscopic analysis of the cultures after various times, as well as by quantitative RT-PCR analysis of a panel of osteoblast and osteoclast markers after nucleic acid extraction. The use of a power meter revealed that the power emitted by the optical fibre of the laser device was markedly reduced compared to the displayed power. This allowed to adjust the LPT parameters to a final energy density exposure of 4 J/cm^2. In these conditions, proliferation of bone marrow mesenchymal stem cells as well as osteoclast or osteoblast differentiation of the corresponding progenitors were found similar in control and LPT conditions. Using the present experimental protocol, the authors concluded that an 808 nm wavelength infrared LPT does not alter murine bone progenitor cell proliferation and differentiation. Moreover these results confirm the necessary use of a power meter to fix LPT protocol parameters.

In the study by Franco [2270], 5 J/cm^2 LPT in passive smoking compromised bone, neoformation was not adequate to stimulate local osteogenesis.The results of ta study by Andrade Gomes [2269] suggest an acceleration of bone mineral density after laser and ultrasound irradiation. Ultrasound irradiation showed the greatest effects and the laser power positively influ-

enced the recuperation of the bone density on the side opposite its application, causing a cross reaction or even exacerbating the inherent action of ultrasound irradiation.

The aim of a study by Patrocínio-Silva [2371] was to evaluate the effects of LPT on bone formation, immunoexpression of osteogenic factors, biomechanical properties and densitometric parameters in diabetic rats. Thirty male Wistar rats were randomly distributed into three experimental groups: control group, diabetic group, and laser-treated diabetic group. DM was induced by streptozotocin (STZ) and after 1 week laser treatment started. An 830 nm laser was used, performed for 18 sessions, during 6 weeks. At the end of the experiment, animals were euthanised and tibias and femurs were defleshed for analysis. Extensive resorptive areas as a result of osteoclasts activity were noticed in DG when compared to control. Laser-treated animals showed an increased cortical area. The immunohistochemical analysis revealed that LPT produced an increased RUNX-2 expression compared to other groups. Similar RANK-L immunoexpression was observed for all experimental groups. In addition, laser irradiation produced a statistically increase in fracture force, bone mineral content (BMC) and bone mineral density compared to DG. The results of this study indicate that the STZ model was efficient in inducing DM 1 and producing a decrease in cortical diameter, biomechanical properties and in densitometric variables. In addition, it seems that LPT stimulated bone metabolism, decreased resorptive areas, increased RUNX-2 expression, cortical area, fracture force, BMD, and BMC.

In the study by Valiati [2411], bone tissue was harvested from two rabbits, processed by deep-freezing and grafted into the calvaria of 12 animals, which were then randomly allocated into two groups: experimental (L) and control (C). Rabbits in group L were irradiated with 830 nm, 4 J/cm^2), applied to four sites on the calvaria, for a total dose of 16 J/cm^2 per session. The total treatment dose after eight sessions was 128 J/cm^2. Animals were euthanised at 35 (n=6) or 70 days (n=6) postoperatively. Deep-freeze-processed block allografts followed by LPT showed incorporation at the graft-host interface, moderate bone remodelling, partial filling of osteocyte lacunae, less inflammatory infiltrate in the early postoperative period, and higher collagen deposition than the control group. Optical microscopy and scanning electron microscopy showed that allograft bone processed by deep-freezing plus LPT is suitable as an alternative for the treatment of bone defects. Use of the deep-freezing method for processing of bone grafts preserves the structural and osteoconductive characteristics of bone tissue.

The aim of a work by Ribeiro [2419] was to evaluate the association of 830 nm and calcitonin in bone repair considering that bone healing remains a challenge to health professionals. Calcitonin has antiosteoclastic action and LPT is a treatment that uses LPT or light-emitting diodes to alter cellular function. Both are used to improve bone healing. Densitometry is a clinical non-invasive valuable tool used to evaluate bone mineral density (BMD).

Sixty male rats were submitted to bone defect with a trephine bur, randomly divided into four groups of 15 animals each: control (C); synthetic salmon calcitonin (Ca); LPT (La); LPT combined with calcitonin (LaCa). Animals from Ca and LaCa received 2UI/Kg synthetic salmon calcitonin intramuscularly on alternate days after surgery. Animals from groups La and LaCa were treated with infrared LPT (830 nm, 10 mW, 20 J/cm^2, 6s, contact mode). Five animals from each group were euthanised 7, 14, and 21 days after surgery and bone defects were analysed by densitometry. Statistical analysis showed a significant difference in BMD values in LaCa group at 7 and 21 days. The results of the densitometric study showed that LPT (830 nm) combined with calcitonin improved bone repair.

Mota [2467] evaluated the therapeutic activity of LPT (670 nm, 30 mW), at doses of 90 J/cm^2, on the process of acute and chronic-phase repair of bone lesions of Wistar rats. Sixty-three adult males were divided into nine groups subjected to bone injury, in order to form the following treatments: T1 (control); T2 (acute-phase); T3 (chronic-phase) which were subdivided into three subgroups (n=7), analysed on the 9th, 17th and 28th days post-surgery, after a period of daily treatment with laser. The animals with acute-phase treatment presented a more extensive endochondral ossification process. Laser-treated animals showed significant increases in serum alkaline phosphatase levels and had an effect on biomechanical property, resulting in a gradual increase in bone stiffness. Laser therapy aided the bone consolidation process and favoured the physiopathologic mechanisms involved in bone tissue repair, and its effects were more prominent when treatment started during the acute phase of the injury.

Distraction osteogenesis (DO)

DO is the application of traction to the callus formed between bone segments and stimulation of bone formation by creating stress on the callus with this traction. Shortening the duration of DO and increasing the capacity of bone formation is important to prevent the possible complications of DO.

A study by Hübler [2053] evaluated the effect of LPT on the chemical composition, crystallinity and crystalline structure of bone at the site of distraction osteogenesis. Five rabbits were subjected to distraction osteogenesis (latency=3 days; rate and frequency=0.7 mm/day for 7 days; consolidation=10 days), and three were given LPT with 830 nm, 40 mW): 10 J/cm^2 dose per spot, applied directly to the distraction osteogenesis site during the consolidation stage at 48 h intervals. Samples were harvested at the end of the consolidation stage. X-ray fluorescence and X-ray diffraction were used to analyse chemical composition, crystallinity and crystalline structure of bone at the distraction osteogenesis site. The analysis of chemical composition and calcium and phosphorus ratios revealed greater mineralisation in the LPT group. Diffractograms showed that the crystalline structure of the samples was similar to that of hydroxyapatites. Crystallinity percentages were greater in rabbits that were given LPT. Crystallinity and the chemical *composition of the bone at the distraction osteogenesis site were similar to the that of the control group. The results showed that LPT had a positive effect on the biomodulation of newly formed bone.*

Unilateral mandibular distractors were applied on 16 female white New Zealand rabbit in a study by Kan [2252]. Eight rabbits were applied LPT with GaAlAs laser on the distraction area during the distraction period. On the post-distraction 28th day, four rabbits from study group and four rabbits from control groups were sacrificed. The rest of the rabbits were sacrificed on post-distraction 56th day. As a result of this study, significant positive effects of LPT on post-distraction 28th day were revealed with all analyses. In histomorphometrical analyses, new bone formation was significantly higher in short-term laser applied group comparing to that of short-term control group. In both microCT and plain radiograph, the highest radio-opacity values were observed in short-term laser group when compared with that of the controls. Even though LPT increased the healing capacity on short-term, it was not sufficient on long-term (post-distraction 56th day) healing. LPT application during the distraction period can activate healing on bone and may decrease the DO period.

In a study by Freddo [1559] extraoral distraction devices were placed in five sheep so as to achieve 1.5 cm of lengthened bone in 60 days. Distraction devices were removed 50, 40, and 33 days after surgery. Four animals were treated with LPT, at different times, and one was used as control (no LPT). When applied during the bone consolidation period, LPT caused an increase in hardness and modulus of elasticity values. On the other hand, animals irradiated with LPT during the latency/activation period presented a delay in bone healing. A period of consolidation of 13 days (early device removal) was associated with relapse. Nanoindentation tests were able to detect slight abnormalities in bone metabolism and proved to be important tools for the assessment of bone quality following distraction osteogenesis. LPT provided increased benefits when applied during the bone consolidation period, once it promoted an increase in hardness and modulus of elasticity values. According to these results, the bone consolidation period should be of at least 3 weeks, so as to prevent relapse.

In a study by Ghoreyshian [1631], 24 adult male rabbits underwent left mandibular body corticotomy. After 5 days of latency, an external distraction device was activated at a rate of 0.5 mm / day for 10 days. Seven doses of a GaAs laser of 200 mW power (3 J/cm^2 per point) were directed at the corticotomy site of 12 rabbits for a total time of 30 seconds every other day while the control group received no laser irradiation. The distraction sites were evaluated by SEM and histological examinations during the 10th, 20th and 40th day of the consolidation phase. Histological examination revealed that new bone formation in 10 days of consolidation in the laser and control groups did not significantly differ, but SEM examinations showed more calcified and even a smoother surface of spongy bone. GaAs laser *seems to be able to improve the process of calcification and bone remodelling in early stages of distraction osteogenesis rather than in later stages.*

The purpose of a study by Miloro [1736] was to determine whether LPT application during distraction osteogenesis could accelerate bone regeneration and decrease the length of the consolidation phase and thereby reduce potential patient morbidity. Nine adult rabbits underwent bilateral mandibular corticotomies and placement of unidirectional distraction devices. Each rabbit served as its own internal control. After a latency of 1 day, distraction progressed bilaterally at 1 mm per day for 10 days. Immediately after each device's activation, the experimental side, chosen randomly, was treated with LPT of 6.0 J × 6 transmucosal sites in the area of the distraction gap. Radiographs were taken presurgically, immediately postsurgically, and weekly until sacrifice, and the bone was analysed using a semiquantitative 4-point scale. Three animals each were sacrificed two, four and six weeks post distraction, and each hemi-mandible was prepared for histological examination in a blinded fashion. Ten mm of distraction was achieved in each rabbit bilaterally. Radiographically, the Bone Healing Score was higher for the laser-treated group at all time periods. Histologically, the area of new bone trabeculation and ossification was more advanced for the laser-treated group, with less intervening fibrovascular intermediate zones in the regenerated bone, at all time periods. The formation of a complete inferior border occurred sooner in the treatment group than in the controls.

A PubMed search for articles related to mandibular distraction osteogenesis was performed by Hong [2251]. Inclusion and exclusion criteria were applied to all experimental studies assessing adjuvant therapies to enhance bone consolidation. A total of 1414 titles and abstracts were initially reviewed; 61 studies were included for full review. Many studies involved growth factors, hormones, pharmacological agents, gene therapy, and stem cells. Other adjuvant therapies included mechanical stimulation, laser therapy, and hyperbaric oxygen. Majority of the studies demonstrated positive bone healing effects and thus adjuvant therapies remain a viable strategy to enhance and hasten the consolidation period. Although most studies have demonstrated promising results, many questions still remain, such as optimal amount, timing, and delivery methods required to stimulate the most favourable bone regeneration.

Fractures

Luger [536] subjected 50 rats to tibial bone fracture with internal fixation. A total of 25 animals were treated with a HeNe laser, 35 mW transcutaneously 30 minutes daily for two weeks. The other 25 animals served as the control. After four weeks the maximal load at failure (MLF), the structural stiffness of the tibia (SST), and the extension maximal load (EML) were measured. The MLF and the SST were found to be significantly elevated, whereas *the EML was reduced. Four non-unions were found in the control group, none in the irradiated group.*

The objective of a study by Kazem Shakouri [2054] was to evaluate the effect of LPT on fracture healing. Thirty rabbits were subjected to tibial bone open osteotomies that were stabilised with external fixators. The animals were divided into two study groups: laser group and control group. Callus development and bone mineral density were quantitatively evaluated by CT; the animals were then killed and the fractures were assessed for biomechanical properties. The results demonstrated that the increasing rate of bone mineral density was higher in the laser (L) group than in the control (C) group. CT at 5 weeks revealed a mean callus density of 297 Hounsfield units (HU) for the control group and 691 HU for the L group, which was statistically significant. In the L group, the mean recorded fracture tension was 190.5 N and 359.3 N for healed and intact bones, respectively, which was statistically significant. The result of the study showed that the use of laser could enhance callus development in the early stage of the healing process, with doubtful improvement in biomechanical properties of the healing bone.

Trelles [108] studied the effects of a HeNe laser on bone fractures (of the tibia) in mice. The administered dose to one point was 2.4 J. The fracture was treated every other day for three weeks. The healing process was studied under an electron microscope. From a histological point of view, the laser group exhibited better healing characteristics than the control group, which was not treated with a laser. The laser group also showed increased vascularisation and faster formation of bone tissue with a tighter mesh of trabeculae. The control group showed poorer vascularisation and more cartilage tissue.

David [942] failed to verify these findings using 0, 2 or 4 J every other day for two to six weeks.

The aim of the study by Pinheiro [2242] was to assess, by light microscopy and histomorphometry, the repair of surgical fractures fixed with internal rigid fixation (IRF) treated or not with IR laser (780 nm, 50 mW, 4 x 4 J/cm² = 16 J/cm²) associated or not to the use of hydroxyapatite and guided bone regeneration. Surgical tibial fractures were created under general anesthesia on 15 rabbits that were divided into 5 groups, maintained on individual cages, at day/night cycle, fed with solid laboratory pelted diet, and had water ad libidum. The fractures in groups II, III, IV, and V were fixed with miniplates. Animals in groups III and V were grafted with hydroxyapatite and GBR technique used. Animals in groups IV and V were irradiated at every other day during two weeks (4 x 4 J/cm², 16 J/cm² = 112 J/cm²). Observation time was that of 30 days. After animal death, specimens were taken, routinely processed to wax, cut and stained with HA and Sirius red, and used for histological assessment. The results of both analyses showed a better bone repair on all irradiated subjects especially when the biomaterial and GBR were used. In conclusion, the results of the present investigation are important clinically as they are suggestive that the association of hydroxyap-

atite, and laser light resulted in a positive and significant repair of complete tibial fractures treated with miniplates.

Because bone healing at the graft site is similar to that of a fracture repair, the purpose of the study by da Silva [1762] was to evaluate the effects of laser irradiation on the repair of rat skull defects treated with autogenous bone graft. A defect measuring 3 mm in diameter was produced in the left parietal bone and filled with an autogenous bone graft obtained from the right parietal bone. The animals were divided into three groups of 20 rats each: non-irradiated control, irradiated with 5.1 J/cm^2, and irradiated with 10.2 J/cm^2. The laser (2.4 mW, 735 nm, 3.4 x 10 W/cm, 3 mm spot size) was applied three times per week for four weeks. A greater volume of newly formed bone was observed in the irradiated group treated with 10.2 J/cm^2. In both irradiated groups, a greater volume of newly formed bone occurred only in the first two weeks.

The purpose of a study by Liu [1876] was to demonstrate the biological effects of LPT on tibial fractures, using radiographic, histological and bone density examinations. A total of 14 white rabbits with surgically induced mid-tibial osteotomies were included in the study; 7 were assigned to a group receiving LPT (LPT-A) and the remaining 7 served as a sham-treated control group (LPT-C). A 830 nm laser and a sham laser (a similar design without laser diodes) were used for the study. Continuous irradiation with a total energy density of 40 J/cm^2 and a power of 200 mW/cm^2 was directly delivered to the skin for 50 seconds at four points along the tibial fracture site. Treatment commenced immediately postsurgery and continued once daily for four weeks. Radiographic findings revealed no statistically significant fracture callus thickness difference between the LPT-A and LPT-C groups. However, the fractures in the LPT-A group showed less callus thickness than those in LPT-C group three weeks after treatment. The average tibial volume was 14.5 mL in the LPT-A group, and 11.25 mL in the LPT-C group. The average contralateral normal tibial volume was 7.1 mL. Microscopic changes at 4 weeks revealed an average grade of 5.5 and 5.0 for the LPT-A group and the LPT-C group, respectively. The bone mineral density (BMD) as ascertained using a grey scale (graded from 0 to 256) showed darker colouration in the LPT-A group (138) than in the LPT-C group (125). The study suggests that LPT may accelerate the process of fracture repair or cause increases in callus volume and BMD, especially in the early stages of absorbing the hematoma and bone remodelling.

The therapeutic outcomes of LPT on closed bone fractures (CBFs) in the wrist and hand were investigated by Chang [2522] in a controlled study. Fifty patients with CBFs in the wrist and hand, who had not received surgical treatment, were recruited and randomly assigned to two groups. The laser group underwent a treatment program in which 830 nm LPT (average power 60 mW, peak power 8 W, 10 Hz, 600 sec, and 9.7 J/cm^2 per fracture site) was administered five times per week for 2 weeks. Participants in a placebo group received sham laser treatment. The pain, functional disability, *grip strength, and radiographic parameters of the participants were evaluated before and after treatment and at a 2-week follow-up. After treatment and at the follow-up, the laser group exhibited significant changes in all of the parameters compared with the baseline. The results of comparing the two groups after treatment and at the follow-up indicated significant between-group differences among all of the parameters.*

Osteoporosis

The aim of a study by Renno [1760] was to investigate the effects of 830 nm, used in two doses, on femora of osteopenic rats. Sixty female animals, divided into six groups, were used: sham-operated control (SC), osteopenic control (OC), sham-operated irradiated at a dose of 120 J/cm² (I120), osteopenic irradiated at a dose of 120 J/cm² (O120), sham-operated irradiated at a dose of 60 J/cm² (I60), and osteopenic irradiated at a dose of 60 J/cm² (O60). Animals were 90 days old when operated. Laser irradiation was initiated eight weeks after operation, and it was performed three times a week for two months. Femora were submitted to a biomechanical test and to a physical properties evaluation. Maximal load of O120 did not show any difference when compared with SC and I120, but it was higher than the O60 group. Wet weight, dry weight, and bone volume of O60 and O120 did not show any difference when compared with SC. The results of the study indicate that laser phototherapy had stimulatory effects on femora of osteopenic rats, mainly at the dose of 120 J/cm².

Osteoporosis affects 30% of postmenopausal women, and it has been recognised as a major public health problem. Based on the stimulatory effects of LPT on proliferation of bone cells found in the study above, Renno [1761] hypothesised that LPT would be efficient in preventing bone mass loss in ovariectomied (OVX) rats. Forty female rats were divided into four groups: sham-operated control (SC), OVX control (OC), sham-operated irradiated at a dose of 120 J/cm² (I120), and OVX irradiated at a dose of 120 J/cm² (O120). Animals were operated at the age of 90 days. Laser irradiation was initiated one day after the operation and was performed three times a week for two months. Femora were submitted to a biomechanical test and a physical properties evaluation. Maximal load of O120 was higher than in control groups. Wet weight, dry weight, and bone volume of O120 did not show any difference when compared with SC. The results of this study indicate that LPT was able to prevent bone loss after OVX in rats.

The purpose of a study by Diniz [1918] was to verify the effect of laser therapy in combination with bisphosphonate on osteopenic bone structure. The 35 Wistar female rats used were divided into five groups: (1) sham-operated rats (control), (2) ovariectomised (OVX'd) rats with osteopenia, (3) OVX'd rats with osteopenia treated with laser, (4) OVX'd rats with osteopenia treated with bisphosphonate, and (5) OVX'd rats with osteopenia treated with bisphosphonate and laser. Groups 3 and 5 were given daily 6 mg doses of bisphosphonate orally. Groups 4 and 5 underwent irradiation with 830 *nm, 50 mW and 4* J/cm^2 *on the femoral neck and vertebral segments (T13-L2). Both treatments were performed over an 8-week period. Rats from the osteopenic control and the osteopenic + laser groups presented marked osteopenia. In the osteopenic + bisphosphonate group, the trabecular bone volume in vertebra L2 was significantly greater than in the osteopenic control group. Notably, in the association between laser and bisphosphonate, the trabecular bone volume was significantly greater in vertebrae L2 and T13 and similar to that in the sham-operated control group. It was concluded that the laser therapy combined with bisphosphonate treatment was the best method for reversing vertebral osteopenia caused by the ovariectomy.*

Clinical studies

In the study by Chang [2507] the therapeutic outcomes of administering 830 nm LPT to treat Closed Bone Fractures (CBFs) in the wrist or hand were examined. Fifty patients with CBFs in the wrist and hand, who had not received surgical treatment, were recruited and randomly assigned to two groups. The laser group underwent a treatment program in which 830 nm LPT (average power 60 mW, peak power 8 W, 10 Hz, 600 sec, and 9.7 J/cm^2 *per fracture site) was administered five times per week for 2 weeks. Participants in a placebo group received sham laser treatment. The pain, functional disability, grip strength, and radiographic parameters of the participants were evaluated before and after treatment and at a 2-week follow-up. After treatment and at the follow-up, the laser group exhibited significant changes in all of the parameters compared with the baseline. The results of comparing the two groups after treatment and at the follow-up indicated significant between-group differences among all of the parameters.*

In a clinical study by Kucerová [1042], the bone density after tooth extraction was measured by digital X-ray. The images taken immediately after extraction and six months later were compared between laser and non-laser patients. There was no difference between these patients at six months. ***This is hardly surprising, since the remodelling of bone is more or less complete after six months, with or without laser. Early comparisons would be more appropriate in order to determine the possible effect of LPT.***

Necrosis of the jawbone has been described in association with systemic bisphosphonate therapy with drugs including zoledronic acid, pamidronate, and alendronate. The extent and clinical characteristics of bisphosphonate-associated osteonecrosis (BON) of the jaw are extremely variable, and range from the presence of fistulae in the oral mucosa or orofacial tissues, to large exposed areas of necrotic bone within the oral cavity. Clinical signs and symptoms commonly reported include pain, swelling, the presence of pus, loose teeth, ill-fitting dentures, and paresthesias of the inferior alveolar nerve when the necrosis affects the mandible. Fractures have also been reported. The treatment of BON of the jaw is still controversial since no therapy has proven to be efficacious as shown by the literature on the subject. In a study by Vescovi [2014], researchers report results achieved *in 28 patients affected by BON of the jaw, and who received treatment by the Nd:YAG laser alone, or in combination with conventional medical or surgical treatments. Clinical variables such as severity of symptoms, presence of pus, and closure of mucosal flaps before and after therapy were evaluated to establish the effectiveness of laser irradiation. The 28 patients with BON were subdivided into four groups: 8 patients were treated with medical therapy only (antibiotics with or without antimycotics and/or antiseptic rinses), 6 patients were treated with medical and surgical therapy (necrotic bone removal and bone curettage), 6 patients were treated with medical therapy associated with laser biostimulation, and 8 patients were treated with medical therapy associated with both surgical therapy and laser biostimulation. Of the 14 patients who underwent laser biostimulation, 9 reported complete clinical success (no pain, symptoms of infection, or exposed bone or draining fistulas), and 3 improved their symptomatology only, with follow-ups between months four and seven. While the results reported in this study are not conclusive, they indicate that LPT has potential to improve management of BON.*

Reviews of the literature on laser bone stimulation have been published by Barber [1253], Pinheiro [1920], Bashardoust Tajali [1889] and Ebrahimi [2278].

Further reading: Chapter 5, BRONJ and Implantology.

Further literature: [213, 258, 413, 414, 430, 437, 438, 439, 440, 466, 484, 516, 642, 962, 1117, 1194, 1238, 1299, 1301, 1309, 1331, 1465, 1764, 1843, 1994]

4.1.10 Burning mouth syndrome

Burning Mouth Syndrome (BMS) is a common disease but still a diagnostic and therapeutic challenge for clinicians. Despite many studies, its nature remains obscure and controversial; nowadays there is no consensus about definition, diagnosis and classification. BMS is characterised clinically by burning sensations in the tongue or other oral sites, often without clinical and laboratory findings. According to the aetiology, BMS cases should be subdivided into three subtypes: BMS by local factors (lfBMS), BMS by systemic factors (sfBMS) and neurological BMS (nBMS), the most frequent, in which the symptom is caused by central or peripheral neurological malfunctions affecting in particular the taste pathway. To establish the type of BMS, both anamnesis and clinical examination, including laboratory tests, are necessary; nBMS cases will be recognised by exclusion of any other type. In case of lfBMS or sfBMS, the treatment of the main pathology will be resolutive; in nBMS cases many authors proposed different pharmacological trials without satisfactory results and the current opinion is that a multidisciplinary approach is required to keep the condition under control [2363].

Literature:

The aim of the study by Kato [2047] was to investigate the effect of LPT on the treatment of burning mouth syndrome. In addition, the laser effect was compared on the different affected oral sites. Eleven subjects with a total of 25 sites (tongue, lower lip, upper lip, and palate) affected by a burning sensation were selected. The affected areas were irradiated once a week for three consecutive weeks with an infrared laser (790 nm). The probe was kept in contact with the tissue, and the mucosal surface was scanned during the irradiation. The exposure time was calculated based on the fluence of 6 J/cm², the output power of 120 mW, and the area to be treated. Burning intensity was recorded through a Visual Analogue Scale before and after the treatment and at the 6-week follow-up. The percentage of the improvement in symptoms was also obtained. Burning intensity at the end of the LPT was statistically lower than at the beginning. Patients reported an 80.4% reduction in the intensity of symptoms after laser treatment. There was no statistical difference between the end of the treatment and the 6-week follow-up, except for the tongue site.

In the pilot study by Romeo [2363] twenty-five of patients, 16 females and 9 males, were randomly selected for LPT. All the patients were irradiated with a double diode laser emitting contemporarily at 650 nm and 910 nm, with a fluence of 0.53 J/cm² for 15 minutes, twice a week for 4 weeks. The areas of irradiation were the sides of the tongue on the path of taste fibres. A NRS (numerical rating scale) evaluation of maximum and minimum pain was registered before and after the treatment. In each case to the total value of NRS rates registered before the treatment was deducted the total NRS rate registered after the treatment. The difference was estimated effective if over two points. The Kruskall-Wallis test revealed the significance of the study and the Dunn's Multiple Comparison test, applied to compare NRS rates before and after the treatment, showed that there is not a statistically relevant difference between min NRS ratings before and after treatment, while there are statistically significant differences between max NRS ratings. No side effects were registered and all the patients completed the therapy without interruption. Seventeen patients (68%) had relevant benefits from the treatment with valid reduction of NRS ratings. In 8 cases the differences of NRS rates were not relevant being under the limit of reliability established in study design. In no case there was a worsening of the symptoms.

A total of 17 patients who had been diagnosed with burning mouth syndrome were treated by Yang [2363] with an 800 nm laser. A straight handpiece was used with an end of 1-cm diameter with the fibre end standing 4 cm away from the end of handpiece. When the laser was applied, the handpiece directly contacted or was immediately above the symptomatic lingual surface. The output used was 3 W, 50 msec intermittent pulsing, and a frequency of 10 Hz, which was equivalent to an average power of 1.5 W/cm² (3 W × 0.05 msec × 10 Hz = 1.5 W/cm²). Depending on the involved area, laser was applied to a 1 cm² area for 70 sec until all involved area was cov-

ered. Overall pain and discomfort were analysed with a 10-cm Visual Analogue Scale. All patients received LPT between one and seven times. The average pain score before the treatment was 6.7 (ranging from 2.9 to 9.8). The results showed an average reduction in pain of 47.6% (ranging from 9.3% to 91.8%). The burning sensation remained unchanged for up to 12 months.

Dos Santos [2364] used 660 nm, 40 mW, 20 J/cm² and 0.8 J per point, 10 sessions. 0.8 J is a low energy per point, but a higher energy density was applied, depending on the use of a small probe. Overall pain reduction was 58%.

4.1.11 Cancer

As explained previously, LPT in iteself does not cause cancer [2231]. There are, on the contrary, some indications that cancer tumours in their initial stage can be positively influenced (i.e. to the patient's benefit) by LPT. The mechanism at work here is thought to be the general stimulation of the immune system. In the same way as bacteria and viruses, cancer cells can be stimulated *in vitro* [594] but generally not *in vivo* due to the presence of the immune system.

LPT has also been shown to ease the symptoms of cancer patients who have received chemo- and/or radiation therapy resulting in oral side-effects (mucositis). This is an example of the use of LPT in oncology where the cancer itself is not treated, but rather the side effects of the cancer therapy [907, 967]. LPT can also, to advantage, be given as a palliative measure to cancer patients in the terminal stage. Mucositis occurs in about 40% of patients receiving chemotherapy, in 80% of those receiving bone marrow transplants and in 100% of those receiving radiotherapy to the head and neck, if the oral cavity is in the irradiated field. Younger patients have a higher incidence of oral complications than older patients receiving similar oncologic treatment [1472]. The type of intraoral local point irradiation now practiced is rather time consuming but compared to the cost of extra days of hospitalisation cost effective - the suffering of the patients not even being considered.

The radioprotective effect of laser light was discovered very early. In a paper from 1966 by McGuff [1856], human adenocarcinomas were implanted in the cheek pouch of hamsters. Roentgen radiation of 1000 r was found to be inhibitory to the tumour growth. Ruby laser irradiation of 214 J proved to have an even better effect. In a following experiment, roentgen and laser energies were reduced to 50% and given at the same time. This proved to further improve the outcome of the therapy, providing a synergistic effect. McGuff et al performed several studies during 1965-1966 [1853-1859] with very interesting effects on various tumours. Different energies were used but, unfortunately, the authors have not been specific about optimal doses, only dose ranges. Although published in well-known scientific journals, these observations seem to have fallen into oblivion.

Research [986,1081] has shown that low doses of irradiation, ionising as well as non-ionising, can protect the cells if the low-dose irradiation is given prior to radiation therapy [1016,1214,1773,1778,1811,1812]. This radioprotective ability of LPT deserves further attention in oncology.

In a review article, Zimin [2125] writes: "Although low-power visible (VIS) and near infrared (nIR) radiation emitted from lasers, photodiodes, and other sources does not cause neoplastic transformation of the tissue, these phototherapeutic techniques are looked at with a great deal of caution for fear of their stimulatory effect on tumour growth. This apprehension arises in the first place from the reports on the possibility that the proliferative activity of tumour cells may increase after their in vitro exposure to light. Much less is known that these phototherapeutic modalities have been successfully used for the prevention and management of complications developing after surgery, chemo- and radiotherapy. The objective of the present review is to summarise the results of applications of low-power visible and near infrared radiation for the treatment of patients with oncological diseases during the last 20-25 years. It should be emphasised that 2-4 year-long follow-up observations have not revealed any increase in the frequency of tumour recurrence and metastasis."

Although LPT is reported to be a safe method to treat the side effects of cancer therapies, the last word is still not said. A study by Sperandio [2148] demonstrated that LPT (660 nm or 780 nm, 40 mW, 2.05, 3.07 or 6.15 J/cm^2) can modify oral dysplastic cells (DOK) and oral cancer cells (SCC9 and SCC25) growth by modulating the Akt/mTOR/CyclinD1 signalling pathway; LPT significantly modified the expression of proteins related to progression and invasion in all the cell lines, and could aggravate oral cancer cellular behavior, increasing the expression of pAkt, pS6 and Cyclin D1 proteins and producing an aggressive Hsp90 isoform. Apoptosis was detected for SCC25 and was related to pAkt levels.

LPT has been shown to be effective in promoting cell proliferation. There is speculation that the biostimulatory effect of LPT causes undesirable enhancement of tumor growth in neoplastic diseases since malignant cells are more susceptible to proliferative stimuli. The study by Gomes Henriques [2514] evaluated the effects of LPT on proliferation, invasion, and expression of cyclin D1, E-cadherin, beta-catenin, and MMP-9 in a tongue squamous carcinoma cell line (SCC25). Cells were irradiated with a 660 nm using two energy densities (0.5 and 1.0 J/cm^2). The proliferative potential was assessed by cell growth curves and cell cycle analysis, whereas the invasion of cells was evaluated using a Matrigel cell invasion assay. Expression of cyclin D1, E-cadherin, beta-catenin, and MMP-9 was analyzed by immunofluorescence and flow cytometry and associated with the biological activities studied. LPT induced significantly the proliferation of SCC25 cells at 1.0 J/cm^2, which was accomplished by an increase in the expression of cyclin D1 and nuclear beta-catenin. At 1.0 J/cm^2, LPT significantly reduced E-cadherin and induced MMP-9 expression, promoting SCC25 invasion. The results of this study demonstrated that LPT exerts a stimulatory effect on proliferation and invasion of SCC25 cells, which was associated with alterations on expression of proteins studied.

It should, again, be underlined that cancer therapy is the sole concern of the specialist. Patients with known malignancies in an area otherwise suitable for LPT should not be treated with LPT by anyone but the specialist. A concern sometimes raised is that we cannot be certain that there is no unknown malignancy in the area selected for LPT. The answer is that the immune stimulation is likely to override the possible stimulation of the malignant cells. Furthermore, LPT in general would be impossible to use if the condition would be a thorough cancer examination before each treatment.

The following studies approach several aspects of oncology; the actual *in vitro* effect on malignant cells, some clinical observations and the radio-protective effect of LPT. The clinical studies on mucositis are reported in 4.1.36. The conclusion is that there is strong scientific support for the use of LPT as a protective and therapeutic method for patients scheduled for chemo- and radiotherapy.

Cost effectiveness

The aim of a study by Bezinelli [2246] was to determine the cost-effectiveness of the introduction of a specialised oral care programme including laser therapy in the care of patients receiving HSCT with regard to morbidity associated with OM. Clinical information was gathered on 167 patients undergoing HSCT and divided according to the presence (n=91) or absence (n=76) of laser therapy and oral care. Cost analysis included daily hospital fees, parenteral nutrition (PN) and prescription of opioids. It was observed that the group without laser therapy (group II) showed a higher frequency of severe degrees of OM with a significant association between this severity and the use of PN, prescription of opioids, pain in the oral cavity and fever > 37.8 degrees C. Hospitalisation costs in this group were up to 30% higher.

78-year-old patient treated for oropharyngeal carcinoma with external radiotherapy. Acute grade 3 dermatitis at 60 Gy (5 x 2 Gy per week). The same patient after three sessions of HeNe irradiation, 25 mW, 4 J/cm² in scanning mode.

Figure 4.3 Radiation-induced dermatitis before and after HeNe therapy.
Courtesy: René-Jean Bensadoun

Literature:

In vitro studies

Schaffer [594] irradiated four cell cultures with 805 nm laser light with fluences between 0 and 20 J/cm². The cell types were (1) murine skeletal myotubes, (2) normal urothelial cells, (3) human squamous carcinoma cells of the gingival mucosa, and (4) urothelial carcinoma cells. The mitotic index of 1, 2, and 4 increased at a fluence of 4 J/cm², whereas a fluence of 20 J/cm² resulted in a slight decrease. The no. 3 cell culture showed a decrease of the mitotic index at both fluences. No differences could be observed if the power density was varied between 10 mW/cm² and 150 mW/cm².

The aim of a study by Pinheiro [1211] was to assess the effect of 635 nm and 670 nm laser irradiation on H.Ep.2 cells in vitro using MTT. It was decided to evaluate the effect of increased doses of laser light on these cells. The cells were obtained from SCC of the larynx. The cultures were kept either at 5% or 10% of FBS. Twenty-four hours after transplantation, the cells were irradiated with laser light (5 mW diode lasers; 635 and 670 nm; beam cross section 1 mm at local light doses between 0.04 and 4.8 J/cm²). For 670 nm, significant differences in the proliferation were observed between the two concentrations of FBS and between irradiated cultures and controls. Although the results were not significant, 635 nm irradiated cells also proliferated more than non-irradiated ones. This occurred under both conditions of nutrition. It was concluded, that irradiation with 670 nm laser light applied at doses between 0.04 and 4.8 J/cm² could significantly increase proliferation of laryngeal cancer cells.

Tamachi [44] has studied the uptake of 5Fluorouracil (5FU) in various experiments using rats. Laboratory rats that received 6 J/cm² of HeNe showed a greater uptake of 5FU than those that were given 5FU only.

Konchugova [214] studied whether LPT, under experimental conditions, could be used to increase cyclophosphamide-developed immune suppression. The experiment suggests that LPT can be used to reduce the therapeutic dosage and its consequent negative side effects.

Ulrich [489] summarises a rodent experiment: 1) Single doses of 830 nm light (1J and 100 J/cm²) do not stimulate or inhibit growth of rhabdomyosarcomas R1H. 2) Fractionated treatment of R1H tumours with 15 or 1500 J/cm² for three weeks does not alter the growth kinetics in comparison to untreated controls. 3) Histological findings showed an increase of tumour necrosis after fractionated irradiation with 1500 J/cm².

The aim of a study by Kreisler [1567] was to investigate the effect of 809 nm laser irradiation on the proliferation rate of human larynx carcinoma cells in vitro. Epithelial tumour cells were obtained from a laryngeal carcinoma and cultured under standard conditions. For laser treatment the cells were spread on 96-well tissue culture plates. Sixty-six cell cultures were irradiated with an 809 nm laser. Another 66 served as controls. Power output was 10 mW (CW) and the time of exposure 75-300 s per well, corresponding to an energy fluence of 1.96-7.84 J/cm². Subsequent to laser treatment, the cultures were incubated for 72 h. The irradiated cells revealed a considerably higher proliferation activity. The differences were highly significant up to 72 h after irradiation.

Joyce [1016] has investigated the potential ability of LPT to induce an adaptive response against the damaging effects of ionising radiation in Indian muntjac fibroblasts. LPT at 660, but not 820 nm, at 11.5 and 23.0 J/cm², induced an apparent adaptive response in the form of a reduction in the frequency of radiation-induced chromosome aberrations, but not in cell survival. There was also a trend towards a reduction in the level of single-stranded and double-stranded DNA breaks induced by ionising radiation when cells were preconditioned with LPT. However, this did not contribute to the reduced chromosome aberration frequency. Further analysis revealed that the reduced aberration frequency was caused by a laser-induced extension of G2 delay. The adaptive response was therefore the result of cell cycle modulation by LPT at a wavelength where there is no known DNA damaging effect to induce the checkpoint mechanisms, which are normally responsible for altering cell cycle progression.

The aim of this study by Mognato [1454] was to investigate the effects of different wavelengths and doses of laser radiation on in vitro cell proliferation. Two human cancer cell lines, HeLa (epithelial adenocarcinoma) and TK6 (lymphoblast) were used. Attention was focused on the combination of the two laser emissions, as it could have a synergic effect greater than the single emissions applied separately. A laser device was used for cell irradiation with a continuous wave diode (808 nm), a pulsed wave diode (905 nm), *and a combination of wave diodes (808 nm + 905 nm), in the dose range of 1-60 J/cm^2. The effect of the combined 808-905 nm laser irradiation was slightly superior to that achieved with either laser alone in HeLa cells. TK6 cellular proliferation was not found to be significantly affected by any of the energy levels and the varying exposure doses investigated. These results are a confirmation of previous [1399] observations carried out on human cells, where only the proliferation of slowly growing cell populations appeared to be stimulated by laser light. HeLa cells grow slower than TK6 cells. The fact that laser stimulates slowly growing cells better than fast growing cells (cancer) may be an important aspect of LPT.*

Effects of combined exposure to a 633 nm laser and gamma-radiation, and laser and protons with the energy of 150 MeV, on the survivabilty of mice fibroblast cells C3H10T1/2 were compared in a study by Voskanian [1811]. Cell suspension was distributed in 2-ml plastic vials with 1 cm in diameter. The time interval between two exposures in a combination was no more than 60 s. Immediately after exposure, a required quantity of cells was inoculated in special vials for survivability assessment. Based on results of the experiment, preliminary and repeated laser treatment was favourable to the survivability of fibroblast cells subjected to gamma- or proton irradiation (dose variation factor was within 1.3 to 2.2). Simultaneous exposure of C3H10T1/2 cells to the laser and proton beams also increased their survivability. The radioprotective effect of the HeNe laser on fibroblasts earlier exposed to ionising radiation is of chief interest, as most of the present-day radioprotectors are effective only if introduced into the organism prior to exposure.

The aim of a study by Renno [1869] was to investigate the effects of 670, 780 and 830 nm laser irradiation on cell proliferation of normal primary osteoblast (MC3T3) and malignant osteosarcoma (MG63) cell lines in vitro. Neonatal murine calvarial osteoblastic and human osteosarcoma cell lines were studied. A single laser irradiation was performed at three different wavelengths, at the energies of 0.5, 1, 5, and 10 J/cm^2. Twenty-four hours after laser irradiation, cell proliferation and alkaline phosphatase assays were assessed. Osteoblast proliferation increased significantly after 830 nm laser irradiation (at 10 J/cm^2), but decreased after 780 nm laser irradiation (at 1, 5, and 10 J/cm^2). Osteosarcoma cell proliferation increased significantly after 670 nm (at 5 J/cm^2) and 780 nm laser irradiation (at 1, 5, and 10 J/cm^2), but not after 830 nm laser irradiation. Alkaline phosphatase (ALP) activity in the osteoblast line was increased after 830 nm laser irradiation at 10 J/cm^2, whereas ALP activity in the osteosarcoma line was not altered, regardless of laser wavelength or intensity. Based on the conditions of this study, the authors conclude that each cell line responds differently to specific wavelength and dose combinations.

The aim of an investigation by Powell [2039] was to compare the cell proliferative effects of a range of doses of LPT at wavelengths of 780, 830 and 904 nm on human breasts and immortalised human mammary epithelial cell lines in vitro. LPT is used in the clinical treatment of post-mastectomy *lymphoedema, despite safety information being limited and circumstantial. This research was the first step in systematically developing guidelines for the safe clinical use of LPT in the management of post-mastectomy lymphoedema. Human breast adenocarcinoma (MCF-7), human breast ductal carcinoma and immortalised human mammary epithelial cell lines were irradiated with a single exposure of laser at 0.5, 1, 2, 3, 4, 10 and 12 J/cm^2 (780 nm) and 0.5, 1, 2, 3, 4, 10 and 15 J/cm^2 (830 and 904 nm). MCF-7 cells were further irradiated with two and three exposures of all three laser wavelengths. XTT colourimetric assays were utilised to assess cell proliferation 24 hours after irradiation. SVCT cell proliferation significantly increased after exposure to a range of doses at 780 and 904 nm irradiation. MDA-MB-435S and Bre80hTERT cell lines showed negligible effects from one exposure of all three wavelengths and no dose response relationships were noted. MCF-7 cells irradiated with 780 nm laser demonstrated an increasing dose response relationship after one exposure and a decreasing dose response relationship after three exposures. The MCF-7 cells irradiated with 904 nm laser demonstrated a decreasing dose response relationship after two and three exposures. Despite certain doses of laser increasing MCF-7 cell proliferation, multiple exposures had no effect, or a decreasing effect, on dose response relationships. Acc. to the authors, before a definitive conclusion can be made regarding the safety of LPT for post-mastectomy lymphoedema, further in vivo research must be conducted.*

Animal studies

In a study by Pavlova [774], the main goal was to establish the capability of laser to oppose the free radical oxidative chain reactions inherent in the effects of radiation. Adequate doses of laser were shown to produce positive effects upon the metabolism similar to those of pharmacologic radioprotectors.

A study by Korolev [1214] showed that exposure of rat adrenals 30 days after radiation (1 Gy) to infrared laser radiation arrested the development of ultrastructural disorders in the cells of the hypothalamus and the parathyroid gland, and enhanced subcellular manifestations of adaptation and rehabilitation processes.

Mikhailov [3] states that an 890 nm diode laser produces a tumourostatic effect at minimal power, while higher doses produce other effects. Altogether 26 rats with implanted Walker carcinosarcoma, 75 with cancer of the mammary glands (implanted) and 188 animals with spontaneous cancer of the mammary glands were used in the study. LPT promoted dystrophic and necrotic changes in the tumoural nodes.

Humzah [286] has used GaAs in cases of neoplastic ulceration with some response.

In a study by Lara [2424], 44 rats were treated with fluorouracil and, in order to mimic the clinical effect of chronic irritation, the palatal mucosa was irritated by superficial scratching with an 18-gauge needle. When all of *the rats presented oral ulcers of mucositis, they were randomly allocated to one of three groups: group I was treated with laser (GaAlAs), group II was treated with topical dexamethasone, and group III was not treated. Excisional biopsies of the palatal mucosa were then performed, and the rats were killed. Tissue sections were stained with haematoxylin and eosin for morphological analyses, and with toluidine blue for mast-cell counts. Group I specimens showed higher prevalence of ulcers, bacterial biofilm, necrosis and vascularisation, while group II specimens showed higher prevalance of granulation tissue formation. There were no significant statistical differences in the numbers of mast cells and epithelial thickness between groups. For the present model of mucositis, rats with palatal mucositis treated with laser showed characteristics compatible with the ulcerative phase of oral mucositis, and rats treated with topical dexamethasone showed characteristics compatible with the healing phase of mucositis. Topical dexamethasone was more efficient in the treatment of rats' oral mucositis than the laser.*

Figure 4.4 Mucositis at day 1 of treatment and at day 6.
Courtesy: Alyne Simões

The aim of the study by da Cunha [1812] was to investigate the effect of LPT (780 nm) on bone tissue submitted to ionising radiation. Twenty-two Wistar rats were randomly divided into four groups: group I, control (n=4), submitted only to radiotherapy; group II, laser treatment starting one day prior to radiotherapy (n=6); group III, laser treatment starting immediately after radiotherapy (n=6); group IV, laser treatment starting four weeks after radiotherapy (n=6). The source of ionising radiation used was Cobalt 60, which was applied in a single dose of 3000 cGy on the femur. The laser groups received seven applications with a 48-h interval in four points per session of DE = 4 J/cm^2*, P = 40 mW, t = 100 sec, with a beam diameter of 0.04 cm*^{2}*. All animals were killed six weeks after radiotherapy. Clinical examination revealed cutaneous erosions on experimental groups (II, III, and IV) starting at the sixth week after radiotherapy. The radiographic findings showed higher bone density in groups II and IV compared to the control group. The results further showed an increase of bone marrow cells, and* *number of osteocytes and Haversian canals in experimental groups II and IV. Further findings disclosed an increase of osteoblastic activity in groups II, III, and IV. LPT on bone tissue in rats presented a positive biostimulative effect, especially when applied before or four weeks after radiotherapy. However, the use of laser in the parameters above should be used with caution due to epithelial erosions.*

The aim of a study by Desmons [1924] was to investigate the effect of laser preconditioning on the re-vascularisation of X-ray irradiated bone. A bone chamber was implanted onto the calvaria of rabbits to study the vascularisation process. Digital pictures were taken of the vascular plexus at the target bone site using a modified digital camera. Vascular density (VD) was determined using image processing. It was defined as the ratio of blood vessel pixels to the total number of pixels in the region of interest. Laser preconditioning was performed with a diode laser (810 nm, 2 W, 3 seconds, 48 J/cm^2, 4 mm). A 12-week follow-up study was performed on 20 rabbits divided into four groups: No 1: control group (n=5), No 2: laser irradiation alone (n=5), No 3: X-ray radiation (18.75 Gy) alone (n=5), No 4: laser preconditioning 24 hours prior to X-ray radiation (n=5). Vascular density remained stable during the 12-week follow up for group No 1. No significant difference was observed between laser irradiation group (No 2) and control group (No 1). The angiolytic action of X-ray radiation was confirmed in groups 3 and 4, which were statistically different from group 1. However, the decrease of the vascularisation was limited in group 4, highlighting a different evolution between group 3 and 4. These results were confirmed by histological analysis. The bone chamber is an effective reproducible method for the longitudinal analysis of the dynamics of vascularisation. These findings have shown that laser preconditioning is capable of preserving vascularisation in an X-ray irradiated bone site, thus suggesting a novel approach for promoting the healing of bone tissue in which the vascular supply has been damaged.

França [1990] divided a group of hamsters into four groups: preventive cryotherapy, preventive laser, therapeutic laser and therapeutic control group. Mucositis was induced in hamsters by an intraperitoneal injection of 5-fluorouracil (5-FU) and superficial scratching. All preventive treatment was performed on the right cheek pouch mucosa. The left pouch mucosa was used for a spontaneous development of mucositis and did not receive any preventive therapy. Laser parameters were: 660 nm, 30 mW, 1.2 J/cm^2, 40 s, spot size 3 mm^2. Cryotherapy was done positioning ice packs in the hamster mucosa 5 min before 5-FU infusion and 10 min afterwards. To study the healing of mucositis, the left pouch mucosa of each hamster in the TLG received laser irradiation on the injured area. Irradiation parameters were kept the same as mentioned above. The control hamsters in the TCG did not receive any treatment. The mucositis degree and the animal's body mass were evaluated. An assessment of blood vessels was made based on immunohistochemical staining. The CG animals lost 15.16% of their initial body mass while the LG animals lost 8.97% during the first five days. The laser treated *animals had a better clinical outcome with a faster healing, and more granulation tissue. The quantity of blood vessels in both the LG and CG were higher than in healthy mucosa. Regarding the therapeutic analysis, the severity of the mucositis in the TLG was always lower than in the TCG. TLG presented a higher organisation of the granulation tissue, parallel collagen fibrils, and an increased angiogenesis.*

The purpose of the study by Tuby [2231] was to determine the long-term safety effect of LPT to the bone marrow (BM) in mice. Eighty-three mice were divided into five groups: control sham-treated and laser-treated at measured density of 4, 10, 18, or 40 mW/cm² at the BM level. The laser was applied to the exposed flat medial part of the tibia 8 mm from the knee joint for 100 sec. Mice were monitored for 8 months and then killed, and histopathology was performed on various organs. No histological differences were observed in the liver, kidneys, brain or BM of the laser-treated mice as compared with the sham-treated, control mice. Moreover, no neoplasmic response in the tissues was observed in the laser-treated groups as compared with the control, sham-treated mice. There were no significant histopathological differences among the same organs under different laser treatment regimes in response to the BM-derived mesenchymal stem cell proliferation following LPT to the BM. In conclusion, LPT applied multiple times either at the optimal dose (which induces photobiostimulation of stem cells in the BM), or at a higher dose (such as five times the optimal dose), does not cause histopathological changes or neoplasmic response in various organs in mice, as examined over a period of 8 months.

These findings by Corazza [2139] suggest that resistance training and LPT can prevent sarcopenia in ovariectomised rats.

The aim of a study by Usumez [2263] was to compare the effectiveness of four different laser wavelengths (660, 810, 980, and 1,064 nm) used for LPT on the healing of mucositis in an animal model of wound healing by investigating the expression of platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-beta), and blood-derived fibroblast growth factor (bFGF). Thirty-five male Wistar albino rats with a weight of 250-300 g body mass and 5 months old were used in the study. All animals were intraperitoneally injected with 100 mg/kg of 5-fluorouracil (5-FU) on the first day and 65 mg/kg of 5-FU on the third day. The tip of an 18-gauge needle was used in order to develop a superficial scratching on the left cheek pouch mucosa by dragging twice in a linear movement on third and fifth days. After ulcerative mucositis were clinically detected on the animals' left cheek pouch mucosa, the laser therapy was started. Four different laser wavelengths (660 nm, 810 nm, 980 nm, and 1064 nm) used for LPT at ED 8 J/cm² daily from the first to the fourth days. Oval excisional biopsy was taken from the site of the wound, and the expression of PDGF, TGF-beta, and bFGF was evaluated. The one-way ANOVA test indicated that expression values of the growth factors, PDGF and bFGF, were significantly affected by irradiation of different wavelengths of lasers. However, expression value of the TGF-

beta was not affected by irradiation of different wavelengths of lasers. The highest PDGF expression was detected in the Nd:YAG laser group and there were no statistically significant differences among the other groups. The highest bFGF expression was detected in 980 nm diode and Nd:YAG laser groups and there were no statistically significant differences among the other groups. These findings suggest that low-level Nd:YAG and 980 nm diode laser therapy accelerate the wound healing process by changing the expression of PDGF and bFGF genes responsible for the stimulation of the cell proliferation and fibroblast growth.

The aim of the study by Lopez [2311] was to investigate the effect of LPT in the prevention and/or treatment of oral mucositis induced by 5-fluorouracil in hamsters. Ninety-six hamsters were divided into four groups (n=24): Control (no treatment); Preventive [LPT from day (D) D-5 to D+5]; Therapeutic (LPT from D+5 to D+15); and Combined (preventive plus therapeutic LPT from D-5 to D+15). The animals received an intraperitoneal injection of 5-FU on Days 0 and 2. The pouch mucosa was scratched on Days 3 and 4. The irradiation parameters were: InGaAlP laser, 660 nm, beam area of 0.036 cm^2, 40 mW, 1.11 W/cm^2, 6.6 J/cm^2, power density applied daily of 39.6 J/cm^2, in punctual mode (six points and six seconds per point) and contact mode, one application per day. The animals were sacrificed on Days 0, 5, 10 and 15 (n=6) and weighed, and the pouch mucosa was removed for histopathological analysis. Similar weight losses ranging from 5% to 10% occurred in all groups. The therapeutic group had significantly lower clinical and histological scores than the other groups at Day 10. This study showed that positive effects on oral mucositis management were obtained only when LPT was applied in the therapeutic protocol (from D+5 to D+15).

The aim of a study by Oton-Leite [2423] was to assess the impact of laser in the quality of life (QOL) of patients receiving radiotherapy. Sixty outpatients were randomly assigned into 2 groups. The laser group received applications and the placebo group received sham laser. QOL was assessed using the University of Washington QOL questionnaire. A decrease in QOL scores was observed in both groups and the reduction in the laser group was significantly lower. Changes in QOL scores regarding pain, chewing, and saliva domains were evident in the placebo group. Both health-related QOL and overall QOL were rated higher by patients who received laser therapy.

4.1.12 Cardiac conditions

A number of studies report on the use of LPT in cardiac surgery. LTP appears to be able to reduce the risk of aneurysm, reduce the necrotic area after infarction, protect damage to erythrocytes in heart-lung machines, reduce the incidence of wound dehiscence after open heart surgery, and reduce complications after stent operations.The cardiac area is easily accessible using fibre optics. The scientific support for the use of LPT for wound healing after cardiac surgery is moderately strong, whereas the use of intraoperatory LPT still needs more clinical research. It appears, though, to have great potential.

Literature:

In vitro studies:

Kipshidze [1124] reports that HeNe laser can influence the vascular endothelian growth factor and proliferaration of human endothelial cells in vitro. These data may have significant importance, leading to the establishment of new methods for endoluminal postangioplasty vascular repair and myocardial photoangiogenesis.

Gavish has shown that LPT (780 nm) increases the aortic smooth muscle cell proliferation and matrix protein secretion and modulates the activity and expression of matrix metalloproteinases. Inflammation is a major component of arteriosclerotic diseases, including aneurysm. Macrophage recruitment and secretion of pro-inflammatory cytokines and the vasodilator, nitric oxide (NO), are central to most immune responses in the arterial wall. The study [1944] was designed to determine the effect of LPT on cytokine gene expression and secretion, as well as the gene expression of inducible nitric oxide synthase (iNOS) and NO production in lipopolysaccharide (LPS)-stimulated macrophages. Murine monocyte/macrophages were irradiated with a 780 nm (2 mW/cm^2, 2.2 J/cm^2) during stimulation with LPS (0, 0.1, and 1 microg/ml). Gene expression of chemokines, cytokines, and iNOS were assessed by RT-PCR. Secretion of interleukin (IL)-1ß and monocyte chemotactic protein (MCP)-1 and NO were assessed by ELISA and the Griess reaction, respectively. LPT reduced gene expression of MCP-1, IL-1, IL-10, IL-1ß, and IL-6 when cells were stimulated by 1 microg/ml LPS. LPT reduced LPS-induced secretion of MCP-1 over non-irradiated cells by 17+/-5% and 13+/-5% at 12 hours (0.1 and 1 microg/ml LPS), and reduced IL-1ß by 22+/-5% and 25+/-9% at 24 hours (0.1 and 1 microg/ml LPS). However, LPT increased NO secretion after 12 hours. These properties of LPT, with its effects on smooth muscle cells reported previously, may be of profound ther-

apeutic relevance for arterial diseases such as aneurysm, where inflammatory processes and a weakening of the matrix structure of the arterial wall are major pathologic components.

Another study by Gavish [1945) was designed to determine the effects of LPT on arterial SMC proliferation, inflammatory markers, and matrix proteins. Porcine primary aortic SMCs were irradiated with a 780 nm laser (1 and 2 J/cm²). Trypan blue exclusion assay, immunofluorescent staining for collagen I and III, Sircol assay, gelatin zymography, and RT-PCR were used to monitor proliferation, collagen trihelix formation, collagen synthesis, matrix metalloproteinase-2 (MMP-2) activity, and gene expression of MMP-1, MMP-2, tissue inhibitor of MMP-1 (TIMP-1), TIMP-2, and IL-1ß, respectively. LPT increased SMC proliferation by 16 and 22% (1 and 2 J/cm², respectively) compared to non-irradiated cells. Immediately after LPT, trihelices of collagen I and III appeared as perinuclear fluorescent rings. Collagen synthesis was increased twofold (two days after LPT: 14.3+/-3.5 microg, non-irradiated control: 6.6+/-0.7 microg, and TGF-ß stimulated control: 7.1+/-1.2 microg), MMP-2 activity after LPT was augmented (over non-irradiated control) by 66+/-18% (2 J/cm²), and MMP-1 gene expression upregulated. However, TIMP-2 was upregulated, and MMP-2 gene expression downregulated. IL-1ß gene expression was reduced. In conclusion, LPT stimulates SMC proliferation, stimulates collagen synthesis, modulates the equilibrium between regulatory matrix remodelling enzymes, and inhibits pro-inflammatory IL-1ß gene expression. These findings may be of therapeutic relevance for arterial diseases such as aneurysm, where SMC depletion, weakened extracellular matrix, and an increase in pro-inflammatory markers are major pathologic components.

Itoh [723] has demonstrated that HeNe laser has a protective effect on the type of damage to the erythrocytes caused by heart-lung machines.

Animal studies

Kipshidze [717] reports that a single endoluminal irradiation with HeNe (1.8 J) prevents restenosis after balloon angioplasty in an atherosclerotic rabbit model.

Kipshidze [344] reports further promising results in the treatment of acute myocardial infarction by guiding HeNe laser light into the heart cavity.

Oron [1097] found that 803 nm LPT reduced the formation of scar tissue following experimentally induced ischemic myocardial infarction in rats and dogs. Following the induction of the infarction, the dogs (24 in the experimental group, 24 in the control group) received laser irradiation epicardially with a dose of 1.08 J/cm². At five to six weeks postop., the dogs were sacrificed and infarction size was determined by TTC staining and histology. The infarct size in the laser group was reduced by 52% as compared to the control group. Catalase enzymatic activity (antioxidant marker) was higher in the laser group. The results were confirmed in a separate study of 83 rats.

In this experiment, the left ventricular dilatation was also reduced by 50-60% in the laser group.

Yaakov [1197] has studied the effect of 804 nm laser on the interstitial scarring in the hearts of rats subjected to experimental heart hypertrophy. The rats were injected with isoproternol (ISO), a substance known to induce hypertrophy without a marked mortality rate in the rat's heart. A careful dosage analysis was performed, resulting in a measured power of 5 mW near the heart, and a power density of 4.5 mW/cm^2 *on the myocardium. ISO treatment resulted in an 11% increase in hypertrophy, which was not altered by laser irradiation. However, a 57% reduction in interstitial scarring in the myocardium was evident in laser-irradiated rats as compared to non-irradiated rats.*

Drugova [1714] studied the effects of low-intensity red light (HeNe or broadband) on lipid peroxidation in isolated rat hearts in the postischemic period. It was established that both laser and wideband luminescent irradiation applied during reperfusion reduced the content of lipid peroxidation products in tissues to a near-control level. Acc. to the authors of the study, the effect is possibly associated with reactivation of antioxidant enzymes.

The effect of HeNe irradiation on the process of angiogenesis in the infarcted rat heart and in the chick chorioallantoic membrane (CAM), as well as the proliferation of endothelial cells in tissue cultures, were investigated by Mirsky [1591]. Formation of new blood vessels in the infarcted rat heart was monitored by counting proliferating endothelial cells in blood vessels. In the CAM model, defined areas were either laser-irradiated or non-irradiated and blood vessel density was recorded in each site in the CAM at various time intervals. Laser irradiation caused a 3.1-fold significant increase in newly formed blood vessels 6 days post infarction, as compared with non-irradiated rats. In the CAM model, a slight inhibition of angiogenesis up to two days post irradiation, and a significant enhancement of angiogenesis in the laser-irradiated foci as compared with the non-irradiated control spots, were evident. The laser irradiation caused a 1.8-fold significant increase in the rate of proliferation in endothelial cells in culture compared to non-irradiated cells.

The aim of a study by Tuby [1730] was to investigate the effect of LPT on the expression of vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS). Myocardial infarction was induced by occlusion of the left descending artery in 87 rats. Laser was applied to intact and post-infarction. VEGF, iNOS, and angiogenesis were determined. Both the laser-irradiated rat hearts post-infarction and the intact hearts demonstrated a significant increase in VEGF and iNOS expression compared to non-laser-irradiated hearts. LPT also caused a significant elevation in angiogenesis.

Whittaker [1912] reports: In vitro, fibroblasts were irradiated for one minute twice a day for four days (5 mW; 780 nm). In addition, one day after infarction, rats were randomly assigned to 5 or 10 mW transdermal irradia-

tion twice a day for four days or to sham treatment. One week after infarction, we measured the remodelling parameters; cavity volume, infarct thickness, and vascular structure, and the healing parameters; collagen content and inflammation. Laser-treated fibroblasts occupied a larger area than controls. Hearts receiving the 10 mW treatment had smaller volumes than sham-treated hearts. Laser treatment reduced infarct thinning and preserved the arterial lumen area; however, collagen did not increase and inflammation was inhibited. In conclusion, LPT attenuated infarct-associated remodelling. In contrast to expectations from the in vitro study, these effects were not a result of enhanced healing.

Clinical studies

Lee [752] successfully used LPT for the relief of cervicothoracic pain syndromes.

De Scheerder [968] has used HeNe laser as an adjunct in coronary stent implantation. The preliminary findings suggest that LPT results in a decrease of in-stent restenosis when used during primary stenting. A long term evaluation is published [1636].

According to Derkacz [1545], the main problem after percutaneous coronary intervention (PCI) is restenosis affecting the site where dilatation is performed. In order to minimise its occurrence, the method of intravascular laser photostimulation (LP) with LPT has been developed. The procedure is carried out during PCI. A special setup was prepared for intravascular photostimulation with a 808 nm wavelength laser diode and a special diffuser, delivering the laser light into the coronary artery. The construction of the device makes it possible to irradiate the coronary artery in the place of previously performed dilatation in a satisfactory and programmable manner and with uniform intensity. Two pilot LP procedures carried out are described below. The patients were diagnosed before treatment and followed up three and six months after the LP procedure with non invasive tests. After six months, a control angiography was also performed. The procedures were well tolerated. In both cases, the follow-up examinations showed no evidence of restenosis. No negative side effects were observed after two procedures.

Based on the results of these previous experiments proving the beneficial effects of laser light on the activity of vascular and inflammatory cells, Derkacz [1636] continued to use LPT to prevent restenosis. Irradiation was performed in 41 patients after stent implantation or balloon angioplasty. Illumination power of 100 mW and an energy dose equal to 9 J/cm^2 was used. Patients were monitored for major adverse cardiac events (MACE) after 30 days and six months. At six months, angiography as a control was performed to assess the influence of LP on the restenosis rate. Results: The angiographic follow-up (n=30) revealed restenosis in 9% and 25% of patients after stent implantation and balloon angioplasty, respectively. The MACE rate was 4.5% and 12.5% in stent and balloon-treated patients, *respectively. Laser phototherapy gives very promising results in restenosis prevention, especially after stent implantation.*

Infrared irradiation of the skin applied to the projections of the heart and its reflexogenic areas is also reported by other authors to be successful. There are many Russian reports on intravascular HeNe irradiation as a treatment modality for patients with heart infarction or other ischemic heart diseases. Reported effects include reduced need of nitroglycerine tablets, decreased number of angina attacks, alleviation of pain, suppression of lipid peroxidation, promotion of antioxidant protection of erythrocyte membranes, reduction of fibrinogen levels, normalisation of antithrombin-III, reduction of arrhythmic deaths as of a two-year check-up, reduction of the activities of the hypophyseoadrenocortical and aldosteron-renin-angiotensin systems. Three to five sessions of 30-40 minutes are frequently used.

Carvalho [1470] analysed forty patients after sternotomy and divided them into two groups. Control Group: submitted to a conventional therapeutic hospital scheme, and Laser Group: GaAlAs laser irradiation after the surgical incision. The laser was a continuous diode with a wavelength of 655 nm; dose 8 J/cm^2; surrounding the surgery incision and starting from the first 12 hours of Post-Operative (PO), third PO and sixth PO. A VAS scale was used in order to analyse the pain related to the wound. The investigators observed in the 3rd PO an average of 4,5 of pain intensity in the Control Group, and 2,8 in the Laser Group. In the sixth PO, an average of 4,1 in the Control Group, and 2,7 in the Laser Group were measured. Morphological analysis of repaired nerves showed that laser accelerated the regeneration process of nerve fibres.

Shoji [1476] has successfully laser treated acute dihiscence in cardiac patients where the saphenous vein has been used in myocardia revascularisation surgery. 655 nm 4 J/cm^2 was applied punctually around the wound.

Chavantes [1480] writes that in the western world cardiovascular disease is the causa mortis leader. There has been a significant increase in the rate of chronic pathologies such as Diabetes mellitus, Obesity, Hypertension. These illnesses are aggravating factors for heart disease, which tend to elevate the morbidity-mortality after conventional risky surgery. The aim in this study was to prevent wound dehiscence and/or incision infection post-surgery, which still represents a therapeutical challenge in the medical field. 112 patients underwent two different protocols to open heart surgery. Laser was applied every third day (two sessions). The Laser Group presented five times less incidence of dehiscence than the Control Group, which stayed twice as long as in-patients. Laser also revealed a decrease of complications, especially dehiscence to one-third compared with placebo. The laser group showed early pain reduction, better healing processes and shorter recovery time.

In a single case study, Dixit [2308] attempts to outline the possible effect of LPT on delayed wound healing and pain in chronic dehiscent sternotomy of a diabetic individual. The methods that were employed to evaluate *changes pre and post irradiation were wound photography, wound area measurement, pressure ulcer scale of healing (PUSH), and Visual Analogue Scale (VAS) for pain. After irradiation, proliferation of healthy granulation tissue was observed with decrease in scores of PUSH for sternal dehiscence and VAS for bilateral shoulders and sternal dehiscence. The investigators found that LPT irradiation could be a novel method of treatment for chronic sternal dehiscence following coronary artery bypass grafting, as it augments wound healing with an early closure of the wound deficit. Hence, this might be translated into an early functional rehabilitation and decreased pain perception of an individual following surgical complication.*

In a study by Kazemi-kho [2044], 30 cases with two or three coronary vessel occlusions (2VD/3VD) underwent LPT post-CABG, and 32 patients acted as a control group. A diode laser (810 nm, 500 mw) was used as LPT protocol for three successive days post-CABG. Repeated measurements of blood cell count (CBC) and cardiac damage markers (CPK, CPK-MB, LDH) accomplished before CABG and through five days of LPT post-operatively were carried out 1 and 12 hours after daily laser irradiation. Mean age of participants was 57.27±11.88 years; and male-to-female ratio was 3/1. Mean cardiac ejection fraction was 49.62±9.04% before and 47.04±7.49% after CABG surgery. Serum CPK-MB level decreased significantly in the LPT group in comparison to the placebo controls during 12 hours of post-laser irradiation measurements. None of the other parameters measured, including BS, CPK, LDH and blood leukocytes, lymphocytes and neutrophiles counts were affected by the laser irradiation during the measurement period. It is concluded that laser irradiation after CABG surgery could lower the cardiac cellular damage and help cardiac tissue repair to occur faster post-operatively.

In a study by Pinto [2520], LPT was valuable in preventing prodromal complications in saphenectomy post myocardial revascularisation.

Further literature: [408, 426, 905, 952, 991, 992, 993, 1124, 1125, 1198, 1199, 2531]

4.1.13 Carpal tunnel syndrome

Repetitive stress movements cause the Carpal Tunnel Syndrome (CTS), which is a debilitating condition resulting in many problems for employers and employees in industrial and office environments.

LPT is a valuable adjuvant treatment modality for this group of patients. The main effect is believed to be reduction of oedema and improved microcirculation in the affected area, since the venous blood flow impairment seems to be the first stage in CTS. However, a correct diagnosis is necessary. For instance, carpal tunnel symptoms caused by pseudoradicular irritation from the C5-C6 region will not respond to irradiation over the carpal area. Patients could, on the other hand, be irradiated in this very area according to Wong [539]. If venous compression in the axilla is the cause of the symptoms, local irradiation over the compressed area in combination with exercise will then be successful. If the carpal area has become very fibrotic, surgery is the only alternative. Under such conditions, LPT will only give a transient pain release and a reduction of the oedema. Complete remission of the symptoms will only be achieved in the earlier phases of the syndrome and in combination with exercise and a change in the working conditions.

A reasonable energy output over the area is 6-8 J per point. Negative studies have used lower energies. As for many other conditions, the diversity of success in reports on LPT on carpal tunnel syndrome may also depend on the inclusion criteria, i.e. the stage of the condition. The success rate of studies is closely related to the dosage. WALT recommendations for 780-830 nm is a minimum of 6 J per point, 2-3 points, and for a GaAs a minimum of 2 J per point (http://waltza.co.za).

LPT of CTS was the first indication to receive an approval by the Food and Drug Administration (FDA) in the USA. This approval is limited to "adjunct use" for obtaining temporary relief of pain associated with CTS. The study [1712] which formed the base of this approval has not been published, but is available on-line.

In conclusion, LPT is an effective treatment modality for mild and moderate carpal tunnel syndrome, provided adequate dosage is applied and differential diagnosis is correct.

Figure 4.5 35 years old diabetic patient patient operated for carpal tunnel syndrome. First photo after removal of sutures, next after one week of LPT. Courtesy: Chrisse Bäckström.

Literature:

Weintraub [538] investigated whether repeated laser light exposure directed at the median nerve could reverse the symptoms and electro-physiological latencies in CTS. The study covered 30 hands displaying moderate to severe CTS. A continuous GaAlAs laser was percutaneously applied at 33 second intervals to five points along the median nerve delivering 9 J/point without discomfort or heat sensations. A complete resolution of pre-treatment symptoms and abnormal physical findings was achieved in 77% of the *cases. Nocturnal complaints were the earliest symptom to disappear, followed by tingling, stiffness and weakness. Normalisation of distal latency was achieved in 11% with a further tendency towards improvement in 23.4%. Work status was maintained with no new interventions, and after completion of the treatment trial 11 patients resumed previously impossible activities.*

Wong [539] observed that CTS patients have poor posture. Upon palpation, they experience pain and tenderness at the spinous processes C5-T1 and the medial angle of the scapula. In 35 such patients, treatment was focused primarily on the posterior neck area and not the wrists and hands. A 100 mW GaAlAs laser was used and directed at the tips of the aforementioned spinous processes, 12-30 J/point. The laser rapidly alleviated pain and tingling in the arms, hands and fingers.

Roig [893] treated 20 patients with carpal tunnel syndrome with a GaAs/HeNe laser, 3.6 J/cm^2. Altogether 20 consecutive sessions, each lasting for 10 minutes, were given. At the end of treatment the outcome for pain and paraesthesia was: complete remission 7 patients, partial remission 8, no improvement 5. As for loss of muscle strength the outcome was: complete recovery 10 patients, partial recovery 5, no improvement 5.

Yu [192] treated car assembly-line workers with good results using a 100 mW GaAlAs laser.

Padua [937] compared the effect of a 830 nm three-diode LPT on primary carpal tunnel syndrome in 17 patients. Neurophysiological parameters and a patient questionnaire were used to evaluate the outcome. Immediately after therapy and 15 days post-therapy there was a positive effect, but at the follow-ups in month 2 and 12, almost all parameters had progressively returned to the pre-treatment pattern and were similar to those of an untreated group.

In the study by Rappl [1282], 72 hands with CTS treated by laser (15 sessions/30 min, over a period of five weeks) were evaluated by a double-blind, randomised study. ENG and VAS (visual analogous scale) were performed prior to and after therapy (830 nm, 400 mW) with an energy of 3 J per point focused on the carpal tunnel, as well as on trigger and acupuncture points. In 38 cases, a red light pen was used. Follow-ups ranged from 8 to 12 months. ENG and VAS improved in 66%, was unchanged in 8% and got worse in 26% of the patients in the laser group after a 12 month period. No improvement was recorded in the control group.

In a double-blind trial by Irvine [1426], 15 CTS patients, 34 to 67 years of age, were randomly assigned to either a control group (n=8) or a treatment group (n =7). Both groups were treated three times per week for five weeks. Those in the treatment group received 860 nm laser at a dosage of 6 J/cm^2 over the carpal tunnel, whereas those in the control group were treated with sham laser. The primary outcome measure was the Levine Carpal Tunnel Syndrome Questionnaire, and the secondary outcome measures were electrophysiological data and the Purdue pegboard test. All patients completed the study without adverse effects. There was a significant symp-

tomatic improvement in both the control and treatment groups. However, there was no significant difference in any of the outcome measures between the two groups. Note that 6 J/cm² was applied, not 6 J per point.

Ekim [1841] reports that laser at 1.5 J per point was no more efficient than placebo, which underlines the importance of being within the therapeutic window and in this case the energy indeed was in the in the lower range.

Another negative low-dose study is that of Bakhtiary [1679], who used 830 nm, 1.8 J per point on five points along the median nerve and the wrist.

The study by Elwakil [1794] was conducted to evaluate the effectiveness of LPT for CTS in comparison to the standard open carpal tunnel release surgery. Out of 54 patients, 60 symptomatic hands suffering from CTS were divided into two equal groups. Group A, was subjected to Helium Neon laser, whereas group B was treated by the open approach for carpal tunnel release. The patients were evaluated clinically and by nerve conduction studies (NCSs) about six months after the treatment. LPT showed overall significant results but at a lower level in relation to surgery. LPT showed significant outcomes in all parameters of subjective complaints except for muscle weakness. Moreover, LPT showed significant results in all parameters of objective findings except for thenar atrophy. However, NCSs expressed the same statistical significance after the treatment by both modalities

The study by Shooshtari [1996] evaluated the effects of LPT through nerve conduction measurements and clinical signs and symptoms. A total of 80 patients were included. Diagnosis of CTS was based on both clinical examination and electromyographic (EMG) findings. Patients were randomly assigned into two groups. Test group (group A) underwent laser therapy (9-11 J/cm²) over the carpal tunnel area. Control group (group B) received sham laser therapy. Pain, hand grip strength, median proximal sensory and motor latencies, and transcarpal median sensory nerve conduction (SNCV) were recorded. After fifteen sessions of irradiation (five times per week), parameters were recorded again and clinical symptoms were measured in both groups. Pain was evaluated by VAS; day-night. Hand grip was measured by Jamar dynometer.There was a significant improvement in clinical symptoms and hand grip in group A. Proximal median sensory latency, distal median motor latency and median sensory latencies were significantly decreased. Transcarpal median SNCV increased significantly after laser irradiation. There were no significant changes in group B, except for changes in the clinical symptoms.

Chang [2020] placed an 830 nm laser directly above the transverse carpal ligament, which is between the pisiform and navicular bones of the tested patients, to determine the therapeutic effect of LPT. Thirty-six patients with mild to moderate degrees of CTS were randomly divided into two groups. The laser group received laser treatment (10 Hz, 50% duty cycle, 60 mW, 9.7 J/cm²), and the placebo group received sham laser treatment. Both groups received treatment for two weeks consisting of a 10 min laser irradiation session each day, five days a week. The therapeutic effects were assessed *on symptoms and functional changes, and with nerve conduction studies (NCS), grip strength assessment, and with a Visual Analogue Scale (VAS), soon after treatment and at the two-week follow-up. Before treatment, there were no significant differences between the two groups for all assessments. The VAS scores were significantly lower in the laser group than in the placebo group after treatment and at the follow-up. After two weeks of treatment, no significant differences were found in grip strengths or for symptoms and functional assessments. However, there were statistically significant differences in these variables at the two-week follow-up. Regarding the findings of NCS, there was no statistically significant difference between groups after treatment and at the two-week follow-up. No side effects were noted.*

A study by Yagci [2060] aimed to compare the short-term efficacy of splinting (S) and splinting plus low-level laser (SLPT) in mild or moderate idiopathic carpal tunnel syndrome (CTS) with a prospective, randomised controlled study. The patients with unilateral, mild, or moderate idiopathic CTS who experienced symptoms over 3 months were included in the study. The SLPT group received ten sessions of laser therapy and splinting while S group was given only splints. The patients were evaluated at the baseline and after 3 months of the treatment. Forty-five patients with CTS completed the study. Twenty-four patients were in S and 21 patients were in SLPT group. In the third-month control, SLPT group had significant improvements on both clinical and NCS parameters (median motor nerve distal latency, median sensory nerve conduction velocities, BQ symptom severity scale, and BQ functional capacity scale) while S group had only symptomatic healing (BQ symptom severity scale). The grip strength of splinting group was decreased significantly. According to clinical response criteria, in SLPT group, five patients had full and 12 had partial recovery; four patients had no change or worsened. In S group, one patient had full and 17 partial recovery; six patients had no change or worsened.

The efficacy of LPT was evaluated by Fusakul [2497] in a total of 66 patients with mild to moderate carpal tunnel syndrome (CTS) with a double-blinded randomised controlled study. The patients were randomly assigned into two groups. Group I received 15 sessions of a laser treatment at a dosage of 18 J per session over the carpal tunnel area with neutral wrist splint. Group II received placebo laser therapy with neutral wrist splint. The patients were evaluated with the following parameters: (1) clinical parameters which consisted of Visual Analogue Scale, symptom severity scale, functional status scale, and pinch strength and grip strength before the treatment and at 5- and 12-week follow-ups and (2) electroneurophysiological parameters from nerve conduction study which were evaluated before the treatment and at 12-week follow-up. Fifty nine patients (112 hands: unilateral CTS=6 hands and bilateral CTS=106 hands) completed the study. Both groups I and II had n=56 hands. Improvements were significantly more pronounced in the LPT-treated group than the placebo group especially for grip strength at 5- and 12-week follow-ups. At 12-week follow-up, distal motor latency of the *median nerve was significantly improved in the LPT group than the placebo group. LPT therapy, as an alternative for a conservative treatment, is effective for treating mild to moderate CTS patients. It can improve hand grip strength and electroneurophysiological parameter with a carry-over effect up to 3 months after treatment for grip strength of the affected hands.*

Two laser acupuncture studies report favourable outcome [1677, 1678].

Further literature: [661, 1152

4.1.14 Cerebral palsy

Cerebral palsy (CP) is an umbrella term denoting a group of non-progressive, non-contagious motor conditions that cause physical disability in human development, chiefly in the various areas of body movement. Scientific consensus still holds that CP is neither genetic nor a 'condition', and it is also understood that the vast majority of cases are congenital, coming at or about the time of birth, and/or are diagnosed at a very young age rather than during adolescence or adulthood.

Literature:

Asagai [660] reports on the use of GaAlAs (100 mW) laser treatment in a group of 1000 patients with cerebral palsy. The laser reduced muscle spasms and increased the mobility of the muscles. Although the duration of the LPT effect was limited to one to several hours, it can be applied in conjunction with conventional functional therapies, thereby enhancing the effects of the latter.

4.1.15 Crural and venous ulcers

Bedsores are common among bedridden patients. This condition is difficult to treat since the actual insult returns shortly after any therapy. HeNe (over the open wound) and GaAs (over the skin areas) have been shown to be valuable in the combined treatment of crural ulcers. Treatment is time-consuming, so scanners are useful. However, point treatment could be given around the dermal periphery of the wound in combination with full-wound scanning. Power output on the open wound should be lower than on the skin. In addition to the irradiation over the open wound and over the wound periphery, a large area surrounding the wound should also be irradiated since the pathology is not solely located in the visible wound area. Irradiation proximal of the wound increases microcirculation into the wounded area.

Literature:

Animal studies

Rakcheev [557] carried out an animal study on 60 guinea pigs and 110 rabbits using HeNe laser on experimental trophic ulcers. Due to the positive effects achieved at 0.75 J/cm^2, a successful clinical study was performed on 56 humans.

The ability of pressure ulcers to heal after the removal of the pressure has been demonstrated by Lanzafame [1447]. Pressure ulcers were created in mice by placing the dorsal skin between two round ceramic magnetic plates for three 12-h cycles. Animals were divided into three groups (n=9 per group) for daily light therapy, 830 nm, 5.0 J/cm² on days 3-13 post ulceration in both groups A and B. A special heat-exchange device was applied in group B to maintain a constant temperature at the skin surface (30 degrees C). Group C served as controls, being irradiated with 5.0 J/cm² using an incandescent light source. Temperature of the skin surface, and temperature alterations during treatment, were monitored. The wound area was measured and the rate and time taken to complete healing were noted. The maximum temperature change during therapy was 2.0 +/- 0.64 degrees C in group A, 0.2 +/- 0.2 degrees C in Group B, and 3.54 degrees C +/- 0.72 in group C. Complete wound closure occurred at 18 +/- 4 days in groups A and B and 25 +/- 6 days in group C. The percentage of the wound closure on day 14 was 75. 4 +/- 7.2% and 77.7 +/- 5.6% for groups A and B, respectively (non-significant differences). However, animals in group C demonstrated a wound closure of 36.3 +/- 4.8%.

Figure 4.7 Woman of 80 years developing this leg ulcer during hospitalisation after hip fracture. 16 weekly laser sessions cured the wound completely. Pain and oedema disappeared after two sessions. Courtesy: Ewa Waerner.

Clinical studies

Skoric [553] administered 1 J/cm² twice a week for seven weeks to ten patients with ulcus cruris. Complete epithelialisation was obtained in four patients, and in all other patients the ulcers became smaller (minimal 4%, maximal 52%).

Bihari [13] treated three groups of patients with crural ulcers, each group consisting of five patients. Group 1 received HeNe laser light, group 2 HeNe and GaAs in combination, and group 3 non-coherent unpolarised red light. Groups 1 and 2 showed excellent healing, with group 2 showing *slightly better results than group 1. Healing in group 3 was poor. The study was double-blind.*

Lievens [352] treated 10 patients aged 65-90 years, all with crural ulcers. In combination with classic treatment, they received GaAs laser light daily for three months. There was a statistically significant reduction in pain, wound surface, and inflammatory symptoms.

Sugrue [556] used infrared laser irradiation in a group of 12 patients with chronic venous ulcers unresponsive to conservative measures. The ulcers were treated for 12 weeks. Two ulcers healed completely and there was a 27% reduction in the other ulcers, 44% in the entire group. The most dramatic effect of LPT was the reduction of ulcer pain, from 7.5 to 3.5 on a VAS scale.

Soriano [559] treated 25 patients, average age 67 years, with therapy-resistant leg ulcers. GaAs laser light at 3 J/cm^2 was administered three days a week for a maximum of 16 weeks. The average treatment time was 10 weeks. 76% of the patients were completely healed, with the best results in the female group. There was a partial response in 8% and a poor response in 16% of the patients. LPT was used parallel to traditional treatment.

In a study extended over six years, Soriano [678] treated 231 patients with venous leg ulcers. The exclusion criteria were diabetes, arterial disease, vasculitis, congestive heart failure and an inability to follow-up after six months. Altogether 122 of 154 patients in the laser group and 46 of 77 patients in the control group (traditional treatment only) completed the study. Wounds were all of Size Rate 4 or larger (diameter major + diameter minor). A 40 mW GaAs laser at 10 000 Hz was used. The laser was applied with the point technique at 3 J/cm^2 per point around the border and onto the bed of the ulcer in a non-contact mode. Three sessions a week were performed for four months, or until the ulcer was completely healed. The results were evaluated either as complete healing, partial healing (more than 50%) or non-healing (less than 50%). In the laser group there was a 70% healing rate and a 14% rate of partial healing. In the control group 26%, of the patients had complete healing and 22% partial healing. In the laser group, only 19% of the ulcers of great size (>16) healed completely, and if the wound was more than one year old the rate of complete healing was 40%. Wounds with an oedema failed to heal with the parameters used.

A total of 55 patients with long lasting chronic venous ulcers, suffering for more than six months without improvement, were treated with LPT by Lichtenstein [677, 1095]. Altogether 42 patients were treated with HeNe laser, and 13 with a 780 nm laser. The follow-up ranged from six months to six years. Wound closure was achieved after 7 to 40 treatments in most of the patients. Complete healing was achieved in 47 patients and moderate improvement in 4 patients. LPT was used parallel to traditional treatment.

Georgadze [558] treated 351 patients with persistent wounds and trophic ulcers in an outpatient clinic. Complete epithelialisation occurred in 236 patients.

Santoianni [560], however, found no effect of HeNe laser at 1 or 4 J/cm² on venous leg ulcers, as compared to a control group receiving only antiseptic local compresses.

In a study by Lundeberg and Malm [612], a 6 mW HeNe laser was used to treat leg ulcers, the stated dose being 4 J/cm². The area of the ulcers varied from 3 cm² to 32 cm², and to achieve the stated dose the period of therapy would thus have had to vary from 33 minutes to 6 hours per session. ***The method by which the dose was calculated is therefore questionable. No indication is given of the method of treatment. If a scanning laser with an unexpanded beam was used, the power density would have been about 0.15 W/cm². If the beam was expanded to a diameter capable of illuminating the whole area of the ulcer at once, the power density when treating the largest ulcer would have been about 0.00019 W/cm², which is close to the level of moonlight when the moon is full. Unless all the parameters are accounted for, it is impossible to evaluate this study.***

The same authors [613] also examined the effect of a GaAs laser on venous ulcers. The parameters stated in the report are: "The wavelength was 904 nm, average output 4 mW, peak power 10 W, pulse repetition rate 3800 Hz and duration 180 ns, and divergence 70 mrad. Energy density was 1.96 J/cm²."

- First of all, the stated energy density must obviously be wrong as the treatment time was said to be 10 minutes per patient regardless of wound size. Wound size in the laser group was in the range 4-52 cm² (average 12 cm²).

- Secondly, from the stated parameters, it is easy to calculate the average output power of the laser to be 6.84 mW, which in 10 minutes would give a total energy level of 4.1 J. For the smallest wound, this would mean 1 J/cm², and for the largest, 0.079 J/cm². The stated figure of 1.96 J/cm² cannot be correct. And, since each ulcer received a different dosage (ranging, for GaAs, from rather high to very low), doubt is cast on the whole report. Further, according to the manufacturer of the laser, a pulse repetition rate of 3800 Hz is not available in any of their equipment.

The two studies above have been used in a Cochrane literature review. In all, four randomised studies were found, two positive and two negative. With the shortcomings of the two studies above in mind, such an evaluation has little substance.

A single blind randomised study on stage III pressure ulcers has been presented by Lucas [943] using a 904 nm multi array with 12 diodes of 8 mW each. An energy density of 1 J/cm² was obtained. The same array was used for all ulcers, regardless of size. There was no statistical difference between the laser group and the control group.

Figure 4.8 Crural ulcer, one year of duration. Before LPT and after four sessions. Courtesy: Chrisse Bäckström

In a study by Telfer [776], LPT was used to treat chronic leg ulcers. Seven patients with 11 leg ulcers were referred to LPT by plastic surgeons. They had a history of ulceration ranging from 3 - 50 years, and five of the patients had breakdowns of previous skin grafts. Laser treatment was administered with 660 nm, 4-6 J/cm² and 880 nm, 4 - 8 J/cm². The patients were treated three to five times per week, 25 - 30 times per course. Three patients underwent two courses of LPT with a three week interval. All patients experienced pain relief after 5 - 10 treatment sessions and decreased the amount of analgesics used. All ulcers in six patients were completely healed, and two ulcers in a seventh patient decreased in size by 75%.

Further literature: [829, 934]

4.1.16 Delayed onset muscular soreness (DOMS)

DOMS is a constant follower of athletic training and several efforts have been made to reduce DOMS with light treatment. In our own experience, GaAs applied immediately after training has a good effect, but there is no scientific documentation. Two clinical studies using a combination of laser and LED:s [1674, 1675] failed to obtain any results, while the most recent one [1888] did find an effect from LED:s only. A laser-only animal study seems to confirm that the effect is dose dependent [1676].

Literature:

A double-blind, placebo-controlled study by Craig [1674] using male subjects (n=60) was conducted to investigate the efficacy of three different frequencies of combined LED/ LPT (CLILT) in alleviating the signs and symptoms of delayed-onset muscle soreness (DOMS). After screening for relevant pathologies, recent analgesic or steroid drug usage, current pain, diabetes, or current involvement in regular weight-training activities, subjects were randomly allocated to one of five experimental groups: Control, Pla-

cebo, or 2.5 Hz, 5 Hz, or 20 Hz CLILT groups (660-950 nm; 31.7 J/cm²; pulsed at the given frequencies for a duration of 12 min; n=12 all groups). Once baseline measurements were obtained, DOMS was induced in the non-dominant arm, which was exercised in a standardised fashion until exhaustion, using repeated eccentric contractions of the elbow flexors. The procedure was repeated twice more to ensure that exhaustion was achieved, after which the subjects were treated according to group allocation. In the CLILT/placebo groups, the treatment head was applied directly to the affected arm at the level of the musculotendinous junction. Subjects returned on two consecutive days for further treatment and assessment. The range of variables used to assess DOMS included range of movement, mechanical pain threshold/tenderness and pain. Measurements were taken before and after treatment on each day, except for the McGill Pain questionnaire, which was completed at the end of the study. Analysis of results using repeated measures and one-factor analysis of variance with relevant post-hoc tests showed significant changes in ranges of movement, accompanied by increases in subjective pain and tenderness for all groups over time; however, such analysis failed to show any significant differences between the groups on any specific day.

In a later study with different light parameters, Craig [1675] used 36 subjects (18 M: 18 F) who were randomly allocated, under double-blind conditions, to one of three experimental conditions: Control, Placebo, and CLILT (660-950 nm; 11 J/cm²; pulsed at 73 Hz). DOMS was induced in a standardised fashion in the non-dominant elbow flexors using repeated eccentric contractions until exhaustion was reached. Subjects returned on five consecutive days, and two days during the following week, for treatment according to group placement and assessments of outcome variables, including range of motion, pain, and tenderness. While analysis of results using repeated measures and one factor ANOVA with post-hoc tests showed significant changes in all variables over time as a result of the induction procedure, there were no significant differences observed between groups.

Vinck [1698] treated DOMS with a 950 nm LED, 160 mW, 3.2 J/cm² and did not find any statistically significant effects.

However, some effects on DOMS from LED therapy were found in a study by Douris [1888] as measured using the Visual Analogue Scale (VAS), McGill Pain Questionnaire, Resting Angle (RANG), and girth measurements. This was a randomised double-blind controlled study with 27 subjects (18-35 years of age) assigned to one of three groups. The experimental group received 8 J/cm² of phototherapy each day for five consecutive days using super luminous diodes with wavelengths of 880 and visible diodes of 660 nm at three standardised sites over the musculotendinous junction of the bicep. The sham group received identical treatment from a dummy cluster. The controls did not receive treatment. The study was completed over five consecutive days: on day one baseline measurements of RANG and upper arm girths were recorded prior to DOMS induction. On days two to five, RANG, girth, *and pain were assessed using VAS and the McGill Pain Questionnaire. The experimental group exhibited a significant decrease in pain associated with DOMS compared to the control and sham groups based upon the VAS at the 48-h period. The McGill Pain Questionnaire showed a significant difference in pain scores at the 48-h period between the experimental and the sham groups. There were no significant differences from day to day and between the groups with respect to girth and RANG.*

Lopes-Martins [1676] investigated if 655 nm laser irradiation can reduce muscular fatigue during tetanic contractions in rats. Thirty-two male rats were divided in four groups receiving laser doses of 0 (control group), 0.5, 1.0 and 2.5 J/cm^2. Irradiation lasted 32, 80 and 160 seconds respectively with a fixed power density of 31.25 mW/cm^2. The total energy doses were 0.08, 0.2 and 0.4 Joules respectively. Electrical stimulation induced 6 tetanic muscle contractions in the tibial anterior muscle. Contractions were stopped when the muscle force fell to 50% of the initial value for each contraction (T50%). There was no significant difference between the 2.5 J/cm^2 laser-irradiated group and the control group in mean T50%-values. Laser-irradiated groups 0.5 J/cm^2 and 1.0 J/cm^2 had significantly longer T50% values than the control group. The relative peak force for the sixth contraction in the laser irradiated groups were significantly higher at 92.2 % for 0.5 J/cm^2, 83.2 % for 1.0 J/cm^2 and 82.9 % for 2.5 J/cm^2 respectively, than for the control group, which had its peak force at 50%. Laser groups receiving 0.5 J/cm^2 and 1.0 J/cm^2 showed significant increases in mean performed work compared both to the control group and their first contraction values. Groups receiving laser irradiation with doses of 1 and 2.5 J/cm^2 also showed significantly lower levels of Creatine Kinase in plasma than the non-irradiated control group.

Muscle strains and other musculoskeletal disorders (MSDs) are a leading cause of work absenteeism and are among the most common and often disabling injuries in athletes. Muscle pain, spasms, swelling, and inflammation are symptomatic of strains. NSAIDs are probably the mainstay of drug treatments for acute musculoskeletal conditions; however, their well-known side effects and low efficacy highlights the necessity of new treatments for such conditions. Ramos [2043] investigated the effects of LPT (810 nm) in rat-induced skeletal muscle strain. Male wistar rats were anaesthetised with halothane prior to the induction of muscle strain. Previous studies have determined that a force equal to 130% of the body weight corresponds to approximately 80% of the ultimate rupture force of the muscle tendon unit. In all animals, the right leg received a controlled strain injury while the left leg served as control. A small weight corresponding to 150 % of the total body weight was attached to the right leg in an appropriate apparatus and left to induce muscle strain twice for 20 minutes with 3 minute intervals. Walking index, C-reactive protein, creatine kinase, vascular extravasation and histological analysis of the tibial muscle were performed after 6, 12 and 24 hours of lesion induction. LPT in an energy dependent manner markedly *or even completely reduced the Walking Index, leading to a better quality of movement. C-reactive protein production was completely inhibited by laser treatment, even more than observed with Sodium Diclofenac inhibition (positive control). Creative Kinase activity was also significantly reduced by laser irradiations. In conclusion, LPT operating in 810 nm markedly reduced inflammation and muscle damage after experimental muscle strain, leading to a highly significant enhancement of walking activity.*

The aim of a study by Sussai [2051] was to investigate the effects of LPT on a decrease in creatine kinase (CK) levels and cell apoptosis. Twenty male Wistar rats were randomly divided into two equal groups: group 1 (control), resistance swimming; group 2 (LPT), resistance swimming with LPT. They were subjected to a single application of InGaAlP laser immediately following the exercise for 40 s at an output power of 100 mW, wavelength 660 nm and 133.3 J/cm^2. The groups were subdivided according to sample collection time: 24 h and 48 h. CK was measured before and both 24 h and 48 h after the test. Samples of the gastrocnemius muscle were processed to determine the presence of apoptosis using terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP) nick end labeling. There was a significant difference in CK levels between groups as well as between the 24 h and 48 h levels in the control group, whereas there was no significant intra-group difference in the LPT group at the same evaluation times. In the LPT group there were 66.3 +/- 13.2 apoptotic cells after 24 h and 39.0 +/- 6.8 apoptotic cells after 48 h. The results suggest that LPT influences the metabolic profile of animals subjected to fatigue by lowering serum levels of CK. This demonstrates that LPT can act as a preventive tool against cell apoptosis experienced during high-intensity physical exercise.

There is anecdotal evidence that LPT may affect the development of muscular fatigue, minor muscle damage, and recovery after heavy exercises. Although manufacturers claim that cluster probes (LEDT) maybe more effective than single-diode lasers in clinical settings, there is a lack of head-to-head comparisons in controlled trials. The study by Leal Junior [2052] was designed to compare the effect of single-diode LPT and cluster LEDT before heavy exercise. This was a randomised, placebo-controlled, double-blind cross-over study. Young male volleyball players (n=8) were enrolled and asked to perform three Wingate cycle tests after 4 x 30 sec LPT or LEDT pretreatment of the rectus femoris muscle with either (1) an active LEDT cluster-probe (660/850 nm, 10/30 mW), (2) a placebo cluster-probe with no output, and (3) a single-diode 810 nm 200 mW laser. The active LEDT group had significantly decreased post-exercise creatine kinase (CK) levels compared to the placebo cluster group and the active single-diode laser group. None of the pre-exercise LPT or LEDT protocols enhanced performance on the Wingate tests or reduced post-exercise blood lactate levels. However, a non-significant tendency toward lower post-exercise blood lactate levels in the treated groups should be explored further. Conclusion: In this experimen-

tal set-up, only the active LEDT probe decreased post-exercise CK levels after the Wingate cycle test.

Further literature: [1699, 1745]

4.1.17 Depression, psychosomatic problems

Using light to treat seasonal depression is a controversial but yet widely used method. Whether or not coherent light would add any specific advantage is not yet known.

Literature:

From a large population of over 5000 chronic pain patients during a 70 month period, Shiroto [844] chose 1800 seriously affected patients to participate in an elective written questionnaire, in addition to the usual oral pain removal assessment session. The longer-term, more chronically affected patients, because of the nature and history of their complaint, tend to exhibit less of a placebo effect than less-affected chronic, subacute or acute pain patients. The laser used was a GaAlAs diode system, 60 mW output, 830 nm, continuous wave, and was used in the contact pressure technique. The questionnaire contained a set of questions on psychological effects following LPT, in addition to the usual pain removal questions. The questionnaire was sent by post four weeks after the final treatment session. A total of 752 patients responded. On the whole, 67.7% of the respondents reported an improvement in general well-being, 60.2% reported increased physical energy, and 56.4% reported improved sleep. Another 47.5% and 41.5% reported increased emotional stability and improved mental vigour, respectively.

The results indicate that, in addition to its effective removal of pain (76%), LPT has a strong systemic psychosomatic effect, which is possibly not attributable to the placebo effect, in the longer-term chronic pain patient.

The authors believe that the mechanism here may be the same as in BLT (Bright Light Treatment) of seasonal depressions*; See chapter 11.1.9 “Bright Light Phototherapy” on page 711.*

The adhesion of human cervical cancer (HeLa) cells to a glass matrix was evaluated by Karu [2421] following their irradiation in a suspension with a pulsed near-infrared (IR) light-emitting diode (wavelength 820 nm, pulse repetition frequency 10 Hz, irradiation dose 16-120 J/cm^2) when melatonin (4 x 10(-11) to 4 x 10(-5) m) is added to cell suspension immediately before or after the irradiation. Also, the dependence of visible-to-near-IR radiation (600-840 nm, 52 J/cm^2) on cell adhesion (action spectrum) is recorded in absence and presence of melatonin (4 x 10(-6) m). It is found that melatonin in pharmacological concentrations (but not in physiological range) inhibited cell adherence. Irradiation of cells before or after melatonin treatment normalises cell adhesion to control level. Melatonin in pharmacological concentrations eliminates stimulation of cell attachment induced by *irradiation. Pre-treatment (but not post-treatment) with melatonin in the physiological concentration eliminates cell adhesion stimulation induced by irradiation. Melatonin modifies the light action spectrum significantly in near IR region (760-840 nm only). Thus, the peak at 820-830 nm characteristic for the light action spectrum is fully reduced.*

4.1.18 Diabetes

In some previous research literature, diabetes can be found as a contra indication for LPT. On the contrary, LPT can be used to an advantage! The circulatory problems of diabetic patients are a great challenge. Schindl [478, 552] early on demonstrated the effectiveness of HeNe laser treatment on limbs with circulatory disorders. Non-healing wounds in diabetic patients are an excellent indication for LPT, and many amputations can be avoided. Genetically diabetic rats have become a standard for wound healing experiments with lasers, and the results from these animal experiments are more relevant than the studies performed on healthy animals. So far there is no evidence that LPT can be used to treat the intrinsic diabetic factors; however, used for the microcirculatory secondary complications, LPT is an excellent option in combination with conventional methods. A lot of pain and amputations could be eliminated if LPT was to become a standardised method.

Figure 4.9 Healing of diabetic necroses after amputation. Courtesy: Nooshafarin Kazemi-kho

Literature:

In vitro studies

Schindl [1136] presents a study aimed at evaluating the possible protective effect of LPT against high glucose-induced delay in proliferation of human endothelial cells. Human umbilical vein endothelian cells were cultured with either standard or elevated concentrations of glucose and were irradiated with 670 nm. Irradiation was performed every other day for one week. Cell proliferation was evaluated on days two, four and seven. The *results demonstrated a dose-dependent protective effect of laser irradiation on high glucose-induced reduction of cell counts on day seven. These data provide further evidence of the beneficial effects of LPT on patients with diabetic microangiopathy.*

The aim of the investigation by Houreld [1864] was to assess morphological, cellular, and molecular effects of exposing wounded diabetic fibroblast cells to He-Ne irradiation at two different doses. Normal human skin fibroblast cells (WS1) were used to simulate a wounded diabetic model. The effect of LPT (5 and 16 J/cm^2 once a day on two non-consecutive days) was determined by analysis of cell morphology, cytotoxicity, apoptosis, and DNA damage. Cells exposed to 5 J/cm^2 showed a higher rate of migration than cells exposed to 16 J/cm^2, and there was complete wound closure by day four. Exposure of WS1 cells to 5 J/cm^2 on two non-consecutive days did not induce additional cytotoxicity or genetic damage, whereas exposure to 16 J/cm^2 did. There was a significant increase in apoptosis in exposed cells as compared to unexposed cells. Based on cellular morphology, exposure to 5 J/cm^2 was stimulatory to cellular migration, whereas exposure to 16 J/cm^2 was inhibitory. Exposure to 16 J/cm^2 induced genetic damage on WS1 cells when exposed to a HeNe laser in vitro, whereas exposure to 5 J/cm^2 did not induce any additional damage.

Another study by Houreld [1871] investigated the effectiveness of helium-neon laser irradiation at increasing intervals on diabetic-induced wounded human skin fibroblast cells (WS1) at a morphological, cellular, and molecular level. The controversies over light therapy can be explained by the differing exposure regimens and models used. No therapeutic window for dosimetry and mechanism of action has been determined at the level of individual cell types, particularly in diabetic cells in vitro. WS1 cells were used to simulate an in vitro wounded diabetic model. The effect of the frequency of HeNe irradiation at a fluence of 5 J/cm^2 was determined by analysis of cell morphology, viability, cytotoxicity, and DNA damage. Cells were irradiated using three different protocols: they were irradiated at 30 min only; irradiated twice at 30 min and at 24 h; or irradiated twice at 30 min and at 72 h post-wound induction. A single exposure to 5 J/cm^2 30 min post-wound induction increased cellular damage. Irradiation of cells at 30 min and at 24 h post-wound induction decreased cellular viability, cytotoxicity, and DNA damage. However, complete wound closure, as well as an increase in viability and a decrease in cytotoxicity and DNA damage, occurred when cells were irradiated at 30 min and at 72 h post-wound induction. Thus, wounded diabetic WS1 cells irradiated with 5 J/cm^2 showed increased cellular repair when irradiated with an adequate amount of time between irradiations, allowing time for cellular response mechanisms to take effect. Therefore, the irradiation interval was shown to play an important role in wound healing in vitro and should be taken into account.

A following study by Houreld [1926] aimed at determining which dose and wavelength would better induce healing in vitro. Diabetic-induced *wounded fibroblasts were irradiated with 5 or 16 J/cm^2 at 632.8, 830, or 1064 nm. Cellular morphology, viability (Trypan blue and apoptosis), and proliferation (basic fibroblast growth factor) were then determined. Cells irradiated with 5 J/cm^2 at 632.8 nm showed complete wound closure and an increase in viability and basic fibroblast growth factor (bFGF) expression. Cells irradiated at 830 nm showed incomplete wound closure and an increase in bFGF expression. Cells irradiated at 1064 nm showed incomplete closure and an increased apoptosis. All cells irradiated with 16 J/cm^2 at all three wavelengths showed incomplete wound closure, an increased apoptosis, and a decreased bFGF expression. This study showed that diabetic-wounded cells respond in a dose- and wavelength-dependent manner to laser light. Cells responded best when irradiated with a fluence of 5 J/cm^2 at a wavelength of 632.8 nm.*

The next study by Houreld [1927] aimed at determining the effect on cellular proliferation, migration, and cytokine interleukin-6 expression in diabetic and diabetic wounded fibroblast cells (WS1) post-laser irradiation. Diabetic and diabetic wounded WS1 cells were irradiated at 632.8 nm (23 mW) with 5 J/cm^2 or 16 J/cm^2. IL-6 level, cellular proliferation (neutral red assay), and morphology were then determined. Diabetic cells irradiated with 5 J/cm^2 showed no significant changes, while diabetic wounded cells showed an increase in IL-6 level, proliferation, and migration. On the other hand, diabetic and diabetic wounded cells irradiated with 16 cm^2 showed a significant decrease in proliferation and evidence of cellular damage, and wounded cells showed no migration. This study showed that phototherapy at the correct fluence level stimulates IL-6 expression, proliferation, and cellular migration in diabetic wounded cells.

A study by Esmaeelinejad [2241] evaluated the effects of LPT on human skin fibroblasts (HSFs) that have been cultured in high glucose concentration media. HSFs were cultured under physiologic glucose condition medium, and then cultured in high glucose concentration medium for one or two weeks prior to LPT. Experimental HSFs were irradiated with three energy densities (0.5, 1, and 2 J/cm^2) once daily on three consecutive days. Release of interleukin-6 (IL-6) and basic fibroblast growth factor (bFGF) were evaluated by the enzyme-linked immunosorbent assay (ELISA) method. Statistical analysis showed three doses of 0.5, 1 and 2 J/cm^2 stimulated the release of IL-6 in HSFs cultured in high glucose concentration medium compared to non-irradiated HSFs that were cultured in the same medium. LPT with 2 J/cm^2 induced the release of bFGF from HSFs cultured in high glucose concentration medium for one or two weeks.

Delayed wound healing is one of the most challenging complications of diabetes mellitus (DM) in clinical medicine.Another study by Esmaeelinejad [2472] aimed to evaluate the effects of LPT on human skin fibroblasts (HSFs) cultured in a high glucose concentration. HSFs were cultured either in a concentration of physiologic glucose (5.5 mM/l) or high glucose media (11.1 and15 mM/l) for either 1 or 2 weeks after which they were subsequently *cultured in either the physiologic glucose or high concentration glucose media during laser irradiation. LLLT was carried out with a HeNe laser unit at energy densities of 0.5, 1, and 2 J/cm^2, and power density of 0.66 mW/cm^{2}on 3 consecutive days. HSFs' viability and proliferation rate were evaluated with the dimethylthiazol-diphenyltetrazolium bromide (MTT) assay. The LPT at densities of 0.5 and 1 J/cm^2 had stimulatory effects on the viability and proliferation rate of HSFs cultured in physiologic glucose (5.5 mM/l) medium compared to their control cultures. All three doses of 0.5, 1, and 2 J/cm^2 had stimulatory effects on the proliferation rate of HSFs cultured in high glucose concentrations when compared to their control cultures. This study showed that HSFs originally cultured for 2 weeks in high glucose concentration followed by culture in physiologic glucose during laser irradiation showed enhanced cell viability and proliferation. Thus, LLLT had a stimulatory effect on these HSFs.*

Figure 4.10 Diabetic foot ulcer before and at late stage of combined laser therapy. Courtesy: Nooshafarin Kazemi-kho.

Animal studies

Yu [528] used an argon pumped dye laser at a wavelength of 630 nm, 20 mW/cm^2, to treat experimental wounds in diabetic mice. Histological evaluations showed that LPT improved wound epithelialisation, cellular content, granulation tissue formation and collagen deposition as compared with the control group.

In a wound healing study on diabetic rats by Reddy [657], the following conclusions were made: 1) the GaAs LPT had no apparent systemic effect on the wound of the side opposite the treated side, and 2) laser photostimula-

tion decreased the healing time for full thickness skin wounds in diabetic animals but had no effect on the biomechanical properties of the tissue once the wound had healed.

Byrnes [1455] used 632 nm to establish the effect of laser on cutaneous wounds in diabetic and non-diabetic mice. An initial series of experiments were done to establish optimal treatment parameters for the aforementioned model. Following the creation of bilateral full-thickness skin wounds, non-diabetic Sand Rats were treated with laser of differing dosages. Wound healing was assessed according to wound closure and histological characteristics of healing. Optimal treatment parameters were then used to treat type II diabetic Sand Rats, while a diabetic control group received no irradiation. In order to elucidate the mechanism behind an improvement in wound healing, the expression of basic fibroblast growth factor (bFGF) was assessed. Significant improvement in wound healing histology and wound closure were found following treatment with 4 J/cm^2 (16 mW, 250-sec treatments for four consecutive days). The 4 J/cm^2 dosage significantly improved histology and closure of wounds in the diabetic group in comparison to the non-irradiated diabetic group. Quantitative analysis of bFGF expression at 36 h post-injury revealed a threefold increase in the diabetic and non-diabetic Sand Rats after LPT.

In a study by al-Watban [1863], the effects of wound healing acceleration on diabetic rats were determined and compared using different laser wavelengths and incident doses. Streptozotocin was applied for diabetes induction. An oval full-thickness skin wound was created aseptically with a scalpel in 51 diabetic rats and six non-diabetic rats on the shaved back of the animals. The study was performed using 532, 633, 810, and 980 nm diode lasers. Incident doses of 5, 10, 20, and 30 J/cm^2 and treatment schedule of three times/week were used in the experiments. The wound area on all rats was measured and plotted on a slope chart. The slope values (mm^2/day), the percentage of relative wound healing, and the percentage of wound healing acceleration were computed in the study. Mean slope values were 6.0871 in the non-diabetic control group, and 3.636 in the diabetic control rats. The percentages of wound healing acceleration were 15.23, 18.06, 19.54, and 20.39 with 532 nm, 33.53, 38.44, 32.05, and 16.45 with 633 nm, 15.72, 14.94, 9.62, and 7.76 with 810 nm, and 12.80, 16.32, 13.79, and 7.74 with 980 nm, using incident doses of 5, 10, 20, and 30 J/cm^2, respectively. There were significant differences in the mean slope value of wound healing on diabetic rats between control groups and treatment groups when using 532, 633, 810, and 980 nm lasers. In conclusion, the wound healing on control rats with diabetes was slower than on control rats without diabetes. LPT at appropriate treatment parameters can enhance the wound healing on diabetic rats. The optimum wavelength in this study was 633 nm, and the optimum incident dose 10 J/cm^2.

In a study by Mirzaei [1877], diabetes was induced in rats by streptozotocin 30 days after its injection. Two sets of skin samples were extracted *under sterile conditions. Fibroblasts that were extruded from the samples were proliferated in vitro, and another set of samples were cultured as organ culture. A 24-well culture medium containing Dulbecco's modified minimum essential medium was supplemented by 12% fetal bovine serum. There were five laser-treated and five sham-exposed groups. A HeNe laser was used, and 0.9-4 J/cm² energy densities were applied four times to each organ culture and cell culture. The organ cultures were analysed by light microscopy and transmission electron microscopy examinations. Statistical analysis revealed that 4J/cm² irradiation significantly increased the fibroblast numbers compared to the sham-exposed cultures.*

In a study by Al-Anzari [2038], Streptozotocin was applied for diabetes induction. An oval full-thickness skin wound was created aseptically with a scalpel in 51 diabetic rats on the shaved back of the animals. The study was performed using 532, 633 nm, 810 nm and 980 nm lasers. Incident doses of 5, 10, 20 and 30 J/cm² and a treatment schedule of three sessions per week were used in the experiments. The rats treated were restrained in a Plexiglas cage without anesthesia during the laser irradiation period. The control group also received the same manipulation, excluding the laser exposure. The wound area on all rats was measured and plotted on a slope chart. The slope values (mm²/day) and the percentage of relative wound healing were computed in the study. The percentage of relative wound healing were 30.64 at 532 nm, 50.41 at 633 nm, 20.1 at 810 nm, and 21.19 at 980 nm. There were significant differences in the mean slope value of wound healing on diabetic rats between treatment and control groups.

The aim of a study by Simões [2121] was to evaluate the effect of laser irradiation on the amylase and the antioxidant enzyme activities, as well as on the total protein concentration of submandibular glands (SMG) of diabetic and non-diabetic rats. Ninety-six female rats were divided into eight groups: D0, D5, D10, and D20 (diabetic animals), and C0, C5, C10, and C20 (non-diabetic animals), respectively. Diabetes was induced by administering streptozotocin and confirmed later by the glycemia results. Twenty-nine days after diabetes induction, the SMG of groups D5 and C5, D10 and C10, and D20 and C20 were irradiated with 5, 10, and 20 J/cm² , respectively. A diode laser (660 nm/100 mW) was used. On the day after irradiation, the rats were euthanised and the SMG were removed. Catalase, peroxidase, and amylase activities, as well as protein concentration, were assayed. Results: Diabetic rats without irradiation (D0) showed higher catalase activity when compared to C0 (0.16 +/- 0.05 and 0.07 +/- 0.01 U/mg protein, respectively). However, laser irradiation of 5, 10, and 20 J/cm² reduced the catalase activity of diabetic groups (D5 and D20) to non-diabetic values. In conclusion, laser irradiation decreased catalase activity in diabetic rats' SMG.

The objective of another study by Simões [2122] was to evaluate the effect of LPT on the glycemic state and the histological and ionic parameters of the parotid and submandibular glands in rats with diabetes. One hundred *twenty female rats were divided into eight groups. Diabetes was induced by administration of streptozotocin and confirmed later according to results of glycemia testing. Twenty-nine days after the induction, the parotid and submandibular glands of the rats were irradiated with 5, 10, and 20 J/cm² using a laser diode (660 nm/100 mW) without diabetes: C5, C10, and C20; with diabetes: D5, D10, and D20, respectively). On the following day, the rats were euthanised, and blood glucose determined. Histological and ionic analyses were performed. Rats with diabetes without irradiation (D0) showed lipid droplets accumulation in the parotid gland, but accumulation decreased after 5, 10, and 20 J/cm² of laser irradiation. A decrease in fasting glycemia level from 358.97+/-56.70 to 278.33+/-87.98 mg/dL for D5 and from 409.50+/-124.41 to 231.80+/-120.18 mg/dL for D20 was also observed. In conclusion, LPT could be explored as an auxiliary therapy for control of complications of diabetes because it can alter the carbohydrate and lipid metabolism of rats with diabetes.*

In the study by Peplow [2250] irradiation of left flank of genetic diabetic mice with 660 nm, 100 mW, 20 seconds/day for 7 days did not significantly alter blood plasma glucose compared to non-irradiated controls. Infrared light would provide for a greater amount of photoenergy penetrating the skin and muscle. Genetic diabetic mice were irradiated with 810 nm wavelength laser to test for anti-diabetic effect. Sixty-five diabetic mice were used. Body weight and water intake of mice were measured daily for 7 days prior to start of treatment (Day 0). Mice were irradiated with 810 nm, 50 mW, 40 seconds/day, 7 days on left flank (n=11), mid-upper abdomen (n=14), or left inguinal region (n=14); some mice were not irradiated (control, n=26). Body weight and water intake of mice were measured to Day 7. On Day 7, mice were fasted for 4 hours, anesthetised and blood collected by cardiac puncture into EDTA-treated tubes. Blood plasma was assayed for glucose and fructosamine. Blood was collected and assayed from non-irradiated non-diabetic mice (n=12). On Day 7 body weight was significantly lower and water intake significantly higher compared to Day 0 for diabetic mice irradiated on left flank, there was no significant change for diabetic mice irradiated on mid-upper abdomen or left inguinal region and also for non-irradiated diabetic mice. On Day 7 blood plasma glucose levels for irradiated diabetic mice were not significantly different to non-irradiated diabetic mice. Blood plasma fructosamine level of diabetic mice irradiated on left inguinal region was significantly lower than for non-irradiated diabetic mice for diabetic mice irradiated on left flank or mid-upper abdomen was not significantly different to non-irradiated diabetic mice. In conclusion, irradiation of left inguinal region in diabetic mice with 810 nm laser has potential to ameliorate diabetes as shown by decreased blood plasma fructosamine.

In a study by Kilík [2502] four round full-thickness skin wounds on dorsum were performed in male adult non-diabetic (n=24) and diabetic (n=24) rats. (635 nm; 5 J/cm², daily dose) was used to deliver power densi-

ties of 1, 5, and 15 mW/cm) three times daily until euthanasia. PMNL infiltration was lower in the irradiated groups (15 mW/cm²). The synthesis and organisation of collagen fibres were consecutively enhanced in the 5 mW/cm² and 15 mW/cm² groups compared to the others in non-diabetic rats. In the diabetic group the only significant difference was recorded in the ratio PMNL/Ma at 15 mW/cm². A significant difference in the number of newly formed capillaries in the irradiated group (5, 15 mW/cm²) was recorded on day six after injury compared to the control group. LPT confers a protective effect against excessive inflammatory tissue response; it stimulates neovascularisation and the early formation of collagen fibres.

The aim of a randomised, placebo-controlled study by Ucero [2294] was to test the hypothesis that LPT could modulate chronic kidney injury. Rats with nephropathy, hypertension, hyperlipidemia, and type II diabetes (strain ZSF1) were subjected to three different conditions of LPT or sham treatment for eight weeks, and then sacrificed ten weeks later. The main findings of this study are that the LPT-treated rats had lower blood pressure after treatment and a better preserved glomerular filtration rate with less interstitial fibrosis upon euthanasia at the end of follow-up. This initial proof-of-concept study suggests that LPT may modulate chronic kidney disease progression, providing a painless, non-invasive, therapeutic strategy, which should be further evaluated.

A study França [2299] evaluated whether LPT influences the healing morphology of injured skeletal muscle. Sixty-five rats were divided as follows: (1) sham; (2) control; (3) diabetic; (4) diabetic sham; (5) nondiabetic cryoinjured submitted to LPT (LPT); (6) diabetic cryoinjured submitted to LPT (D-LPT); and (7) diabetic cryoinjured non-treated (D). Diabetes was induced with streptozotocin. Anterior tibialis muscle was cryoinjured and received LPT daily (780 nm, 5 J/cm², 10 s per point; 0.2 J; total treatment, 1.6 J). Euthanasia occurred on day 1 in groups 1, 2, 3, and 4 and on days 1, 7, and 14 in groups 5, 6, and 7. Muscle samples were processed for H&E and Picrosirius Red and photographed. Leukocytes, myonecrosis, fibrosis, and immature fibres were manually quantified using the ImageJ software. On day 1, all cryoinjured groups were in the inflammatory phase. The D group exhibited more myonecrosis than LPT group. On day 14, the LPT group was in the remodelling phase; the D group was still in the proliferative phase, with fibrosis, chronic inflammation, and granulation tissue; and the D-LPT group was in an intermediary state in relation to the two previous groups. Under polarised light, on day 14, the LPT and D-LPT groups had organised collagen bundles in the perimysium, whereas the diabetic groups exhibited fibrosis. LPT can have a positive effect on the morphology of skeletal muscle during the tissue repair process by enhancing the reorganisation of myofibres and the perimysium, reducing fibrosis.

Firat [2310] aimed to investigate the effects of LPT on palatal mucoperiostal wound healing and oxidative stress status in experimental diabetic rats. 44 Wistar rats were used in this study. Experimental diabetes was *induced in all of the rats using streptozotocin. A standardised full thickness wound was made in the mucoperiosteum of the hard palates of the rats using a 3 mm biopsy punch. The rats were divided into groups: 1 (control group, non- irradiated), and 2 (experimental group, irradiated). Treatment using a GaAlAs laser at 940 nm and at dose of 10 J/cm^2 began after surgery, and was repeated on the 2nd, 4th, and 6th days post-surgery. Seven animals from each group were killed on the 7th, 14th, and 21st day after surgery. Biopsies were performed for the histological analysis and blood samples were collected by cardiac puncture for biochemical analysis. The histopathological findings revealed reduced numbers of inflammatory cells, and increased mitotic activity of fibroblasts, collagen synthesis, and vascularisation in rats in group 2. The total oxidative status was significantly decreased in the laser-treated group on the 21st day.*

Clinical studies

In a double-blind placebo-controlled study, Schindl [552] applied a single dose of 30 J/cm^2 of HeNe light to 15 patients with diabetic microangiopathy. Following a single transcutaneous irradiation, a statistically significant rise in skin temperature was recorded through infrared thermography. In the sham irradiated group, there was a small but significant drop in temperature.

Grubnik [527] used HeNe laser irradiation in a group of patients with diabetic gangrene. During the amputation of the lower limb, intravenous HeNe was given. Percutaneous irradiation was applied after the operation. LPT improved healing as compared to a group of similar size where no laser was applied.

In a study by Landau [658], 50 patients with chronic diabetes foot ulcers were treated with topical hyperbaric oxygen alone (15 patients), or in combination with LPT. Altogether 43 of the patients were cured of ulcers.

Zinman [1430] conducted a randomised, double-masked, sham therapy-controlled clinical trial in 50 patients with painful diabetic sensorimotor polyneuropathy. There was a positive trend, but the measured effect was not statistically significant.

Unfortunately, this study cannot be evaluated since the documentation of the actual LPT is poor. The only information given about these essential facts is "The LILT device had a wavelength of 905 nm and an average power of 0-60 mW. All LILT treatments were for 5 min per site." Which output was used? Pulse repetition rate? Dose? Power density? The scientific value of this study is therefore small but the impact on Canadian health policies probably greater. The Medline information about laser parameters is non-existent, and all that remains for Medline readers is a seemingly negative study.

Kazemi-Khoo [1726] treated seven Type2 diabetic patients with grades II and III diabetic foot ulcers with LPT. The mean duration of diabetes was 10.5 years and the ulcers were present from an average of 6.5 months *before treatment. The mean value for glycosylated hemoglobin was 8.14 mg/dl (range: 6-12.2), and foot blood flow in the Doppler ultra-sonography was normal. The author used LPT through local irradiation of the ulcer bed with 660 nm; power: 25 mW; 0.6-1 J/cm^2 and ulcer margins with 980 nm; power: 200 mW; 4-6 J/cm^2 , along with intravenous laser irradiation with 650 nm; power: 1.5 mW for 15-20 min, in addition to laser acupuncture with infrared laser (1 J/cm^2) for LI-11, LI-6, SP-6, PC-6, ST-36 and GB-34 points. Sessions were every other day for 10-15 sessions, and then continued twice weekly until complete recovery was achieved. After approximately 19 sessions complete recovery was achieved in all cases, and there were no relapses or other problems with ulcers after approximately 6 months (range: 2-10 months) of follow-ups. With this treatment regimen, there were no side-effects reported by the patients.*

In a study by Kazemi-Kho [2048], 10 diabetic type 2 patients received 7-12 sessions of intravenous blue light laser, 450 nm, 2.5 mW. Serum blood sugar (BS) was measured before and after treatment. Mean BS level before treatment was 333.8 mg mean value and mean BS level after treatment were 210.5. Serum blood sugar decreased significantly.

Obradovic [2162] divided 300 dental patients into three equal groups: Group 1 consisted of patients with periodontitis and type 1 DM (diabetes mellitus), Group 2 of patients with periodontitis and type 2 DM, and Group 3 of patients with periodontitis (control group). After oral examination, smears were taken from gingival tissue, and afterward all of the patients received oral hygiene instructions, removal of dental plaque, and full-mouth scaling and root planing. A split-mouth design was applied; on the right side of jaws LPT (670 nm, 5 mW, 14 min/day) was applied for five consecutive days. After the therapy was completed, smears from both sides of jaws were taken. Investigated parameters were significantly lower after therapy compared with values before therapy. After therapy on the side subjected to LPT, there was no significantly difference between patients with DM and the control group. It could be concluded that LPT as an adjunct in periodontal therapy reduces gingival inflammation in patients with DM and periodontitis.

The study by Kajagar [2414] was conducted to evaluate the efficacy of LPT in diabetic ulcer healing dynamics. To determine mean percentage reduction of wound area in study and control groups. A total of 68 patients with Type 2 DM having Meggitt-Wagner Grade I foot ulcers of at least more than 4 weeks duration, less than 6 × 6 cm^2 with negative culture were studied. Patients were randomised into two groups of 34 each. Patients in study group received LPT with conventional therapy and those in control group were treated with conventional therapy alone. Healing or percentage reduction in ulcer area over a period of 15 days after commencement of treatment was recorded. Mean age of the patients was 50.94 years in control group and 54.35 years in study group. There was no significant difference between control and study group with respect to mean FBS and HbA1c levels, suggesting no biochemical differences between two groups. Initial ulcer area was

2608.03 mm^2 in study group and 2747.17 mm^2 in control group. Final ulcer area was 1564.79 mm^2 in study group and 2424.75 mm^2 in control group. Percentage ulcer area reduction was 40.24 ± 6.30 mm^2 in study group and 11.87 ± 4.28 mm^2 in control group.

The objective of the study by Saied [2463] was to examine skin blood flow in diabetic patients having disease-related skin lesions, and to evaluate possible improvement imposed by LPT as a new treatment modality. Thirty patients (in addition to 15 controls receiving conventional treatment = group II and 15 others receiving no treatment = group III) having diabetes-related skin lesions were tested for skin blood flow by laser Doppler flowmetry. Group I patients received LPT by a specified dosimetry. This was by combined uniform HeNe and infrared lasers delivered by a scanner over the affected area. This study used a paired t test to determine the significance of blood flow recovery after treatment within each group while Independent t test compared results between the three groups. The most frequently detected diabetes specific skin lesions were dryness, nail changes, hair loss, infections, itching, and frank eczema-like reactions, mostly in combinations (76%). This pattern appears specific for Egyptians as it is different from data registered in foreign literature. The minimum perfusion flow improved from 16.45 before LPT to 25.94 after, while maximum flow recovered from 32.91 to 48.47 and basal perfusion changed from 24.68 to 34.84 blood perfusion units. The percentage change in perfusion values was 23.17. All these were statistically significant. The study demonstrates that diabetes-linked skin lesions have a special pattern in Egyptians and are apparently caused by deranged skin blood flow. The deficit is measurable by laser flowmetry and can be partially reversed by LPT.

Further literature: [477, 526, 1080, 1179, 1185, 1203, 1275, 1277, 1493]

4.1.19 Duodenal/gastric ulcer

HeNe laser treatment of duodenal ulcers using a gastroscope has been reported in at least 25 Russian studies. With the arrival of successful pharmaceutical treatment, these findings may no longer be as attractive as previously, but still demonstrate the healing effect of HeNe on mucosa.

Literature:

Garkavoy [339] treated 622 patients with gastric and duodenal ulcers with a HeNe laser through a gastroscope. The treatment was administered with a power of 12 mW for three to five minutes a session. The healing rate of duodenal ulcers was 91% and of gastric ulcers 93% by the end of the eighth week.

Karu [1795] reports that even non-coherent red light can be used for this superficial condition and the results were the same for coherent and non-coherent light.

4.1.20 Epicondylitis

Epicondylitis refers to an inflammation of an epicondyle. Lateral epicondylitis, is known as tennis elbow, while medial epicondylitis, is known as golfer's elbow. Epicondylitis is known to be a difficult-to-treat condition. LPT has in the past often been used as a "last resort", and has thus been tried on the most difficult cases. But LPT should be one of the first treatment modalities to be used, preferably in combination with traditional therapies. All wavelengths can be used, since the condition is superficial in the epicondylar area, but in our experience GaAs seems to work best. Trigger points in the shoulder and arm, if any, should also be laser treated, and there are more such trigger points on the lateral side than on the medial side. The possibility of an entrapment between C5-6 should also be considered.

As always, the success rate depends on suitable doses and methods of application. In the literature, as will be seen below, the outcome of LPT for epicondylitis appears to be hard to predict. But, as always, it is a matter of using reasonable parameters. We therefore quote the entire abstract of the review by Bjordal [1925], which is a typical illustration of the difficulties in finding the correct parameters and of evaluating the literature without being aware of these: “Recent reviews have indicated that low level level laser therapy (LLLT) is ineffective in lateral elbow tendinopathy (LET) without assessing validity of treatment procedures and doses or the influence of prior steroid injections. Systematic review with meta-analysis, with primary outcome measures of pain relief and/or global improvement and subgroup analyses of methodological quality, wavelengths and treatment procedures. 18 randomised placebo-controlled trials (RCTs) were identified with 13 RCTs (730 patients) meeting the criteria for meta-analysis. 12 RCTs satisfied half or more of the methodological criteria. Publication bias was detected by Egger's graphical test, which showed a negative direction of bias. Ten of the trials included patients with poor prognosis caused by failed steroid injections or other treatment failures, or long symptom duration or severe baseline pain. The weighted mean difference (WMD) for pain relief was 10.2 mm [95% CI: 3.0 to 17.5] and the RR for global improvement was 1.36 [1.16 to 1.60]. Trials which targeted acupuncture points reported negative results, as did trials with wavelengths 820, 830 and 1064 nm. In a subgroup of five trials with 904 nm lasers and one trial with 632 nm wavelength where the lateral elbow tendon insertions were directly irradiated, WMD for pain relief was 17.2 mm [95% CI: 8.5 to 25.9] and 14.0 mm [95% CI: 7.4 to 20.6] respectively, while RR for global pain improvement was only reported for 904 nm at 1.53 [95% CI: 1.28 to 1.83]. Doses in this subgroup ranged between 0.5 and 7.2 Joules. Secondary outcome measures of painfree grip strength, pain pressure threshold, sick leave and follow-up data from 3 to 8 weeks after the end of treatment, showed consistently significant results in favour of the same LPT subgroup. No serious side-effects were reported. LPT administered with optimal doses of 904 nm and possibly 632 nm wavelengths directly to the lateral elbow tendon insertions, seem to offer short-term pain relief and less disability in LET, both alone and in conjunction with an exercise regimen. This finding contradicts the conclusions of previous reviews which failed to assess treatment procedures, wavelengths and optimal doses."

In a systemic review by Coombes [2179] the authors state that the positive short term effect of corticosteroid injections for the management of tendinopathy is well documented. However, they express surprise at the high evidence of a negative effect at 6 months as well as at 1 year, as compared to no therapy at all. LPT therefore seems to be an attractive option to corticosteroids [2110].

Trigger points can be given 4-6 J per point, but the intensity over the actual epicondyle, being superficial, should be lower and the power density not more than 100 mW/cm^2, according to WALT guidelines.

Literature:

Some early studies were negative [230, 231], but in these cases acupuncture points and/or local points and very low doses were used. The same authors [208] later achieved promising results using local points at 3.6 J per point, but in non-contact mode. Positive findings were also reported in the early literature by Gudmundsen [242].

In a two-centre study, Simunovic [607] treated 324 patients, 50 with epicondylitis ulnaris and 274 with epicondylitis radialis. All in all 32% of the patients were acute and 68% chronic cases. All patients had previously been treated with various methods such as TENS, ultrasound, drugs and surgery. The patients were divided into three treatment groups. One received 830 nm laser light on trigger points only, the second was treated only with a scanner, and the third group received a combined treatment. The third group was the most successful. In the three groups together, complete relief of pain and restored functional ability were achieved in 82% of the acute patients and in 66% of the chronic cases. One centre had more powerful lasers available. Though the same doses were used at both centres, this latter group was slightly more successful. Another 41 patients with bilateral problems were selected for a cross-over study. Minimal dose in unilateral cases was 20 J, which could be increased step-by-step up to 60 J.

Simunovic [1134] has also compared laser and visible incoherent polarised light in the treatment of epicondylitis, given over 12 sessions. Altogether 40% of the patients in the laser group obtained 100% pain relief. In the non-coherent group, there was a maximal pain relief of 70%.

The negative outcome in the study by Krasheninnkoff [1188] might be explained by the rather high dosage applied for this superficial condition (13.2 J/cm^2). The high drop-out rate of 25% also compromises this study. Too high a dose is also a possible reason for the negative outcome of the study by Papadopuolos [1189] – 30 J/cm^2.

Terashima [126] treated 23 patients with lateral humeral epicondylitis and 40 patients with de Quervain's disease with GaAlAs laser. In the epi-

condylitis group, movement pains and soreness were positively affected in 61% of the cases, and in 70% of the cases in the de Quervain group. Movement pains were eradicated in 13% of all cases.

Cieslar [627] treated 182 patients with epicondylitis humeri in a double-blind study. After 5-7 sessions, distinct pain relief was obtained, and after 10-15 sessions movement pains and palpation had disappeared. Three different wavelengths were used (904, 850, and 633). The percentage of patients who had much or slight improvement was 87%. There was no significant difference between the three wavelengths used.

Konstantinovic [554] compared the effect of corticosteroid infiltration, LPT (GaAs 1 J/cm²) and laser plus corticosteroid infiltration in combination. On day 7, the combined therapy demonstrated a significantly higher analgesic effect.

Nd:YAG (1064 nm) laser was used in a study by Basford [656]. Seven sites on the most symptomatic extremity were irradiated, three times a week for four weeks. There was no significant improvement. Total delivered energy was 220 Joules, but due to a large spot size (4.9 cm²) the dose expressed in J/cm² was only 0.542.

In a review of the literature on shoulder tendinitis/bursitis and lateral epicondylalgia, Bjordal [732] summarises: "The methodological quality of the four LPT trials for lateral epicondylalgia is slightly higher than the five best trials with steroid injections for lateral epicondylalgia. Total sample size of high quality LPT trials is about two-thirds of the total sample of high quality steroid injections trials on the same diagnosis. The four LPT trials should serve as a valid platform for making conclusions on clinical effects of LPT for lateral epicondylalgia. Inadequate treatment procedures or poor methodological quality were found in the three trials that reported no significant effects of LPT. Evidence of clinical effects from LPT was found at all four lateral epicondylalgia trials using acceptable methods. The results in these trials were significantly in favour of active LPT with confidence intervals not including zero. The trial with fewest treatments per week had the lowest success rate. Best clinical effects were seen in patients with short duration of symptoms (less than a month)."

Bjordal has also summarised data from the literature regarding the treatment of tendinitis:

- A synthesis of doses from 4 laboratory trials on inflamed collagen-producing cell cultures gives the following dose for optimal reduction of tendon tissue inflammation: Dose: 3-8 J/cm², Intensity: 5-21 mW/cm².

- A synthesis of 10 laboratory trials investigating collagen proliferation gives the following optimal dose for stimulation of tendon regeneration: Dose: 0.2-4 J/cm². Intensity: 2-10 mW/cm².

- For the treatment of tendinitis, an optimal suggested dosage at target location will be: Dose: 0.2-4 J/cm². Intensity: 2-10 mW/cm².

- Treatment should be applied daily for at least five days to reduce inflammation, and for at least 10 days to increase collagen production.

The aims of the study by Oken [1825] were to evaluate the effects of LPT and to compare these with the effects of brace or ultrasound (US) treatment in tennis elbow. The study design used was a prospective and randomised, controlled, single-blind trial. Fifty-eight outpatients with lateral epicondylitis were included in the trial. The patients were divided into three *groups: 1) brace group-brace plus exercise, 2) ultrasound group-US plus exercise, and 3) laser group-LPT plus exercise. Patients in the brace group used a lateral counterforce brace for three weeks, US plus hot pack in the ultrasound group, and laser plus hot pack in the LPT group. In addition, all patients were given progressive stretching and strengthening exercise programmes. Grip strength and pain severity were evaluated by Visual Analogue Scale (VAS) at baseline, at the second week of treatment, and at the sixth week of treatment. VAS improved significantly in all groups after the treatment and in the ultrasound and laser groups at the sixth week. Grip strength of the affected hand increased only in the laser group after treatment, but was not changed at the sixth week. There were no significant differences between the groups on VAS and grip strength at baseline and at follow-up assessments. The results show that, in patients with lateral epicondylitis, a brace has a shorter beneficial effect than US and LPT in reducing pain, and that LPT is more effective than the brace and US treatment in improving grip strength.*

The aim of a study by Lam [1862] was to evaluate the effectiveness of 904 nm LPT in the management of lateral epicondylitis. Thirty-nine patients with lateral epicondylitis were randomly assigned to receive either active laser with an energy dose of 0.275 J per tender point (laser group) or sham irradiation (placebo group) for a total of nine sessions. The outcome measures were mechanical pain threshold, maximum grip strength, level of pain at maximum grip strength as measured by the Visual Analogue Scale and the subjective rating of physical function with Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire. Significantly greater improvements were shown in all outcome measures in the laser group compared to the placebo group, except in the two subsections of DASH. This study revealed that LPT in addition to exercise is effective in relieving pain, and in improving the grip strength as well as the subjective rating of physical function of patients with lateral epicondylitis.

A study by Stergioulas [1874] was undertaken to compare the effectiveness of a protocol of laser combined with plyometric exercises, and a protocol of placebo laser in combination with the same exercise programme, in the treatment of tennis elbow. Fifty patients who had tennis elbow participated in the study and were randomised into two groups. Group A (n=25) was treated with a 904 nm GaAs laser, pulse repetition rate of 50 Hz, average power 40 mW and energy density 2.4 J/cm^2, plus plyometric exercises, and group B (n=25),which received placebo laser plus the same plyometric exercises. During eight weeks of treatment, the patients of the two groups received 12 sessions of laser or placebo, two sessions per week (weeks one to four), and one session per week (weeks five to eight). Pain at rest, at palpation on the lateral epicondyle, during resisted wrist extension, middle finger test, and strength testing were evaluated using Visual Analogue Scales. The grip strength, the range of motion and a weight test were also evaluated. Parameters were determined before the treatment, at the end of the eight-

week-course of treatment (week 8), and eight weeks after the end of treatment. In relation to group B, group A had (1) a significant decrease in pain at rest at the end of the eight-week-long treatment, and at the end of the follow-up period, (2) a significant decrease in pain at palpation and pain on isometric testing after eight weeks of treatment and at the eighth week follow-up, (3) a significant decrease in pain during a middle finger test at the end of eight weeks of treatment and at the end of the follow-up period, (4) a significant decrease in pain during grip strength testing after eight weeks of treatment and at the eighth week follow-up, (5) a significant increase in the wrist range of motion at the eighth week follow-up, (6) an increase in grip strength after eight weeks of treatment and at the eighth week follow-up, and (7) a significant increase in the weight-test after eight weeks of treatment and at the eighth week follow-up. The results suggested that the combination of laser with plyometric exercises was a more effective treatment than placebo laser combined with the same plyometric exercises at the end of the treatment, as well as at the follow-up.

Previous studies have used class 3B lasers with power outputs of less than 0.5 W. Roberts [2309] evaluated a dual wavelength (980/810 nm) class 4 laser with a power output of 10 W for the purpose of determining the efficacy of class 4 laser therapy in alleviating the pain and dysfunction associated with chronic epicondylitis. Sixteen subjects volunteered for laser therapy, or an identically appearing sham instrument in a randomised, placebo-controlled, double-blinded clinical trial. Subjects underwent clinical examination (pain, function, strength, and ultrasonic imaging) to confirm chronic tendinopathy of the extensor carpi radialis brevis tendon, followed by eight treatments of 6.6 +/- 1.3 J/cm^2 (laser), or sham over 18 days. The exam protocol was repeated at 0, 3, 6 and 12 months post-treatment. No initial differences were seen between the two groups. In the laser treated group handgrip strength improved by 17 +/- 3%, 52 +/- 7%, and 66 +/- 6% at 3, 6, and 12 months respectively; function improved by 44 +/- 1%, 71 +/- 3%, and 82 +/- 2%, and pain with resistance to extension of the middle finger was reduced by 50 +/- 6%, 93 +/- 4%, and 100 +/- 1% at 3, 6 and 12 months, respectively. In contrast, no changes were seen until 12 months following sham treatment (12 months: strength improved by 13 +/- 2%, function improved by 52 +/- 3%, pain with resistance to extension of the middle finger reduced by 76 +/- 2%). No adverse effects were reported at any time.

The authors write: "These findings suggest that laser therapy using the 10 W Class 4 instrument is efficacious for the long-term relief of the symptoms associated with chronic epicondylitis. The potential for a rapidly administered, safe and effective treatment warrants further investigation." This conclusion must be questioned. Not only that a 10 W laser poses a much higher risk of burning and eye injury and is more expensive than a class 3B laser - a Class 3B laser is quicker! The high output forces a sweeping motion or irradiation from a distance, thereby causing a lot of energy loss at the deep target. The time spent was 5 minutes, which is much

more than a conventional class 3B session for this condition. With a 3B laser in firm contact over tender points and a sweeping motion over the actual condyle, more sufficient energy can be applied in 2-3 minutes. The authors of the paper above swept over an area of 45 cm². By spreading the light over a large area, using a wide beam area and irradiating from a distance, the dose became 6.6 J/cm² and the power density only 22 mW/cm² , which is very low. 3.000 J, but is "more" really better? Irradiating in contact with 10 W is not possible, but with a 3B laser in firm contact, an optimal penetration is achieved and less time is required. Yes, it was a 10 Watt laser and yes, 3.000 joules was delivered, however it had a very large beam area and treatment was delivered over a very large area (45 cm²) in a "painting fashion". The fluence (dose) was 6.6 J/cm² and the power density was a tiny 22 mW/cm², consequently treatment time was a hefty 5 minutes. Less can be more!

A total of 2 reviews and 20 RCTs were included in the literature analysis by Dingemanse [2289]. Different electrophysical regimes were evaluated: ultrasound, laser, electrotherapy, ESWT, TENS and pulsed electromagnetic field therapy. Moderate evidence was found for the effectiveness of ultrasound versus placebo on mid-term follow-up. Ultrasound plus friction massage showed moderate evidence of effectiveness versus laser therapy on short-term follow-up. On the contrary, moderate evidence was found in favour of laser therapy over plyometric exercises on short-term follow-up. For all other modalities only limited/conflicting evidence for effectiveness or evidence of no difference in effect was found. Potential effectiveness of ultrasound and laser for the management of LE was found.

Further literature: [821, 1055, 1167]

4.1.21 Erythema multiforme major

Erythema multiforme minor is a self-limiting condition, believed to be triggered by HSV viruses. It generally resolves within a week. Erythema myltiforme major, also called Stevens Johnson syndrome (SJS) is a progressive, fulminating, severe variety of the erythema multiforme major, with extensive mucocutaneous epithelial necrosis. It is a potentially life-threatening mucocutaneous drug reaction with systemic symptoms and signs with significant morbidity and mortality. Oral stomatitis has been associated with SJS and as caused by extensive keratinocyte apoptosis.

Figure 4.11 Young boy suffering from erythema multiforme major, unable to eat and in pain. Able to eat after few LPT sessions and completely healed at 10th session. Courtesy: Alyne Simões.

Literature:

Simões [2091] reports on the resolution of SJS in a young man. After five days of hospitalisation, the LPT was initiated. As the patient was not able to drink or eat any solid food, a tube was used for his nutrition. He was also unable to speak, swallow or open the mouth and reported severe pain. Clinical examination revealed swollen, bleeding and crusted lips and diffuse intraoral ulcerative lesions. At the beginning of the treatment, the patient showed a great improvement in all oral symptoms. At the end of the first laser irradiation, the patient was able to eat gelatin, through a syringe, with his father's assistance. On the second day, the crusts were dryer and lesions on the tongue had decreased. The condition was completely healed within 10 sessons.

4.1.22 Fibrositis/fibromyalgia

The origin of fibrositis is not known, and there is at present no effective treatment to offer this large group of mainly female patients. LPT is unlikely to cure a fibrositis patient. However, LPT does have a good pain relieving effect and will improve the quality of life of these patients. If the painful areas are treated, there is a rapid alleviation of pain. Repeated treatment further reduces pain, and sessions can soon be held at longer intervals. A suitable initial dose to test the patient's general reaction is 6-8 J per painful point. Superpulsed GaAs- and high powered GaAlAs lasers have proved to be quite useful in treating these patients, since they provide the higher kind of power densities important in pain therapy.

Literature:

Longo [636] treated 846 patients with fibromyositic rheumatism during a 15-year period. Diodes and carbon dioxide lasers were used. About *two-thirds of the patients benefited from the treatment with regard to local pain, hypomobility, and phlogosis.*

Thorsen [703] could not find any effect of GaAlAs laser on localised fibromyalgia in the neck and shoulder regions. The laser had a power of 30 mW and each treated point received 0.9 J and a maximum of 9 J per treatment. ***This is, however, a low dose and power density for this indication.***

A randomised, single-blind, placebo controlled study was conducted by Gür [1226] to evaluate the efficacy of GaAs LPT in 40 female patients with fibromyalgia. The treatment was carried out daily for two weeks, weekends excepted. At the end of the therapy, there was a significant difference between the two groups for parameters such as pain, muscle spasm, morning stiffness and tender points.

The aim of a study by Matsutani [2429] was to assess the efficiency of a treatment composed of muscle stretching exercises, associated or not to laser therapy at tender points, for patients with fibromyalgia (FM), in view of bettering their quality of life. Twenty FM patients were randomly assigned to two groups: one submitted to laser therapy and stretching (LSG, n=10), and the other only to stretching exercises (SG, n=10). The Visual Analogue Scale of pain (VAS) and dolorimetry at tender points were used to assess pain; life quality was evaluated by means of the Fibromyalgia Impact Questionnaire (FIQ) and the 36-item Short-Form Health Survey (SF-36). After the treatment programme, both in LSG and SG were detected pain reduction, higher pain threshold at tender points, lower mean FIQ scores and higher SF-36 mean scores. No significant differences were found between both groups. The stretching exercises programme proposed is efficient to reduce pain and painful sensibility at tender points, thus enhancing patients' quality of life. Laser therapy has not shown advantages when added to muscle stretching exercises.

The laser was 830 nm, 30 mW. It is unclear if each point received 3 J or the claimed 3 J/cm^2. Both seem to be very low for pain therapy. Gür used 904 nm, 11.2 mW, 180 s per point, so 2 J, but claimed 2 J/cm^2, which is unlikely, too. Would require a laser eye of 1 cm^2, which is unusual. 904 nm is known to require lower energy for pain, but both the studies above - one positive and one negative - are using suboptimal energies for pain therapy*.*

The purpose of another study by Gür [1281] was to examine the effectiveness of LPT and low-dose amitriptyline therapy, and to investigate effects of these therapy modalities on clinical symptoms and quality of life (QOL) in patients with fibromyalgia. Seventy-five patients with fibromyalgia were randomly allocated to active (GaAs) laser (25 patients), placebo laser (25 patients) and amitriptyline therapy (25 patients). All groups were evaluated to establish the reduction of pain, number of tender points, skin fold tenderness, morning stiffness, sleep disturbance, muscular spasm, and fatigue. Depression was evaluated by a psychiatrist according to the Hamilton Depression Rate Scale and DSM IV criteria. Quality of life of the patients *was assessed according to the Fibromyalgia Impact Questionnaire (FIQ). In the laser group, patients were treated at each tender point daily for two weeks, except weekends, each point being approximately 2 cm^2. The same unit was used for the placebo treatment group, for which no laser beam was emitted. Patients in the amitriptyline group took 10 mg daily at bedtime throughout the eight weeks. A significant difference was observed in clinical parameters for pain intensity, morning stiffness and fatigue in favour of the laser group. A significant difference was observed in morning stiffness, FIQ and depression in the amitriptyline group compared to the placebo group after therapy. Additionally, a significant difference was also observed in depression scores in the amitriptyline group in comparison to the laser group after therapy. This study suggests that both amitriptyline and laser therapies are effective on clinical symptoms and QOL in fibromyalgia, and that GaAs LPT is a safe and effective treatment of fibromyalgia cases. Furthermore, the study suggests that the GaAs LPT can be used as a monotherapy or as a supplementary treatment to other therapeutic procedures.*

A study by Panton [2174] evaluated the effects of laser therapy on pain, Fibromyalgia (FM) impact, and physical function in women diagnosed with FM. The study was a double-blind, randomised control trial. Testing was completed at the university and Rheumatologist office and treatment was completed at a chiropractic clinic. Participants: Thirty-eight (38) women (52+/-11 years; mean+/-standard deviation) with FM were randomly assigned to one of two treatment groups, LPT (n=20) or sham therapy SLPT (n=18). Both groups received treatment twice a week for 4 weeks. Treatment consisted of application of LPT or SLPT over seven tender points located across the neck, shoulders, and back. Treatment was blinded to women and was administered by a chiropractic physician for 7 minutes. Participants were evaluated before and after treatment for number and sensitivity of tender points, completed the FM Impact Questionnaire (FIQ) and the pain question of the FIQ, and were measured for function using the continuous scale physical functional performance (CS-PFP) test. There were significant interactions for pain measured by the FIQ and for upper body flexibility measured by the CS-PFP with the LPT improving significantly compared to SLPT. There was a time effect for the measure of FM impact measured by the FIQ, indicating that FM impact significantly improved from pre- to post-treatment in LPT, while no change was observed in the SLPT. This study provides evidence that LPT may be a beneficial modality for women with FM in order to improve pain and upper body range of motion, ultimately reducing the impact of FM.

Further literature: [333]

4.1.23 Headache/Migraine

This very common complaint may have a variety of different causes. Myogenically conditioned headache responds well to GaAs and GaAlAs laser treatment administered to tender points and muscle attachments, 6-8 J per point. The practitioner should also take into account peripheral tender points in the neck and shoulders. The common correlation between myogenic headache and bruxism/clenching should be observed.

"Migraine" comes from the Greek "hemi crania", literally "half head". Even though not all migraines are single-sided, this is still a fairly good diagnosis. The cause of migraine is thought to relate to fast-acting dilation of cranial blood vessels. The treatment of migraine is based on irradiation of the occipital nerve paths. Furthermore, irradiation of the carotid arteries will stimulate the vascular system of the brainstem. This should be followed by local pain point irradiation. While migraine is a typical female condition, the Horton type of headache is a typical male vascular condition, which is also worth trying to treat with LPT.

A clear differential diagnosis is essential when treating “headaches”.

Literature:

Wong [120, 975, 984] treated 20 patients with migraine or symptoms resembling migraine with a GaAlAs laser. The pain disappeared after one to five minutes. The effect was reported to be contingent on dosage and choice of treatment point.

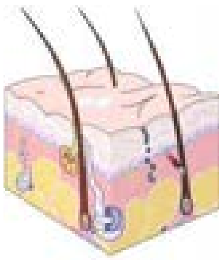
Two laser acupuncture papers [1569, 1827] report positive results.

Further literature: [1520]

4.1.24 Haemorrhoids

In the treatment of first and second-degree haemorrhoids, the HeNe laser is an effective, simple and harmless clinical procedure, representing an alternative to medication or surgery, according to Trelles [706]. Therapy is carried out at intervals of five days for a total of six treatment sessions. LPT was effective in pain alleviation from the first session, and the final result was excellent.

The aim of the report by Khorsand [2045] is to compare the effect of LPT and botox injections in the treatment of anal fissure. Altogether 26 patients with resistance to conventional treatment were allocated into two groups (n=13). The case group was injected with 40 units of botox to the anal sphincter. The control group received LPT with 650 nm, 30mW, 1 J/cm² plus 980 nm, 200 mW, 2.4 J/cm², for 5-10 sessions. The researcher visited the patients after two weeks. As for symptoms (pain, bleeding, itching, and spasms of the sphincter) there were no statistically significant differences between the two groups before and after the treatment. The statistical analysis showed a significant difference in the reduction of symptoms before and after treatment in both groups. People responding to conventional treatment are candidates for surgery. Injection of botox is a chemical sphinctrotomy. The present study showed that LPT can heal fissures as successfully as botox injections. Botulinum toxin metabolises after three to six months and a repetition of treatment may be needed. LPT has an effect on wound healing, pain *reduction as well as reducing sphincter tonicity, and the results may be more long-lasting than for botox.*



4.1.25 Hair loss

In one of Endre Mester's first experiments on rats [733], it was found that, on the shaved parts of the body, the coat grew back faster in areas that had been treated with a ruby laser. This led to a certain amount of interest in the possibilities of stimulating hair growth in humans. It is generally thought that the stimulation of hair growth with LPT is fictional, but this is only partly correct. One indication that seems to have acceptable results is LPT for alopecia areata. This is a rapid and complete loss of hair in one or several patches, usually on the scalp, affecting both males and females equally. It is thought to be an autoimmune disease which is treated with different modalities with varying success. Laser treatment of different wavelengths has been used in the management of this problem.

There are basically three types of "hair laser". The first one looks like a hood hair dryer, and it used to contain a HeNe laser tube with a maximum output of 6 mW. Nowadays, a number of GaAlInP laser diodes are generally used, with a somewhat longer wavelength (670 nm) and a higher output. The laser light is distributed via hundreds of small fibre-optic conductors over the whole of the inside of the hood. One problem is that there is a loss of energy in any area with hair, even if the hair is thin. These "hood hair dryer lasers" seem to work in many cases, but no convincing documentation has been put forward.

The second kind of "hair laser" is a normal HeNe or GaAlInP laser probe. Since the probe is held in direct contact with the scalp, the dosage level reached locally is much higher than in the "laser hair dryer", but the application method requires more work. Nevertheless, it still requires many treatment sessions and there is no guarantee of a successful result.

The third piece of equipment looks like a combe and the GaAlInP light comes out of the ends of the combe [1644].

Linear polarised near-infrared light has also been used to treat alopecia areata [1686].

Literature:

Animal studies

Fourteen mice with induced Alopecia areata were used in a study by Wikramanayake [2333]. Two were killed to confirm AA through histology. The remaining 12 mice were randomised into two groups; group I received HairMax LaserComb (655 nm, beam diameter <5 mm; divergence 57 mrad; nine diodes) for 20 s daily, three times per week for a total of 6 weeks; group II was treated similarly, except that the laser was turned off (sham-treated). After 6 weeks of LaserComb treatment, hair regrowth was observed in all the *mice in group I (laser-treated) but none in group II (sham-treated). On histology, increased number of anagen hair follicles was observed in laser-treated mice. On the other hand, sham-treated mice demonstrated hair follicles in the telogen phase with no hair shaft.*

Shukla [2464] report the results of a study carried out to investigate the effect of helium-neon laser (irradiation on the hair follicle growth cycle of testosterone-treated and untreated mice. Both histology and optical coherence tomography (OCT) were used for the measurement of hair follicle length and the relative percentage of hair follicles in different growth phases. A positive correlation was observed for the lengths of hair follicles measured by both methods. Further, the ratios of the lengths of hair follicles in the anagen and catagen phases obtained by both methods were nearly the same. However, the length of the hair follicles measured by both methods differed by a factor of 1.6, with histology showing smaller lengths. He-Ne laser irradiation (at approximately 1 J/cm^2) of the skin of both the control and the testosterone-treated mice was observed to lead to a significant increase in % anagen, indicating stimulation of hair growth. The study also demonstrates that OCT can be used to monitor the hair follicle growth cycle, and thus hair follicle disorders or treatment efficacy during alopecia.

Clinical studies

Waiz [1706] studied the effect of 904 nm in the treatment of alopecia areata. Sixteen patients with 34 resistant patches that had not responded to different treatment modalities for alopecia areata were enrolled in the study. In patients with multiple patches, one patch was left as a control for comparison. Patients were treated on a four-session basis, once a week, with a 904 nm laser. A photograph was taken of each patient before and after treatment. The treated patients were 11 males and 5 females. Their ages ranged from 4 to 50 years and the duration of their condition had lasted from 12 months to 6 years. Regrowth of hair was observed in 32 patches while only 2 patches failed to show any response. No regrowth of hair was observed in the control patches. The regrowth of hair appeared as terminal hair in its original colour in 29 patches while 3 patches appeared as a white villous hair. In patients who showed response, the response was detected as early as one week after the first session in 24 patients, while another 8 patients started to show response from the second session.

Avram [2063] investigated the efficacy of LPT in enhancing hair growth. Seven patients were exposed to LPT twice weekly for 20 minutes each time over a period of 3-6 months. Five patients were treated for a total of 3 months and two were treated for 6 months. Videomicroscopic images were taken at baseline, 3 months, and 6 months, and analysed for changes in vellus hair counts, terminal hair counts, and shaft diameter. Both videomicroscopic and global images underwent blinded review for evidence of subjective improvement. Patients also answered questionnaires assessing hair growth throughout the study. Neither patients nor physicians conducting the *study received any financial compensation. The results indicate that on average patients had a decrease in the number of vellus hairs, an increase in the number of terminal hairs, and an increase in shaft diameter. However, paired i-testing indicated that none of these changes was statistically significant. Also, blinded evaluation of global images did not support an improvement in hair density or calibre. The authors suggest that LPT may be a promising treatment option for patients who do not respond to either finasteride or minoxidil, and who do not want to undergo hair transplantation. This technology appears to work better for some people than for others. Factors predicting who will most benefit are yet to be determined.*

Androgenetic alopecia (AGA) is a common disorder affecting men and women. Finasteride and minoxidil are well-known, effective treatment methods, but patients who exhibit a poor response to these methods have no additional adequate treatment modalities. A study by Kim [2271] was designed as a 24-week, randomised, double-blind, sham device-controlled trial. Forty subjects with AGA were enrolled and scheduled to receive treatment with a helmet-type, home-use LPT device emitting wavelengths of 630, 650, and 660 nm or a sham device, for 18 minutes daily. Investigator and subject performed phototrichogram assessment (hair density and thickness) and global assessment of hair regrowth for evaluation. After 24 weeks of treatment, the LPT group showed significantly greater hair density than the sham device group. Mean hair diameter improved statistically significantly more in the LPT group than in the sham device group. Investigator global assessment showed a significant difference between the two groups, but that of the subject did not. No serious adverse reactions were detected.

Forty-four males (18-48 yo, Fitzpatrick I-IV, Hamilton-Norwood IIa-V) were recruited in a study by Lanzafame [2430]. A transition zone scalp site was selected; hairs were trimmed to 3 mm height; the area was tattooed and photographed. The active group received a unit containing 21, 5 mW lasers (655 ± 5 nm), and 30 LEDS (655 ± 20 nm), in a bicycle-helmet like apparatus. The placebo group unit appeared identical, containing incandescent red lights. Patients treated at home every other day × 16 weeks (60 treatments, 67.3 J/cm² irradiance/25 minute treatment), with follow up and photography at 16 weeks. A masked 2.85 cm² photographic area was evaluated by another blinded investigator. The primary endpoint was the percent increase in hair counts from baseline. Forty-one patients completed the study (22 active, 19 placebo). No adverse events or side effects were reported. Baseline hair counts were 162.7 ± 95.9 (n=22) in placebo and 142.0 ± 73.0 (n=22) and active groups respectively. Post Treatment hair counts were 162.4 ± 62.5 (n=19) and 228.7 ± 102.8 (n=22), respectively. A 39% percent hair increase was demonstrated (28.4 ± 46.2 placebo, n=19; 67.2 ± 33.4, active, n=22). Deleting one placebo group subject with a very high baseline count and a very large decrease, resulted in baseline hair counts of 151.1 ± 81.0 (n=21) and 142.0 ± 73.0 (n=22), respectively. Post treatment hair counts were 158.2 ± 61.5 (n=18) and 228.7 ± 102.8 (n=22), resulting in a

35% percent increase in hair growth (32.3 ± 44.2, placebo, N= 18; 67.2 ± 33.4, active, n=22). LPT of the scalp at 655 nm significantly improved hair counts in males with androgenetic alopecia.

Randomised, sham device-controlled, double-blind clinical trials were conducted by Jimenez [2496] at multiple institutional and private practices. A total of 146 male and 188 female subjects with pattern hair loss were screened. A total of 128 male and 141 female subjects were randomised to receive either a lasercomb (one of three models) or a sham device in concealed sealed packets, and were treated on the whole scalp three times a week for 26 weeks. Terminal hair density of the target area was evaluated at baseline and at 16- and 26-week follow-ups, and analyzed to determine whether the hypothesis formulated prior to data collection, that lasercomb treatment would increase terminal hair density, was correct. The site investigators and the subjects remained blinded to the type of device they dispensed/received throughout the study. The evaluator of masked digital photographs was blinded to which trial arm the subject belonged. Seventy-eight, 63, 49, and 79 subjects were randomised in four trials of 9-beam lasercomb treatment in female subjects, 12-beam lasercomb treatment in female subjects, 7-beam lasercomb treatment in male subjects, and 9- and 12-beam lasercomb treatment in male subjects, compared with the sham device, respectively. Nineteen female and 25 male subjects were lost to follow-up. Among the remaining 122 female and 103 male subjects in the efficacy analysis, the mean terminal hair count at 26 weeks increased from baseline by 20.2, 20.6, 18.4, 20.9, and 25.7 per cm2 in 9-beam lasercomb-treated female subjects, 12-beam lasercomb-treated female subjects, 7-beam lasercomb-treated male subjects, and 9- and 12-beam lasercomb-treated male subjects, respectively, compared with 2.8, 3.0, 1.6, 9.4 and 9.4 in sham-treated subjects. The increase in terminal hair density was independent of the age and sex of the subject and the lasercomb model. Additionally, a higher percentage of lasercomb-treated subjects reported overall improvement of hair loss condition and thickness and fullness of hair in self-assessment, compared with sham-treated subjects. No serious adverse events were reported in any subject receiving the lasercomb in any of the four trials.

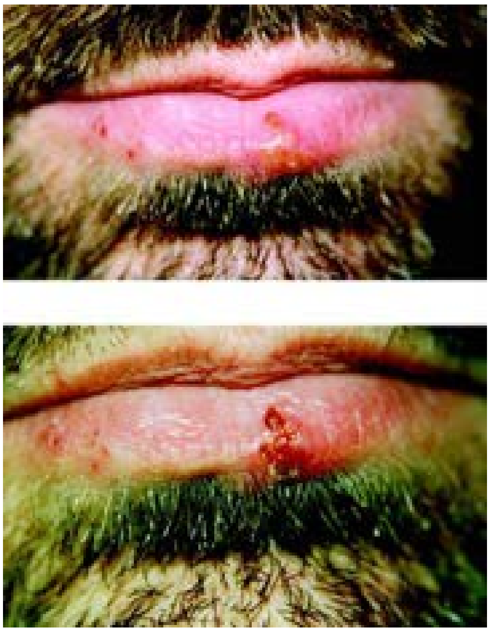
The lack of well-defined clinical studies in this area is underlined in the literature review by Gupta [2324].

Further literature: [332, 631, 1643, 1686, 1740, 2360]

4.1.26 Herpes simplex

Herpes simplex (HSV-1) is commonly encountered in the practice of dentistry. As students in the seventies, we learned that it disappears by itself after two weeks, but if treated, it heals within 14 days. There are now more effective treatment methods, and best by far is LPT. Conventional therapies limit the pain and may shorten the healing procedurem, but only LPT will affect the relapse rate.The mechanisms are still not fully understood.

Figure 4.12 Picture on top shows typical labial HSV-1, three days after outbreak. GaAlAs 6 J applied with an immediate



HSV-1 on day 1 and 2.
Note crust formation.

The results of treatment depend on the stage of the virus cycle in which the treatment begins. Patients often describe how the virus has a "favourite place", and experienced patients know where and when the blisters will appear, even before anything is visible. The use of a laser produces the best results in this prodromal stage, and may even prevent the attack. It also seems that a herpes sore is reluctant to return to a place where it has been treated before.
The later in the attack we treat, the poorer the results. However, even in the later stages of an attack, we can offer tangible (or perhaps even total) relief from the symptoms and an acceleration of the healing process. The dosage is determined by the patient. When obvious relief has been provided, we can stop treatment. In the prodromal stage, 1-2 J is often sufficient. If the attack is somewhat advanced before we can begin treatment, irradiation should be repeated one to three times - an appropriate dosage is 4-6 J per sore. Looking in the literature, wavelength does not seem to be important, nor the energy, nor the coherent light itself [2352]. So in spite of its obvious clinical efficacy, the mechanisms behind the effect are still unclear.

If the herpes attacks are treated every time they manifest themselves, it appears that they return at longer and longer intervals [908, 2473]. It could be the case that LPT has a short-term effect on symptoms and a long-term effect on the onset of the virus per se.

Herpes labialis in the vesicle phase should optimally be treated by first opening the vesicle and removing the fluid before applying LPT [2205].This can be performed with an Er:YAG laser in a pain free and sterile fashion [2206].

HSV2 (genital) has been treated in two studies, but with a rather poor outcome. The poor result in HSV2 patients is a bit surprising, considering the excellent effect of LPT on HSV-1 and to some degree on zoster.

Literature:

In vitro studies

Gilioli [102] studied the effects of GaAs on herpes simplex virus in vitro. It was found that the viral plaque was stimulated by laser light. The stimulating effect was greater for HSV-1 than for HSV-2. The anti-viral effect in vivo presumably depends on an immune-stimulating effect.

Tardivo [358] observed the behaviour of cells infected with HSV under a GaAs laser, 30 mW. Doses of 4 and 12 J were given. A lesser cytopathic effect was noted in the irradiated cells than in the control cells, more evident at 4 J. The two cell lines were incubated for seven days, frozen, and the released viruses inoculated in a new culture. An absence of cytopathic effect was noted in the cells infected with viruses derived from the cultures that received 12 J initially.

In an in vitro study by Hubacek [1036], HeNe laser had a cytopathogenous effect on HSV-1 from 0.45 J/cm^2. On increasing the dose to 6 J/cm^2, no antiviral effect was noted.

In a study by Perrin [1009] it was observed that, in the ear experimental model of HSV latency, repeated exposure to infrared laser radiation of cervical ganglia following HSV inoculation appears to specifically hinder the establishment of virus latency in mice.

In an in vitro experiment by Eduardo [1893], epithelial cells and HSV-1 virus in culture were studied. Cells were irradiated with 660 or 780 nm using different dosages in four groups: 1) irradiation of non-infected epithelial cells, 2) epithelial cells irradiated prior to infection with the virus, 3) virus irradiated prior to infecting the epithelial cells, and 4) irradiation of HSV-1 infected cells. The irradiated epithelial cell growth was enhanced, but the only effect seen in cells infected with the virus was that the cell viability was prolonged if irradiated prior to infection. Thus, prolongation of cell survival may be one of the mechanisms at work.

Clinical studies

Landthaler [239] used a krypton laser (with a wavelength of 647 nm) to treat recurrent herpes simplex in loco, zoster, and postherpetic neuralgia. Treatment consisted of 50 mW, at 90 seconds per cm^2, each area 3 cm^2. Patients with recurrent HSV had symptom-free periods between outbreaks of 30 ± 19 days. After daily treatment sessions for 10 days, the average period between outbreaks was 73 ± 50 days. Seven of nine patients with herpes labialis experienced significant improvement, while only one of three with herpes glutealis improved. Two of four patients with acute zoster were freed from discomfort. Five of eight with postherpetic neuralgia experienced alleviation of pain or total pain relief.

Vélez-González [360] treated 60 patients suffering from herpes simplex in the oral (HSV-1) or genital (HSV2) area. Three groups in each category received (I) 200 mg Acyclovir orally plus placebo laser, (II) placebo Acyclovir and HeNe laser light at 8 J/cm^2, or (III) Acyclovir and HeNe, in a *randomised, double-blind study. Relapses on the lips and face were significantly reduced in the group treated with HeNe laser plus Acyclovir, as compared with the groups treated with Acyclovir or HeNe only. The number of relapses per year before and after treatment was 5.2/2.8 for group I, 7.83/1.16 for group II, and 7.28/1.28 for group III. There was no significant difference between the latter groups. However, healing time was shorter in the group that received a combination of treatments. The effects on the HSV2 groups were low for all 3 treatment modalities.*

Hachenberger [60] reports the results of treating 93 patients with a HeNe laser. Pain disappeared quickly and healing occurred within three days. In no case did the herpes reappear at the same site, and relapses were less frequent.

Michels [416] summarises eight years of experience in treating herpes simplex with HeNe laser light; 582 cases of HSV-1, and 34 cases of HSV2. Healing was fast and without side-effects. By and large 10% of the cases suffered relapses in loco, but all were patients with immune deficiency or a strong allergic background.

An important aspect of LPT of HSV-1 has been described by Schindl [908], namely the possibility of treating patients with recurrent herpes attacks even during the symptom-free period. Fifty patients with recurrent perioral herpes simplex infections (at least once a month for more than six months) were treated with 690 nm, 80 mW laser, energy density 48 J/cm^2, in a double-blind study. Patients received daily irradiations for 2 weeks, 10 sessions in all. The treatment was given during a recurrence-free period and the irradiation was given at the site of the original herpes simplex infection. If both lips were involved, both upper and lower lips were treated. Patients were monitored for 52 weeks. The mean recurrence-free interval in the laser group was 37.5 weeks (range; 2-52 weeks), and in the placebo group 3 weeks (range 1-20 weeks). No side effects were noted.

Almeida-Lopes [1531] has shown that HSV-1 can be treated advantageously by irradiation of the involved lymph nodes. Microbes in wounds can be stimulated or suppressed by different wavelengths and doses [1496]. Therefore, irradiating the lymph nodes eliminates this potentially negative effect.

Guerra [1420] compared laser with traditional therapies in a group of 116 patients. Patients in the laser group received 670 nm, 1.2 J per blister in the prodromal stage and 2.4 J in the crust and secondarily infected stages, plus 1 J at the C2-C3 vertebras. All in all 116 patients in the HSV-1 group received LPT while the rest received traditional therapy, such as Acyclovir cream or pills and palliative therapies. One of the dentists was responsible for the diagnosis, treatment and evaluation, respectively, to allow for a semi-blinded procedure. Patients were controlled daily during the first week to monitor healing, and monthly for one year to check for any recurrences. A very obvious effect of the LPT was found for both initial healing as well as for the number of recurrences.

A case-control study by Imbronito [2027] evaluated the presence of herpes simplex virus type I (HSV-1), Epstein-Barr virus type I (EBV-1), human cytomegalovirus (HCMV), Aggregatibacter actinomycetemcomitans (previously Actinobacillus actinomycetemcomitans), Porphyromonas gingivalis, Prevotella intermedia, and Tannerella forsythia (previously T. forsythensis) in patients with generalised AgP (AgP group), CP (CP group), or gingivitis (G group) and in healthy individuals (C group). Subgingival plaque samples were collected with paper points from 30 patients in each group. The nested polymerase chain reaction (PCR) method was used to detect HSV-1, EBV-1, and HCMV. Bacteria was identified by 16S rRNA-based PCR. HSV-1, HCMV, and EBV-1 were detected in 86.7%, 46.7%, and 33.3% of the AgP group, respectively; in 40.0%, 50.0%, and 46.7% of the CP group, respectively; in 53.3%, 40.0%, and 20.0% of the G group, respectively; and in 20.0%, 56.7%, and 0.0% of the C group, respectively. A. actinomycetemcomitans was detected significantly more often in the AgP group compared to the other groups (P <0.005). P. gingivalis and T. forsythia were identified more frequently in AgP and CP groups, and AgP, CP, and G groups had higher frequencies of P. intermedia compared to the C group. In Brazilian patients, HSV-1 and EBV-1, rather than HCMV, were more frequently associated with CP and AgP. The impact of LPT in periodontal therapy can possibly and partly be an anti-viral effect.

Foyaca-Sibat [2033] studied the effect of LPT in 46 cases of HIV related post neuralgia in different age-groups (21 to 61 years) and with a varying duration of the illness ranging from 3 months to 3 1/2 years in the present investigation. The affected areas were irradiated from a distance of 5 cm using the probe of a GaAs laser, 12x70 W peak power, at a PRR of 1000 Hz, each area being exposed for a time period of five minutes and six seconds. In each case, the laser therapy was given for 15 consecutive days and the effect of the therapy was evaluated after the 5th, 10th, and 15th laser application during the treatment with the help of a Visual Analogue Scale (VAS). Patients started responding to the therapy after an average of 2.58 laser applications and VAS steadily decreased as the therapy progressed. After completion of therapy, 37 (80.4%) out of 46 cases showed excellent relief, and the remaining 9 (19%) cases showed partial relief, which could be due to multiple factors like prolonged duration of illness, involvement of ophthalmic division of trigeminal nerve and formation of scarring and keloids. No side effects were observed either during the treatment or in the follow-up period of 10 weeks.

The use of LPT to suppress infections caused by Herpes simplex viruses 1 and 2 was evaluated by Ferreira [2059], after one to five applications. A gradual reduction in replication of Herpes simplex viruses 1 and 2 was observed, with 68.4% and 57.3% inhibition, respectively, after five applications.

In a study by Muñoz Sanchez [2150], 232 patients with herpes simplex type 1 virus symptoms were consecutively selected for either LPT or conven-

tional therapy, including acyclovir cream or tablets. One of the dentists was responsible for the diagnosis, a second dentist for the treatment, and and a third for the evaluation, to allow for a semi-blinded procedure. Patients in the laser group received 670 nm laser irradiation, 40 mW, 1.6 J, 2.04 J/cm², 51 mW/cm² per blister in the prodromal stage and 4.8 J in the crust and secondarily infected stages, plus 1.2 J at the C2-C3 vertebrae. Patients were monitored daily during the first week to control healing, and monthly for 1 year to check on recurrence. In a consecutive study, 322 patients receiving LPT were followed during 5 years to observe the period of occurrences. An obvious effect of LPT was found for both initial healing and for the length of the recurrence periods.

The aim of a study by de Carvalho [2383] was to evaluate the effectiveness of LPT in prevention and reduction of severity of labial manifestations of herpes labialis virus. Seventy-one patients, divided into experimental (n=41) and control (n=30) groups were followed up for 16 months. Patients in the control group were treated topically with aciclovir and patients in the experimental group were subjected to laser phototherapy (one session per week, 10 weeks): 780 nm, 60 mW, 3.0 J/cm² or 4.5 J/cm² on healthy (no HSV-1 infection) and affected (with HSV-1 infection) tissues. Patients in the experimental group presented a significant decrease in dimension of herpes labialis lesions and inflammatory oedema. The reduction in pain level and monthly recurrences did not reach statistical significance. This study represents an in vivo indication that this treatment should be further considered as an effective alternative to therapeutic regimens for herpes labialis lesions.

A literature review by de Paula Eduardo [2126] summarises: Recurrent herpes labialis is a worldwide life-long oral health problem that remains unsolved. It affects approximately one third of the world population and causes frequent pain and discomfort episodes, as well as social restriction due to its compromise of aesthetic features. In addition, the available antiviral drugs have not been successful in completely eliminating the virus and its recurrence. Currently, different kinds of laser treatment and different protocols have been proposed for the management of recurrent herpes labialis. Therefore, the aim of the present article was to review the literature regarding the effects of laser irradiation on recurrent herpes labialis and to identify the indications and most successful clinical protocols. The literature was searched with the aim of identifying the effects on healing time, pain relief, duration of viral shedding, viral inactivation, and interval of recurrence. According to the literature, none of the laser treatment modalities is able to completely eliminate the virus and its recurrence. However, laser phototherapy appears to strongly decrease pain and the interval of recurrences without causing any side effects. Photodynamic therapy can be helpful in reducing viral titer in the vesicle phase, and high-power lasers may be useful to drain vesicles. The main advantages of the laser treatment appear to be the absence of side effects and drug interactions, which are especially helpful for older and immunocompromised patients. Although these results indi-

Figure 4.13 Herpes Simplex day one, two and seven.
Courtesy: Jeanette Deumer

cate a potential beneficial use for lasers in the management of recurrent herpes labialis, they are based on limited published clinical trials and case reports. The literature still lacks double-blind controlled clinical trials verifying these effects and such trials should be the focus of future research.

Deumer [2473] treated 101 HSV-1 patients with 810 nm, 1000 mW, 30 seconds per mm^2 of ulcer (30 J). The patients were treated twice within 24 hours and all had the same treatment, regardless of skin colouration and phase of the infection. The irradiation was performed with a 300 µm fibre from a distance of some 8 mm from the ulcer. The elimination of pain by the treatment was 97% (n=101). Under treatment, already 67% of patients were painless either directly or after one hour. After two days of treatment, in 95 out of 101 patients, the crust stage was reached. The initial starting situation of the herpes simplex virus -1 infection was irrelevant. This observational study was conducted in the years 2008 to 2010 and brought about a third *characteristic phenomenon associated with the laser treatment - the recurrence rates of treated HSV -1 patients were drastically reduced.*

Dougal [2352] has successfully used 1072 nm LED in a clinical study.

Further literature: [43, 61, 222, 628, 822, 1043, 1892, 1942, 1943, 2450]

4.1.27 Immune system modulation

The general aspect of immune modulation is one of the most important aspects of LPT. Systemic effects are always obtained since any irradiation involves the circulatory system.

Literature:

Takaduma [373] reports the effects of LPT on the immune system:"The human immune system acts as a defence mechanism against exogenous or indigenous potentially harmful bodies, such as bacteria and viruses. The major histocompatibility complex (MHC class I and class II antigens) form key elements of legitimate body components, and the organisation of MHC molecules allows T-lymphocytes to distinguish between legitimate and foreign bodies. On detection of a foreign component, T-cells activate the necessary pathways for destruction of the foreign body. Occasionally however the system breaks down and the result is a disease of an autoimmune nature. Both visible light and infrared LPT have been shown to act on immune system cells in a number of ways, activating the irradiated cells to a higher level of activity. Infrared LPT has been shown to increase both the phagocytic and chemotactic activity of human leukocytes in vitro, for example. This is an example of photobiological activation. Photobiological cell-specific destruction is also possible using doses of low incident laser energy on cells which have been photosensitised for the specific wavelength of the laser, such as in photodynamic therapy (PDT) for superficial cancers. LPT has also been shown to act directly and selectively on the autoimmune system, restoring immunocompetence to cells. Although much more research needs to be done, there are enough experimental and clinical data to show that the laser, and LPT in particular, has a possibly exciting role both in immunobiological therapy for diseases of the immune system, and to activate and boost the normal reaction of the immune system components."

Kólarová [655] reports that doses of 5 to 10 J/cm^2 induced a significant increase of the phagocytic activity of leukocytes in vitro.

Duan [1163] has demonstrated a respiratory burst in bovine neutrophils after HeNe irradiation.

Schindl [581] describes an experiment on the immune modulating effect of a HeNe laser as follows: "Escherichia coli endotoxin preimmunised rabbits were used to determine the influence of transcutaneously applied low-power laser light on differential blood count and rectal temperature. After three initial immunisations, animals were either boostered with 5 ng/kg of endotoxin or injected with pyrogen-free saline and subsequently under-

went irradiation using two different wavelengths of red laser light and sham irradiation respectively. The differential blood count of laser-treated animals was characterised by significantly higher lymphocyte values and lower neutrophil values at twenty hours (boostered rabbits) and twenty-three hours (non-boostered rabbits) after irradiation. Differential blood cell counts returned to baseline levels within 23 hours in the boostered animals, whereas in the non-boostered rabbits lymphocytes showed a tendency to further increase. Recording of rectal temperature revealed a further rise after laser application, changes being of greater magnitude and longer duration in the non-boostered animals. These results seem to indicate that a single low-power laser irradiation can modulate immune responses depending on the immunological status of the organism."

In a study by Inoue [405], a 830 nm laser has been shown to suppress the tuberculin reaction in a well-known immunological test for the evaluation of cellular immunity in vivo.

Funk [565, 731] has shown that HeNe laser affects cytokine production in human peripheral blood mononuclear cells in vitro.

The leukocyte stimulating effects of HeNe have been described by Klebanov [1006, 1007] and Mester [23].

Katsuyama [662] has found a suppressive effect of diode laser irradiation on picryl contact sensitivity in a rat model. The thickness of the right ear was used as an indicator of the immune response to various doses of 830 nm laser irradiation. LPT suppressed the cutaneous inflammation due to picryl contact sensitivity in an exposure-time dependent manner, and this suppressive effect was restricted to within the irradiation site.

Yu [590] used an argon pumped dye laser at a wavelength of 630 nm to study the effect of LPT on the immune system. Rats with experimentally induced sepsis (cecal ligation) received LPT, 5 J/cm^2. On day 60, the survival rate was 79% in the laser group and 42% in the control group. Ex vivo lymphocyte proliferation was 180 in the laser group and 130 in the control group. Enhanced lymphocyte ATP synthesis was observed in the laser group.

To study the possible side effects of laser immunotherapy, Novoselova [1768] monitored the productions of cytokines, nitric oxide (NO), and heat shock protein 70 (Hsp70) in mice subjected to a periodic laser exposure for one month. Helium-neon laser radiation with the power of 0.2 mW/cm^2 and a wavelength of 632.8 nm was applied on two different mouse skin surfaces, i.e. a thymus projection area or a hind limb. Healthy NMRI male mice were irradiated repeatedly with laser light for one minute with 48-h intervals for 30 days. The animals were divided into three groups of 25 mice. The first and the second group were exposed to laser light on the thymus and hind limb area, respectively. The third sham-irradiated group served as a control. Early and prolonged effects of laser radiation on the levels of NO (by Griess assay), Hsp70 (by Western blot assay), tumour necrosis factors (TNF-alpha and TNF-ß) (by cytotoxic assay using L929 cells as targets), and interleukin-2 (IL-2) (by ELISA assay) were determined. The dynamics of immune *responses to low-power laser light intensity was shown to be dependent on two factors, i.e. the cumulative dose and the localisation of the irradiated surface. Moreover, various populations of cells demonstrated different sensitivity to laser radiation, with T cells being more responsive among examined cell populations. Low-intensity laser light induced an immune cell activity when the exposure duration did not exceed 10 days, while a more prolonged period of treatment generated more severe changes in the immune system, up to immunosuppression. The treatment of the thymus zone resulted in more pronounced changes in the cytokine production as well as in NO and Hsp70 synthesis. Low-power laser irradiation showed more effective immunomodulatory effects when applied on the thymus projection area. The rise in IL-2 and Hsp70 production related to a short-term effect of laser application may be reversed after repeating the laser treatment.*

Mikhailov [982] reports on the use of 890 nm laser treatment of the autoimmune thyroiditis. Forty-two patients were given 10 applications at 2.4 J/cm². The irradiated areas were the thymus projection zones (area of the sternum at a level of the second edge), vascular junction (left axillary area) and thyroid gland. A control group of a similar size was given L-thyroxin, 100 mg/day. The clinical effect in all laser patients was a decreased feeling of squeezing in the area of the thyroid gland, and a decrease of the facial oedema. The gland became softer palpatively and its size was reduced according to the ultrasound examination. The number of patients catching a cold during the winter decreased. The immunoregulatory index (Th/Ts) normalised from 7.5 to 4.2%. The laser effect was still noticeable in 78% of the patients 4 months after treatment. This index was only slightly changed in the control group.

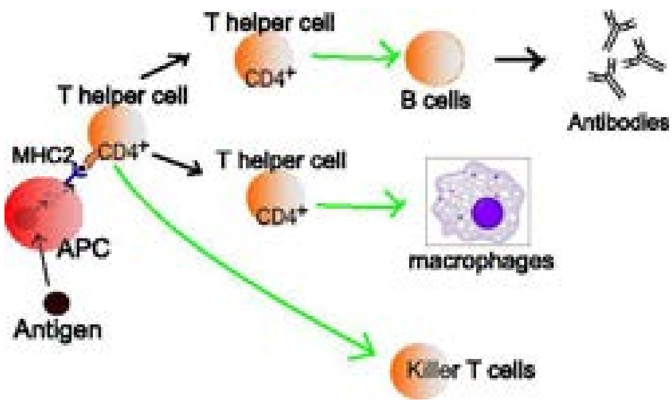


Figure 4.14 Lymphocyte activation (Wikipedia)

Currently, no effective therapy is available for CAT. Thus, the objective of a study by Höfling [1251] was to evaluate the efficacy of LPT in patients with CAT-induced hypothyroidism by testing thyroid function, thy-

roid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and ultrasonographic echogenicity. A randomised, placebo-controlled trial with a 9-month follow-up was conducted from 2006 to 2009. Forty-three patients with a history of levothyroxine therapy for CAT-induced hypothyroidism were randomly assigned to receive either 10 sessions of LPT, 830 nm, 50 mW, fluence 707 J/cm^2. Laser group, n=23) or 10 sessions of a placebo treatment (Placebo group, n=20). The levothyroxine was suspended 30 days after the LPT or placebo procedures. Thyroid function was estimated by the levothyroxine dose required to achieve normal concentrations of T(3), T(4), free-T(4) (fT(4)), and thyrotropin after 9 months of postlevothyroxine withdrawal. Autoimmunity was assessed by measuring the TPOAb and TgAb levels. A quantitative computerised echogenicity analysis was performed pre- and 30 days postintervention. The results showed a significant difference in the mean levothyroxine dose required to treat the hypothyroidism between the L group (38.59±20.22 g/day) and the P group (106.88±22.90 g/day). Lower TPOAb and greater echogenicity were also noted in the L group. No TgAb difference was observed. These findings suggest that LPT was effective at improving thyroid function, promoting reduced TPOAb-mediated autoimmunity and increasing thyroid echogenicity in patients with CAT.

In a study by Oliveira [2295], the experimental model of the delayed type hypersensitivity (DTH) reaction to ovalbumin (OVA) was used to evaluate the immunomodulating effects of LPT, which is used as an adjuvant therapy in medicine, dentistry, and physical therapy because of its potential anti-inflammatory and analgesic effects observed in several studies. The effects of LPT (780 nm, 0.06 W/cm^2 of radiation, 3.8 J/cm^2) in reaction to ovalbumin in Balb/C mice were examined after the induction phase of the hypersensitivity reaction. The animals treated with azathioprine (AZA), the animals that received a vehicle instead of ovalbumin, and those not immunised served as controls (n=6 for each group). Footpad thickness measurements and hematoxylin-eosin histopathological exams were performed. Proliferation tests were also performed (spontaneous, in the presence of concanavalin A and ovalbumin) to determine the production in mononuclear cells cultures of tumour necrosis factor-alpha (TNF-alpha), INF-gamma, and IL-10. In the group of animals irradiated with lasers and in the group treated with AZA, footpad thickness measurements were significantly reduced in comparison to the control group. This reduction was accompanied by a very significant reduction in the density of the inflammatory infiltrate and by a significant reduction in the levels of TNF-alpha, INF-gamma, and IL-10. LPT radiation was shown to have an immunomodulating effect on DTH to OVA in Balb/C mice.

Further literature: [645]

4.1.28 Inflammation

The effect of LPT on inflammation is addressed in many chapters of this book. The anti-inflammatory effect of LPT has been widely studied. LPT seems to have a similar effect to steriods and NSAIDs, but without the severe side effects of these very common pharmaceuticals [2245].

Recently, the understanding of the mechanism at work has been improved by using genetic technology. This technology has also to a certain extent explained why there are so few side effects of LPT. In an effort to clarify the molecular based mechanism of the anti-inflammatory effects of laser irradiation, Abiko [1860] used a rheumatoid arthritis (RA) rat model with human rheumatoid synoviocytes (MH-7) challenged with IL-1, treated with laser or dexamethasone (DEX), monitored by gene expressions and analysed by the signal pathway database. RA rats were generated by the immunisation of type-II collagen, after which foot paws and knee joints became significantly swollen. The animals were laser treated and the swelling rates measured. MH-7 was challenged with IL-1ß and gene expression levels monitored, using the Affymetrix Gene Chip system, and the signal pathway database analysed using the Ingenuity Pathway Analysis (IPA) tool. LPT significantly reduced swellings in the rats' foot paws and knee joints and made it possible for them to walk on their hind legs. LPT altered many gene expressions of cytokines, chemokines, growth factors and signal transduction factors in IL-ß induced MH-7. IPA revealed that LPT as well as DEX kept the MH7A at a normal state to suppress mRNA levels of IL-8, IL-1ß, CXC1, NFkB1 and FGF13, which were enhanced by IL-1ß treatment. However, certain gene expression of inflammatory factors were reduced by LPT, but were enhanced by DEX. LPT reduced inflammatory factors through altering signal pathways by gene expression levels. Interestingly, LPT altered useful targeted gene expressions, whereas DEX randomly altered many gene expressions, including the unwanted genes for anti-inflammation. Dexomethasone is a steroid known for having a long range of serious side effects. Thus, genome based gene expression monitored by the Gene Chip system together with a signal pathway based database provide unprecedented access to elucidate the mechanism of the biostimulatory effects of LPT.

Yamada [1054] has compared corticosteroids, LPT and a combination of the two in a study comprising seven patients in each group. The effect of LPT was comparable to that of corticosteroids, but the combined therapy showed the best outcome. The laser was a 150 mW GaAlAs laser and the LPT was performed over the area of paralysis (36 J per session), the stylomastoid foramen (10.8 J) and the stellate ganglion (63.7 J). The number of sessions in the laser group ranged from 21 to 66 for 5-12 weeks. In the combined therapy group, success was achieved within 14-31 sessions, after 3-10 weeks.

Steroids are frequently used to treat inflammation. Some studies report a reduced effect of LPT in the presence of steroids, while others have found positive results of LPT even in the presence of steroids. However, steroids are known to delay wound healing through a reduction of leukocyte migration and a suppression of interleukins, while LPT is known to stimulate wound healing. In a study by Pessoa [1455], 48 rats were used, and after the execution of a wound on the dorsal region of each animal, they were divided into four groups (n=12), receiving the following treatments: G1 (control), wounds and animals received no treatment; G2, wounds were treated with laser; G3, animals received an intraperitoneal injection of sodium phosphate of dexametasone, dosage 2 mg/kg of body weight; G4, animals received steroids and wounds were treated with laser. The laser emission device used was a 904 nm unit, in a contact mode, with 2.75 mW gated with 2.900 Hz during 120 sec. After a period of 3, 7 and 14 days, the animals were sacrificed. The results showed that the wounds treated with steroid had a delay in healing, while laser accelerated the wound healing process. Additionally, wounds treated with laser in the animals also treated with steroids, presented a differentiated healing process with a larger collagen deposition as well as a decrease in both the inflammatory infiltrated and in the delay on the wound healing process. Laser accelerated healing, delayed by the steroids, acting as a biostimulative coadjutant agent, balancing the undesirable effects of the steroids on the tissue's healing process. The effect of LPT is almost as potent as dexametasone [1840], but, again, without side effects.

The aim of the study by de Almeida [2245] was to analyse the effects of sodium diclofenac (topical application), cryotherapy, and LPT on pro-inflammatory cytokine levels after a controlled model of muscle injury. For such, we performed a single trauma in tibialis anterior muscle of rats. After 1 h, animals were treated with sodium diclofenac (11.6 mg/g of solution), cryotherapy (20 min), or LPT (904 nm; superpulsed; 700 Hz; 60 mW mean output power; 1.67 W/cm^2; 1, 3, 6 or 9 J; 17, 50, 100 or 150 s). Assessment of interleukin-1 and interleukin-6 (IL-1 and IL-6) and tumour necrosis factor-alpha levels was performed at 6 h after trauma employing enzyme-linked immunosorbent assay method. LPT with 1 J dose significantly decreased IL-1, IL-6, and TNF-alpha levels compared to non-treated injured group as well as diclofenac and cryotherapy groups. On the other hand, treatment with diclofenac and cryotherapy does not decrease pro-inflammatory cytokine levels compared to the non-treated injured group. Therefore, the authors conclude that 904 nm LPT with 1 J dose has better effects than topical application of diclofenac or cryotherapy in acute inflammatory phase after muscle trauma.

N.B. The best anti-inflammatory effect was obtained with the lowest energy selected. This confirms the findings by Castano [1840].

Reis [1904] investigated the role of extracellular matrix elements and cells during the wound healing phases following the use of LPT and anti-inflammatory drugs. Thirty-two rats were submitted to a wound inflicted by a 6-mm-diameter punch. The animals were divided into four groups: sham treated, those treated with the GaAlAs laser (4 J/cm^2, 9 mW, 670 nm), those treated with dexamethasone (2 mg/kg), and those treated with both LPT and dexamethasone. After three and five days, the cutaneous wounds were assessed by histopathology using polarised light and ultrastructural assessments by transmission electron microscopy. Changes seen in polymorphonuclear inflammatory cells, oedema, mononuclear cells, and collagen fibre deposition were semi-quantitatively evaluated. The laser-treated group demonstrated an increased collagen content and a better arrangement of the extracellular matrix. Fibroblasts in these tissues increased in number and were more synthetically active. In the dexamethasone group, the collagen was shown to be non-homogenous and disorganised, with a scarcity of fibroblasts. In the group treated with both types of therapy, fibroblasts were more common and they exhibited vigorous rough endoplasmic reticulum, but they had less collagen production compared to those seen in the laser group. Thus, LPT alone accelerated post-surgical tissue repair and reduced oedema and the polymorphonuclear infiltrate, even in the presence of dexamethasone.

It might therefore be prudent to avoid a combination of steroids and laser, if this is clinically feasible. There seems to be no negative effects from the combination of the two but a reduction of the total effect of laser. Since steroids in many clinical situations have undesired side effects, LPT could be a good alternative. This is confirmed in a study by Lopes-Martins [1456]. In this study, the classical experimental mice-model of carrageenan-induced pleurisy was used to investigate if the anti-inflammatory effect of LPT could be blocked by the steroid agent mifepristone. For the intervention group, mifepristone was injected into the pleural cavity an hour prior to the carrageenan injection. Pleurisy was then induced by an intrathoracic injection of carrageenan (0.5mg/cavity), or LPS from E. coli (250 mg/ cavity) in mice. Laser irradiation (650 nm) was then carried out three times with hourly intervals on the skin at the injection site for both groups. Laser was administered with a previously established optimal accumulated dose of 7.5 J/cm^2. While laser after four hours effectively reduced inflammation almost to pre-injection levels of neutrophil cell counts, the anti-inflammatory effect was blocked after pre-injection of mifepristone.

Meloxicam is an NSAID which significantly decreases symptoms of pain, function, and stiffness in patients, with a low incidence of gastrointestinal side effects. Meloxicam has been shown, especially at its low therapeutic dose, to selectively inhibit COX-2 over COX-1. LPT has been shown to have an effect equivalent to Meloxicam [1868].

Some studies showing a reduction of PGE_2 are:
[243,357,582,718,1008,1276,1461,1560,1800].

Reduction of IL1-ß: [188, 370, 1314, 1815, 1891].

Research indicates that lower intensity and longer exposure are favourable when treating inflammation [1821,1840]. Higher intensities and shorter time spans will be more effective against pain itself, but in many instances the long term result will be better if the inflammation (causing the pain) is the main target of the therapy.

Below is a summary of some of the most interesting studies in this field.

Literature:

In vitro studies

The study by Protasiewicz [2260] was conducted in order to examine the influence of laser illumination on the endothelial inflammatory response. Human umbilical vein endothelial cells (HUVECs) isolated from umbilical cord, cultured in standard conditions, were harvested and passaged in 24-well plates. Laser influence on HUVEC inflammatory response was measured by stimulating them with Interleukin-1beta (IL-1beta) followed by laser light illumination. An 808 nm laser and light energy doses of 1.5 and 4.5 J/cm² were used (50 mW for 90 and 270 s respectively). The response was measured by assessing Cluster of differentiation 54 (CD54), Cluster of differentiation 62E (CD62E), Monocyte chemotactic protein-1 (MCP-1) expression and von Willebrand factor (vWF) release, at 6 and 24 h after stimulation. The MCP-1 and vWF activity in cell supernatants was measured with an enzyme-linked immunosorbent assay (ELISA) kit. Cytofluorometry was used to assess CD54 and CD62E expression. MCP-1 concentration in supernatants from HUVECs was significantly lower 6 h after 4.5 J/cm² stimulation compared to IL-1beta stimulated cells. No changes in MCP-1 levels after IL-1beta stimulation plus 1.5 J/cm² illumination, compared to IL-1beta stimulated HUVECs were noted. IL-1beta stimulation significantly enhanced the concentration of vWF and the expression of CD54 and CD62E. Both energies of laser light illumination inhibited the ILbeta-induced increase of CD54 and CD62E concentration. vWF activity after illumination was comparable to that of unstimulated cells. There were no significant differences in the viable cell count between the groups tested. Thus, LPT diminishes the pro-inflammatory and pro-coagulant activity of IL-1beta-stimulated HUVECs.

The purpose of a study by Wu [2293] was to investigate the anti-inflammatory effect of LPT on human adipose-derived stem cells (hADSCs) in an inflammatory environment. The experiment showed that the hADSCs expressed Toll-like Receptors (TLR) 1, TLR2, TLR3, TLR4, and TLR6 and that lipopolysaccharide (LPS) significantly induced the production of pro-inflammatory cytokines (Cyclooxygenase-2 (Cox-2), Interleukin-1beta (IL-1beta), Interleukin-6 (IL-6), and Interleukin-8 (IL-8)). LPLI markedly inhibited LPS-induced, pro-inflammatory cytokine expression at an optimal dose of 8 J/cm². The inhibitory effect triggered by LPLI might occur through an increase in the intracellular level of cyclic AMP (cAMP), which acts to down-regulate nuclear factor kappa B (NF-kappaB) transcriptional activity. These data collectively provide insight for further investigations of the potential application of anti-inflammatory treatment followed by stem cell therapy.

Animal studies

Aimbire [1815] studied the effect of LPT on lung permeability and the IL-1ß level in LPS-induced pulmonary inflammation. Rats were divided into 12 groups (n=7 for each group). Lung permeability was measured by quantifying extravasated albumin concentration in lung homogenate, inflammatory cells influx was determined by myeloperoxidase activity, IL-1ß in BAL was determined by ELISA and IL-1ß mRNA expression in trachea was evaluated by RT-PCR. The rats were irradiated on the skin over the upper bronchus at the site of tracheotomy after LPS. LPT attenuated lung permeability. In addition, there was a reduced neutrophil influx, myeloperoxidase activity and both IL-1ß in BAL and IL-1ß mRNA expressions in trachea obtained from animals subjected to LPS-induced inflammation showed a reduction. In conclusion, LPT reduced the lung permeability by a mechanism in which the IL-1ß seems to have an important role.

Aimbire [1800] further reports on the effect of 660 nm laser on mRNA levels of neutrophils anti-apoptotic factors in lipopolysaccharide (LPS)-induced lung inflammation. Mice were divided into eight groups (n=7 for each group) and irradiated with an energy dosage of 7.5 J/cm². The Bcl-xL and A1 mRNA levels in neutrophils were evaluated by Real Time-PCR (RT-PCR). The animals were irradiated after exposure time of LPS. LPT and an inhibitor of NF-kappaB nuclear translocation (BMS 205820) attenuated the mRNA levels of Bcl-xL and A1 mRNA in lung neutrophils obtained from mice subjected to LPS-induced inflammation. LPT reduced the levels of anti-apoptotic factors in LPS inflamed mice lung neutrophils by an action mechanism in which the NF-kappaB seems to be involved. The purpose of a study by Aimbire [1560] was to investigate the effect of LPT on rat trachea hyperreactivity (RTHR), bronchoalveolar lavage (BAL) and lung neutrophils influx after Gram-negative bacterial lipopolysacharide (LPS) intravenous injections. The RTHR, BAL and lung neutrophils influx were measured over different intervals of time (90 min, 6 h, 24 h and 48 h). The energy density (ED) that produced an anti-inflammatory effect was 2.5 J/cm², reducing the maximal contractile response and the sensibility of trachea rings to methacholine after LPS. The same ED produced an anti-inflammatory effect on BAL and lung neutrophils influx. The Celecoxib COX-2 inhibitor reduced RTHR and *the number of cells in BAL and lung neutrophils influx of rats treated with LPS. Celecoxib and laser reduced the PGE_2 and TXA2 levels in the BAL of LPS-treated rats. These results demonstrate that 685 nm LPT produced anti-inflammatory effects on RTHR, BAL and lung neutrophils influx in association with inhibition of COX-2-derived metabolites.*

The purpose of another study by Albertini [1580] was to investigate the effect of LPT on the acute inflammatory process. Male rats were used. Paw oedema was induced by a sub-plantar injection of carrageenan, the paw volume was measured before and one, two, three and four hours after the injection, using a hydroplethysmometer. To investigate the action mechanism of the GaAlAs laser on inflammatory oedema, parallel studies were performed using adrenalectomised rats or rats treated with sodium diclofenac. Different laser irradiation protocols were employed for specific energy densities (EDs), exposure times and repetition rates. The rats were irradiated with laser for 80 s each hour. The EDs that produced an anti-inflammatory effect were 1 and 2.5 J/cm², reducing the oedema by 27% and 45.4%, respectively. The ED of 2.5 J/cm² produced anti-inflammatory effects similar to those produced by the cyclooxigenase inhibitor sodium diclofenac at a dose of 1 mg/kg. In adrenalectomised animals, the laser irradiation failed to inhibit the oedema. These results suggest that LPT possibly exerts its anti-inflammatory effects by stimulating the release of adrenal corticosteroid hormones.

The aim of the study by Ferreira [1733] was to evaluate the analgesic effect of the LPT with a HeNe laser on acute inflammatory pain, verifying the contribution of the peripheral opioid receptors and the action of LPT on the hyperalgesia produced by the release of hyperalgesic mediators of inflammation. Male rats were used. Three complementary experiments were done. (1) The inflammatory reaction was induced by injecting carrageenin into one of the hind paws. Pain threshold and volume increase of the oedema were measured by a pressure gauge and plethysmography, respectively. (2) The involvement of peripheral opioid receptors on the analgesic effect of the laser was evaluated by simultaneous injections of carrageenin and naloxone into one hind paw. (3). Hyperalgesia was induced by injecting PGE_2 for the study of the effect of the laser on the sensitisation increase of nociceptors. A HeNe laser of 2.5 J/cm² was used for irradiation. The researchers found that HeNe stimulation increased the pain threshold by a factor of 68% to 95% depending on the injected drug. They also observed a 54% reduction in the volume increase of the oedema after being irradiated. The analgesic effect seems to involve hyperalgesic mediators instead of peripheral opioid receptors.

Interleukin 1ß (IL-1ß), tumour necrotic factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma) play important roles in inflammation, while platelet-derived growth factor (PDGF), transforming growth factor-ß (TGF-ß) and blood-derived fibroblast growth factor (bFGF) are the most important growth factors of periodontal tissues. The aim of a study by Safavi [1891] *was to investigate the effect of HeNe laser on the gene expression of these mediators in rats' gingiva and mucosal tissues. Twenty male Wistar rats were randomly assigned to four groups (A(24), A(48), B(24), B(48)) in which A(24) and A(48) were cases and B(24) and B(48) were controls. An incision was made on gingiva and mucosa of the labial surface of the rats' mandibular incisors. Group A(24) was irradiated twice with 24-hour intervals, while the inflamed tissues of group A(48) were irradiated three times with continuous HeNe laser at a dose of 7.5 J/cm² for 300 s. An energy of 5.1 J was given to the 68 mm² irradiation zone. Rats were killed 30 min after the last irradiation of case and control groups, then an excisional biopsy was performed. Gene expression of the cytokines was measured using reverse transcriptase-polymerase chain reaction (RT-PCR) technique. The gene expression of IL-1ß and IFN-gamma was significantly inhibited in the test groups while the gene expression of PDGF and TGF-ß was significantly increased. The case and control groups did not differ significantly in the gene expression of TNF-alpha and bFGF, These findings suggest that HeNe laser irradiation decreases the amount of inflammation and accelerates the wound healing process by changing the expression of genes responsible for the production of inflammatory cytokines.*

In the work by Bortone [1826], the author evaluated if LPT alters the kinin receptor's mRNA expression in carrageenan-induced rat paw oedema. Experimental groups were designed as followed: A1 (Control-saline), A2 (Carrageenan-only), A3 (Carrageenan+laser 660 nm) and A4 (Carrageenan+laser 684 nm). Oedema was measured by a plethysmometer. Subplantar tissue was collected for the quantification of the kinin receptor's mRNA by Real time-PCR. LPT of both 660 and 684 nm wavelengths administrated 1 h after the carrageenan injection was able to promote a reduction of the oedema produced by carrageenan. In the A2 group, B1 receptor expression presented a significant increase when compared to the control group. Kinin B1 receptor mRNA expression significantly decreased after LPT of both 660 or 684 nm. Kinin B2 receptor mRNA expression also diminished after both laser irradiations. The results suggest that the expressions of both kinin receptors are modulated by LPT, possibly contributing to its anti-inflammatory effect.

The aim of the study by Lopes-Martins [1619] was to investigate the effect of LPT, 650 nm, on acute inflammatory pleurisy. A classical experimental model of pleurisy was used in a sample of 40 Balb male mice, randomly divided into five groups. Inflammation was induced by carrageenan (0.5 mg/cavity) administered by intrathoracic injections. Four groups received the inflammatory agent, and one received injections of sterile saline solution. At the first, second and third hour after injections, irradiation was performed using the same power (2.5 mW), but with different irradiation times. The energy densities at each of the three treatment sessions were 0 J/cm² (placebo), 3 J/cm², 7.5J/cm², and 15 J/cm², respectively. Total and differential cell analysis at the fourth hour after induction of pleurisy showed a *significant reduction of inflammatory cell migration for all groups treated with active laser. However, four hours after injection, the most significant reduction of leukocyte cell migration was seen in the 7.5 J/cm² group. The greatest reduction of inflammatory cells was registered for neutrophils.*

A study by Viegas [1868] evaluated the action of LPT on the modulation of inflammatory reactions during wound healing in comparison with Meloxicam. standardised circular wounds were made on the backs of 64 Wistar rats. The animals were divided into four groups according to the selected postoperative therapies: group A, control; group B, administration of Meloxicam; and groups C and D irradiation with red (685 nm) and infrared (830 nm) laser energy, respectively. The animals were killed at 12, 36, and 72 h after the procedure and on day seven. Microscopic analysis revealed a significant vascular activation of irradiated sites during the first 36 h. Only group B showed decreases in the intensity of polymorphonuclear infiltrates and oedema. Group D showed a higher degree of organisation and maturation of collagen fibres than the other groups at 72 h. The animals in group C showed the best healing pattern on day seven. The anti-inflammatory action of Meloxicam was confirmed by the results obtained in this research. The quantification of interleukin-1ß mRNA by real-time polymerase chain reaction (PCR) did not show any reduction in the inflammatory process in the irradiated groups when compared to the other groups.

A study by Correa [1875] was designed to study the effect of a GaAs laser, 4 mW, on inflammatory cell migration in lipopolysaccharide (LPS)-induced peritonitis in mice. Sixty male mice were randomly divided into five groups, and one group was given an intraperitoneal sterile saline injection. In the remaining four groups, peritonitis was induced by an intraperitoneal LPS injection. Animals in three of the LPS groups were irradiated at a single point over the peritoneum with doses of 3 J/cm², 7.5 J/cm², and 15 J/cm², respectively. The fourth group injected with LPS was an LPS-control group. At 6 hours after injection the groups irradiated with doses of 3 J/cm² and 7.5 J/cm² had a reduced number of neutrophil cells in the peritoneal cavity compared with the LPS-control group, and there were significant differences in the number of neutrophils in the peritoneal cavity between the LPS-control group and the groups irradiated with doses of 3 J/cm² (42%) and 7.5 J/cm² (70%). In the group irradiated with 15 J/cm², neutrophil cell counts were lower than, but not significantly different from, LPS controls (38%). At 24 hours after injection, both neutrophil and total leukocyte cell counts were lower in all the irradiated groups than in the LPS controls. The 3J/cm² exposure group showed the best results at 24 hours, with reductions of 77% in neutrophil and 49% in leukocyte counts.

A sample of 48 female Wistar rats were divided into control and experiential groups by Boschi [1940]. An inflammation was induced by carrageenan (0.2 ml) being injected into the pleural cavity. At 1, 2, and 3 hours after induction a 20 mW, 660 nm laser was used in the four laser groups, with different doses and treatment patterns. One group received a single dose *of 2.1 J while the other three groups received a total energy of 0.9, 2.1, and 4.2 J. Four hours later the exudate volume, total and differential leukocytes, protein concentration, NO, IL-6, IL-10, TNF-alpha, and MCP-1 were measured from the aspirated liquid. All the treatment patterns and quantity of energy studied showed a significant reduction of the exudate volume. Using an energy output of 0.9 J only NO, IL-6, MCP-1 and IL-10 were significantly reduced. On the other hand, higher energies (2.1 and 4.2 J) significantly reduced all variables independent of the treatment pattern. The neutrophil migration has a direct correlation to the TNF-alpha and NO concentration. Thus, 660 nm induced an anti-inflammatory effect characterised by inhibition of either total or differential leukocyte influx, exudation, total protein, NO, IL-6, MCP-1, IL-10, and TNF-alpha, in a dose-dependent manner. Under these conditions, laser treatment with 2.1 J was more effective than with 0.9 and 4.2 J.*

Castano [1840] tested LPT on rats that had zymosan injected into their knee joints to induce inflammatory arthritis. The author compared illumination regimens consisting of a high and a low fluence (3 and 30 J/cm²), delivered at a high and a low irradiance (5 and 50 mW/cm²) using 810 nm laser light daily for five days, with a positive control of conventional corticosteroid (dexamethasone) therapy. Illumination with 810 nm laser was highly effective at reducing swelling (almost as good as dexamethasone), and a longer illumination time (10 or 100 minutes compared to 1 minute) was more important in determining effectiveness than either the total fluence delivered or the irradiance. LPT induced reduction of joint swelling correlated to a reduction in the inflammatory marker serum prostaglandin E_2*(PGE*$_2$*).*

The aim of a work by Meneguzzo [2034] was to investigate the effects of infrared 810nm on the acute inflammatory process by the irradiation of lymph nodes, using the classical model of carrageenan-induced rat paw oedema. Thirty mice were randomly divided into five groups. The inflammatory induction was performed in all groups by a sub-plantar injection of carrageenan (1mg/paw). The paw volume was measured before and 1, 2, 3, 4 and 6 hours after the injection using a plethysmometer. Myeloperoxidase (MPO) activity was analysed as a specific marker of neutrophil accumulation at the inflammatory site. The control group did not receive any treatment (GC); GD group received sodium diclofenac (1mg/kg) 30 minutes before the carrageenan injection; GP group received laser irradiation directly on the paw (1 Joule, 100mW, 10 sec) 1 and 2 hours after the carrageenan injection; GLY group received laser irradiation (1 Joule, 100mW, 10 sec) on the inguinal lymph nodes; GP+LY group received laser irradiation on both paw and lymph nodes 1 and 2 hours after the carrageenan injection. MPO activity was similar in the sodium diclofenac as well as in the GP and GLY groups, but significantly lower than the GC and GP + LY groups. Paw oedema was significantly inhibited in GP and GD groups when compared to the other groups. Interestingly, the GP+LY groups presented *the biggest oedema, even bigger thanin the control group. LPT showed an anti-inflammatory effect when the irradiation was performed on the site of lesion or at the correlated lymph nodes, but showed a pro-inflammatory effect when both paw and lymph nodes were irradiated during the acute inflammatory process.*

Fukuda [2214] evaluated the modulation of proinflammatory (interleukin-6, IL-6; tumour necrosis factor-alpha, TNF-gamma; and interferon-gamma, IFN-gamma) and anti-inflammatory cytokines (transforming growth factor-1ß, TGF-1ß) in the inflammation processes in vivo with low-level laser action. 50 isogenic mice were randomly distributed into three groups: control (no surgical procedure, n=10), sham (surgical procedure with three standard cutaneous incisions, followed by an abdominal muscle incision and suture, n=20), and laser (same procedure followed by laser exposure, n=20). The sham group was divided into three subgroups: sham I (euthanasia and evaluation, 36 h after surgical procedure), sham II (euthanasia and evaluation, 60 h after surgical procedure), and sham III (euthanasia and evaluation, 84 h after surgical procedure). The laser group was also divided in three subgroups: laser I (a single laser session, 12 h after surgery), laser II (two laser sessions, 12 and 36 h after surgery), and laser III (three laser sessions, 12, 36, and 60 h after surgery). All animals in the laser groups received three points per session of continuous 780 nm, 20 mW, 10 J/cm^2, 20 s per point, 0.4 J). After euthanasia, spleen mononuclear cells were isolated and cultured for 48 h. Concentrations of IL-6, TNF-alpha, IFN-gamma, and TGF-1ß were obtained by enzyme-linked immunosorbent assay method. There was a significant difference between the IL-6 and TNF-alpha concentrations in the 60-and 84-h evaluations when the laser and sham groups were compared to the control group except for laser II in the TNF-alpha analysis. The IFN-gamma concentration analysis showed a significant difference only in sham II when compared to the control group. Thus, there was a modulatory effect of TNF-alpha and IFN-gamma in the laser group, particularly in the 60-h postoperative evaluation. There was no significant difference between the laser, sham, and control groups for TGF1ß analysis. The laser application decreased the TNF-alpha and IFN-gamma release in vivo of spleen mononuclear cells in mice, especially after two exposure sessions. However, there was no modulation of the IL-6 and TGF-1ß release.

The aim of a study by de Almeida [2215] was to analyse the effects of sodium diclofenac (topical application) and LPT on morphological aspects and gene expression of biochemical inflammatory markers. We performed a single trauma in tibialis anterior muscle of rats. After 1 h, animals were treated with sodium diclofenac (11.6 mg g(-1) of solution) or LPT (810 nm; continuous mode; 100 mW; 1, 3 or 9 J; 10, 30 or 90 s). Histological analysis and quantification of gene expression (real-time polymerase chain reaction-RT-PCR) of cyclooxygenase 1 and 2 (COX-1 and COX-2) and tumour necrosis factor-alpha (TNF-alpha) were performed at 6, 12 and 24 h after trauma. LPT with all doses improved morphological aspects of muscle tissue, show-

ing better results than injury and diclofenac groups. All LPT doses also decreased COX-2 compared to injury group at all-time points and to diclofenac group at 24 h after trauma. In addition, LPT decreased TNF-alpha compared both to injury and diclofenac groups at all-time points. LPT mainly with dose of 9 J is better than topical application of diclofenac in acute inflammation after muscle trauma.

A rabbit model of endophthalmitis was established by Ma [2422] to evaluate the antiinflammatory effect of LPT as an adjunct to treatment for Staphylococcus epidermidis endophthalmitis. Rabbits were randomly divided into three groups to receive intravitreal injections into their left eye: group A received 0.5 mg vancomycin (100 mcrl), group B received 0.5 mg vancomycin + 0.2 mg dexamethasone (100 mcrl), and group C received 0.5 mg vancomycin (100 mcrl) and laser irradiation (10 mW, 632 nm) focused on the pupil. Slit lamp examination and B-mode ultrasonography were conducted to evaluate the symptoms of endophthalmitis. Polymorphonuclear cells and tumour necrosis factor alpha (TNF-alpha) in aqueous fluid were measured at 0 h, and 1, 2, 3, 7 and 15 days. A histology test was conducted at 15 days. B-mode ultrasonography and histology revealed that groups B and C had less inflammation than group A at 15 days. Groups B and C had fewer polymorphonuclear cells and lower levels of TNF-alpha in aqueous fluid than group A at 2, 3 and 7 days. There was no significant difference between groups B and C. There was no significant difference between groups A, B and C at 15 days. As an adjunct to vancomycin therapy to treat S. epidermidis endophthalmitis, LPT has an antiinflammatory effect similar to that of dexamethasone.

Clinical studies

Konstantinovic [554] compared the effect of corticosteroid infiltration, LPT (GaAs 1 J/cm^2) and laser plus corticosteroid infiltration in combination. On day seven, the combined therapy demonstrated a significantly higher analgesic effect.

Seven patients with bilateral Achilles tendinitis (14 tendons), who had aggravated symptoms caused by pain-inducing activities, were included in a study by Bjordal [1461]. A total of 1.8 Joules for each of three points along the Achilles tendon with a 904nm infrared laser or placebo laser were administered to the Achilles tendons in a random order to which patients and therapist were blinded. Inflammation was examined by invasive microdialysis for measuring the concentration of the inflammatory marker PGE$_2$ in the peritendinous tissue, ultrasound with Doppler measurement of peri- and intratendinous blood flow, and pressure pain algometry. PGE$_2$ levels were significantly reduced at 60, 75, and 90 minutes after active laser compared both to pretreatment levels and to placebo. Changes in pressure pain threshold (PPT) differed significantly between groups. PPT increased by a mean value of 0.19 kg/cm^2 after treatment in the active laser group, while pressure pain threshold was reduced by -0.20 kg/cm^2 after placebo.

Markovic [1911] found that LPT enhanced the effect of intramuscular DEX after third molar extractions.

4.1.29 Inner ear conditions

(See chapter 4.1.54 “Tinnitus, vertigo, Ménière´s disease” on page 419.)

4.1.30 Laryngitis

Although the literature is scarce, there is clinical experience of treating actors with temporary overloading of their voices. Suggested IR dosage is 4 J on five to six sites over the projection of the larynx.

Literature:

Hubacek [1036] reports positive results from treating laryngitis, using transcutaneous irradiation.

Reflux laryngitis is a common clinic complication of nasogastric intubation (NSGI). A study by Marinho [2274] aimed to analyse the protective effect of single and combined therapies with LPT at the doses of 2.1 J and 2.1+1.2 J with a total irradiation time of 30 s and 30+30 s, respectively, on a model of neurogenic reflux laryngitis. NSGI was performed in Wistar rats, assigned into groups: NGI (no treatment), NLT17.5 (single therapy), and NLT17.5/10.0 (combined therapy, applied sequentially). Additional non-intubated and non-irradiated rats were use as controls (CTR). Myeloperoxidase (MPO) activity was assessed by colourimetric method after the intubation period (on days 1, 3, 5, and 7), whereas paraffin-embedded laryngeal specimens were used to carry out histopathological analysis of the inflammatory response, granulation tissue, and collagen deposition 7 days after NSGI. Significant reduction in MPO activity and in the severity of the inflammatory response and improvement in the granulation tissue was observed in NLT17.5/10.0 group. Mast cells count was significantly decreased in NGI and NLT17.5 groups whereas no difference was observed between NLT17.5/10.0 and CTR groups NLT17.5/10.0 group also showed better collagenisation pattern, in comparison to NGI and NLT17.5 groups. This study suggests that the combined therapy successfully modulated the inflammatory response and collagenisation in experimental model of NSGI-induced neurogenic laryngitis.

The intention of another study by Marinho [2275] was to analyse the effect of LPT in a model of reflux-induced laryngitis. The animals were randomly put into three groups: control-non-intubated; nasogastric intubation-intubated; and nasogastric intubation with laser therapy-intubated treated with 105 J/cm² laser irradiation. For the induction of laryngitis, the animals were anesthetised and a nasogastric tube was inserted through the nasopharynx until it reached the stomach, for 1 week. Thereafter, measurement of myeloperoxidase activity and the histopathological procedures were performed. In conclusion, the authors observed that 105 J/cm² infrared laser *reduced the influx of neutrophils in rats, and it improved the reparative collagenisation of the laryngeal tissues.*

4.1.31 Lichen

Oral lichen planus (OLP) is an inflammatory disease that can be painful, mainly in the atrophic and erosive forms. Numerous drugs have been used with dissimilar results, but most treatments are empirical. However, to date, the most commonly employed and useful agents for the treatment of OLP are topical corticosteroid.

Literature:

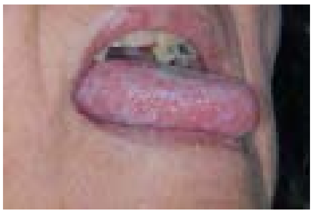


Figure 4.15 Oral lichen (Wikipedia)

Cafaro [2272] studied a prospective cohort of 30 patients affected by OLP, who received LPT with a 980 nm laser. Outcome variables, statistically evaluated, were: the size of lesions; visual analogue score of pain and stability of the therapeutic results in the follow-up period. Eighty-two lesions were treated. The authors reported significant reduction in clinical scores of the treated lesions and in reported pain. No detailed complications or therapy side effects were observed during the study. This study suggests that LPT could be a possible treatment choice for patients with unresponsive symptomatic OLP, also reducing the possible invasiveness correlated with other therapies.

In a study by Jajarm [2392] thirty patients with erosive-atrophic OLP were randomly allocated into two groups. The experimental group consisted of patients treated with the 630 nm laser. The control group consisted of patients who used Dexamethasone mouth wash. Response rate was defined based on changes in the appearance score and pain score (VAS) of the lesions before and after each treatment. Appearance score, pain score, and lesion severity was re-duced in both groups. No significant differences were found between the treatment groups regarding the response rate and relapse. The study demonstrated that LPT was as effective as topical corticosteroid therapy without any adverse effects and it may be considered as an alternative treatment for erosive-atrophic OLP in the future.

A comparative evaluation of LPT and CO_2 laser therapies was performed by Agha-Hosseini [2393], for the treatment of oral lichen planus (OLP). In a randomised open clinical trial, 28 patients with 57 lesions were randomly assigned to two groups. One group received CO_2 laser therapy, the other received LPT for 5 sessions every other day. Participants were examined before the treatment, after 2 weeks, and at 1, 2 and 3 months, to assess the changes in sign and symptom scores. Improvements in size of lesions, in pain and clinical response scores were achieved in both groups. After 3 *months, clinical response showed 100% and 85% partial to complete improvement in LPT and CO_2 laser surgery, respectively. This demonstrates a quick and pronounced beneficial effect in controlling symptoms related to OLP. Both methods may be effective in the treatment of OLP, and can be used as alternative therapy alongside stand-ard treatment modalities. The present study showed that LPT displayed better results than CO_2 laser therapy as alternative or additional therapy, but further investigations in comparison with standard treatment modalities with a prolonged follow-up period will be necessary to confirm the efficacy of laser therapy in the treatment of OLP.*

Dillenburg [2526] sought to compare the efficacy of laser phototherapy (LPT) to topical clobetasol propionate 0.05% for the treatment of atrophic and erosive OLP. Forty-two patients with atrophic/erosive OLP were randomly allocated to two groups: clobetasol group (n=21): application of topical clobetasol propionate gel (0.05%) three times a day; LPT group (n=21): application of laser irradiation using InGaAlP diode laser three times a week. Evaluations were performed once a week during treatment (Days 7, 14, 21, and 30) and in four weeks (Day 60) and eight weeks (Day 90) after treatment. At the end of treatment (Day 30), significant reductions in all variables were found in both groups. The LPT group had a higher percentage of complete lesion resolution. At follow-up periods (Days 60 and 90), the LPT group maintained the clinical pattern seen at Day 30, with no recurrence of the lesions, whereas the clobetasol group exhibited worsening for all variables analysed. These findings suggest that the LPT proved more effective than topical clobetasol 0.05% for the treatment of OLP.

Further literature: [697, 724, 972, 2493]

4.1.32 Low back pain

This is certainly a difficult problem to treat, and LPT is by no means a panacea. It has, however, proven to be a valuable option in the hands of physiotherapists and chiropractors. High doses of infrared are essential. Relative lack of success in published studies is probably due to low dosages. WALT dosage recommendation per session for low back pain is a minimum of 8 J per point, 40 J in totalt for GaAlAs. For GaAs, the minimum is 4 J per point, not less than 10 J in total.

Literature:

Tasaki [125] treated 18 patients with low back pain with a GaAlAs laser at 30-80 mW. The sessions lasted 2-10 minutes and led to full pain relief. Pain relief took six to eight hours to take effect among the patients who did not experience it immediately.

Basford [1062] performed a double-blind, placebo-controlled, randomised clinical trial on patients with low back pain. Sixty-three ambulatory men and women between the ages of 18 and 70 years with symptomatic non-radiating low back pain of more than 30 days' duration and normal neurological examination results participated. Subjects were bloc randomised into two groups by a computer-generated schedule. All underwent irradiation for 90 seconds at eight symmetric points along the lumbosacral spine three times a week for four weeks by a masked therapist. The Nd:YAG laser emitted 542 mW/cm^2. The subject's perception of benefits gained, level of function as assessed by the Oswestry Disability Questionnaire, and lumbar mobility were evaluated. The treated group had a time-dependent improvement in two of the three outcome measures: perception of benefits and level of function. These results were most marked at the midpoint evaluation and end of treatment, but tended to lessen at the one-month follow-up. Lumbar mobility did not differ between the groups at any time.

In another clinical study by Zati [1537], a high power defocused Nd:YAG laser was used in patients suffering from low back pain caused by intervertebral disk herniation. The effect of laser irradiation was compared to TENS and Katoprofen. The most striking feature of the LPT was that the pain relief was more long lasting than the other therapies.

A study by Djavid [1849] was a randomised trial with concealed allocation, blinded assessors and intention-to-treat analysis. Sixty-one patients with low back pain for at least 12 weeks participated. One group received LPT alone, one received LPT and exercise, and a third group received placebo LPT and exercise. LPT was performed twice a week for 6 weeks. Outcomes were pain severity measured using a 10-cm Visual Analogue Scale, lumbar range of motion measured by the Schober Test and maximum active flexion, extension and lateral flexion, and disability measured by the Oswestry Disability Index on admission to the study, after 6 weeks of intervention, and after another 6 weeks without intervention. There was no greater effect of LPT compared with exercise for any outcome, at either 6 or 12 weeks. There was also no greater effect of LPT plus exercise compared with exercise for any outcome at 6 weeks. However, in the LPT plus exercise group pain had reduced by 1.8 cm, lumbar range of movement increased by 0.9 cm on the Schober Test and by 15 deg of active flexion, and disability reduced by 9.4 points (more than in the exercise group at 12 weeks). In chronic low back pain, LPT combined with exercise seems to be more beneficial than exercise alone in the long term.

In a recent Cochrane analysis [1787]of the effect of LPT on low back pain the authors write: "Six RCTs with reasonable quality were included in the review. All of them were published in English. There is some evidence of pain relief with LPT, compared to sham therapy for subacute and chronic low-back pain. These effects were only observed at short-term and intermediate-term follow-ups. Long-term follow-ups were not reported. There was no difference between LPT and comparison groups for pain-related disabil-

ity. There is insufficient evidence to determine the effectiveness of LPT on antero-posterior lumbar range of motion compared to control group in short-term follow-up. The relapse rate in the LPT group was significantly lower than in the control group at six months follow-up period according to the findings of two trials. No side effects were reported. However, we conclude that there are insufficient data to draw firm conclusions. There is a need for further methodologically rigorous RCTs to evaluate the effects of LPT compared to other treatments, different lengths of treatment, different wavelengths and different dosages. Comparison of different LPT treatments will be more reasonable if dose calculation methods are harmonised."

The aim ofa study by Konstantinovic [2124] was to investigate the clinical effects of LPT in patients with acute low back pain (LBP) with radiculopathy. Acute LBP with radiculopathy is associated with pain and disability and the important pathogenic role of inflammation. LPT has shown significant anti-inflammatory effects in many studies. A randomised, double-blind, placebo-controlled trial was performed on 546 patients. Group A (182 patients) was treated with nimesulide 200 mg/day and additionally with active LPT; group B (182 patients) was treated only with nimesulide; and group C (182 patients) was treated with nimesulide and placebo LPT. LPT was applied behind the involved spine segment using a stationary skin-contact method. Patients were treated 5 times weekly, for a total of 15 treatments, with the following parameters: wavelength 904 nm; PRR 5000 Hz; 100 mW average power; power density of 20 mW/cm^2 and dose of 3 J/cm^2; treatment time 150 sec at whole doses of 12 J/cm^2. The outcomes were pain intensity measured with a Visual Analogue Scale (VAS); lumbar movement, with a modified Schober test; pain disability, with Oswestry disability score; and quality of life, with a 12-item short-form health survey questionnaire (SF-12). Subjects were evaluated before and after treatment. Statistical analyses were done with SPSS 11.5. Statistically significant differences were found in all outcomes measured, but were larger in group A than in B and C. The results in group C were better than in group B. The results of this study show better improvement in acute LBP treated with LPT used as additional therapy.

Another study by Konstantinovic [2332] included 66 patients with acute low back pain (LBP) and radiculopathy who had been randomly divided into three groups (22 patients each) received three different doses of LPT. The patients were treated 5 times weekly, for a total of 10 treatments, with the following parameters: 904 nm, 3,000 Hz, average power 25 mW; energy 0.1 J per point in the first group, 1 J per point in the second and 4 J per point in the third group; daily treatment time and accumulated energy were 16 s and 0.4 J in the first group, 160 s and 4 J in the second group and 640 s and 16 J in the third group, respectively. The parameters of assessment before and after the therapy were: lumbar and leg pain measured by Visual Analogue Scale (VAS), local and general functional changes. Highly significant improvements were noted in all the groups after LPT with respect to all *the investigated parameters. The VAS scores were significantly lower in all the groups without a difference between the groups. Functional improvements were better in the third group treated with the energy of 4 J per point than in other two groups. In conclusion, three different energies were equally effective in alleviating lumbar and leg pain without side effects, but the energy of 4 J per point seemed to be more effective in improving the activities of daily living and lumbar mobility.*

The aim of the study by Alayat [2479] was to compare the effect of LPT alone or combined with exercise, in the treatment of chronic low back pain (CLBP). A total of 72 male patients participated in this study. Patients were randomly assigned into three groups and treated with LPT plus exercise (HILT + EX), placebo laser plus exercise (PL + EX), and LPT alone in groups 1, 2, and 3, respectively. The outcomes measured were lumbar range of motion (ROM), pain level by Visual Analogue Scale (VAS), and functional disability by both the Roland Disability Questionnaire (RDQ) and the Modified Oswestry Disability Questionnaire (MODQ). ROM significantly increased after 4 weeks of treatment in all groups, then significantly decreased after 12 weeks of follow-up, but was still significantly more than the baseline value in groups 1 and 2. VAS, RDQ, and MODQ results showed significant decrease post-treatment in all groups, although the RDQ and MODQ results were not significantly different between groups 2 and 3. LPT combined with exercise appears to be more effective in patients with CLBP than either LPT alone or placebo laser with exercise.

Hsieh [2345] conducted a double-blind randomised placebo-controlled study to investigate the effects of short-term 890 nm light therapy in patients with chronic low back pain in a rehabilitation clinic. Thirty-eight women and 22 men with chronic low back pain (mean age, 60.3 years; range, 32-80 years) received 40-min sessions of hot-pack therapy combined with active or placebo 890 nm light therapy (6.24 W, 34.7 mW/cm^2 for 40 min, total energy = 83.2 J/cm^2) over the lower back three times weekly for 2 weeks. Compared to the baseline measurements, participants in the treatment group reported significant reductions in fear-avoidance beliefs regarding physical activity and work and in the severity of disability.

Further literature: [551, 621, 956, 1061, 1304]

4.1.33 Mastitis

Mastitis is the inflammation of breast in connection with pregnancy, breastfeeding or weaning. Since one of the most prominent symptoms is tension and engorgement of the breast, it is thought to be caused by blocked milk ducts or milk excess. It is relatively common; estimates range depending on methodology between 5-33%. LPT is supposedly reducing the inflammatory process, reducing pain and increasing vessel volume.

Literature:

LPT of mastitis has been successfully used on dairy cattle and Herzog [1002] reports good effects on 66 mothers, using 830 nm, 30 mW, 0.5-2 J per point. Kovalev [1003] reports positive results for this indication, using HeNe on 329 mothers. HeNe was more effective than 890 nm GaAs. Havlik [1039] also reports positive results when using GaAlAs for mastitis. On the other hand, Stoffel [1004] reports that HeNe 25 mW had no effect on bovine mastitis. ***However, the irradiation area of 7.5 cm in diameter produces a very low energy density.***

Dotsenko [1005] and Skobelkin [1272] have used defocused carbon dioxide laser successfully for human lactation mastitis.

The objective of a study by Posso [1298] was to investigate the analgesic action of LPT on nipple pain during breastfeeding. Forty women in the immediate puerperium were studied. The patients were divided into two groups: Control group - application of plain light on the nipple for 40 seconds; Laser group - application of InGaAlP with the wavelength of 685 nm, a power of 100 mW and a fluence of 4 J/cm^2 on the nipple for 40 seconds. The intensity of pain was measured before and on the 1st and 10th minute after LPT application, using a Visual Analogue Scale. In the control group, the intensity of pain was the same at the 1st and 10th minute after the application of plain light. In the laser group, the intensity of pain was smaller at the 1st and 10th minute after the application of LPT, this being statistically significant.

LPT has been used in parturient patients for postpartum mastitis and nipple soreness. However, previous studies have revealed hormonal and physiological effects of LPT on the lactation status. Therefore, Mokmeli [2069] selected 20 healthy women scheduled for caesarean section. They were randomly divided into two groups: a LPT group and a control group. LPT was delivered as follows: (1) irradiation with 980 nm (100 mW, 3.3 J/cm^2, total energy 60 J), and 650 nm (30 mW, 1.5 J/cm^2, total energy 27 J) to the incision line, and (2) intravenous laser irradiation at 2.5 mW and 650 nm for 15 min on three consecutive postoperative days. Except for LPT, all the therapeutic conditions in both groups were identical. Blood prolactin levels were measured in the groups on the third postoperative day, and tissue samples were taken from the wound margins for histological evaluation on the 10th postoperative day. Although there was a difference between blood prolactin levels in the two groups, the difference was not statistically significant. However, there was a statistically significant difference in the mean lymphocyte counts and number of vessel lumina, with higher numbers seen in the LPT group. LPT after cesarean section thus has no serious deleterious effects on lactation, and it helps to modulate metabolic processes and promotes wound healing post-surgery.

In a study by Schaffer [907], three women with painful mastitis from irradiation after breast cancer with ionising radiation, and a male with a radiation ulcer, were treated with 780 nm, 5 J/cm^2. The healing of the ulcers *was controlled using MRI measurement before and after treatment. In all patients, a complete clinical remission was noted following LPT. The results were confirmed by a decrease in inflammatory changes as depicted in MRI imaging.*

The same indication is reported by Schindl [967]. Three patients with radiation ulcers following breast cancer therapy were treated with HeNe laser, 30 J/cm^2, three times weekly. At the 36-month control, no patient showed any recurrence of the radiation ulcers or neoplasm.

One of the successful treatments for cyclical mastalgia is bromocriptine evening primrose combination. A double blind study by Saied [2465] was applied on 80 patients with cyclical mastalgia. They were randomly divided into two groups (A and B). In group A, patients were treated by bromocriptine/evening primrose. To group B, LPT with specified dosimetry was applied, using a device that delivers He-Ne laser combined with 4 infra-red diode laser. Evaluation of treatment was both subjective (using VAS) and objective (studying the degree of drop in plasma cortisol level). The drop of plasma cortisol with treatment was studied using the student -t distribution. A good response was observed in the laser group in 82.5%, compared to 63.9% in the bromocriptine/evening primrose group. There was a significant difference before and after treatment in both groups. This difference was more for the drug treated group than for the laser treated group, but in the latter, it acted on a wider sector of patients.

4.1.34 Microcirculation

Improving the microcirculation in tissue is one of the most important aspects of LPT. The self-healing capacity of the body will improve considerably if more blood is circulating in the tissue. Improved microcirculation in the region will also enhance the uptake of concomitant pharmaceutical agents.

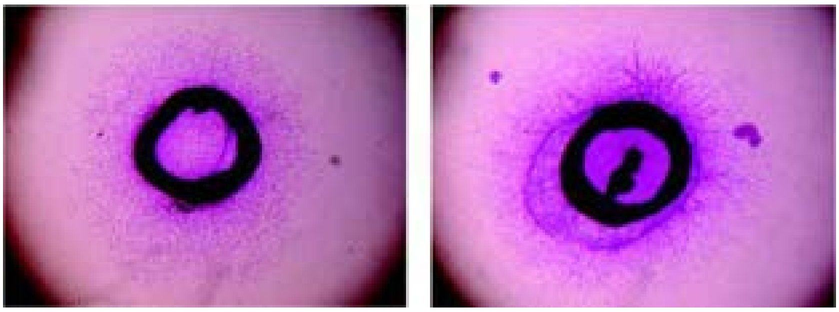


Figure 4.16 Rat aortas without (left) and with LPT (right). Note formation of new microvessels. Courtesy: Levon Gasparyan.

Literature:

In vitro studies

Vascular endothelial growth factor (VEGF) is one of the most important growth factors for endothelium. VEGF induces angiogenesis and endothelial cell proliferation and it plays an important role in regulating vasculogenesis. The aim of a study by Gasparyan [1626] was to investigate the influence of red laser light on angiogenesis in vitro, and to compare with the effects of VEGF applications. Thoracic aortal rings were prepared from Sabra rats. Samples from group 1 served as control, group 2 samples were incubated with VEGF, group 3 samples were irradiated with laser (660 nm, 20 mW) in a drop (10 /l) of the medium for 10 min, and group 4 samples were incubated with VEGF and received 10 min of laser irradiation. The stained samples were photographed by a camera connected to a microscope. Laser irradiation activated the process of angiogenesis. In the control group (without VEGF or laser irradiation), angiogenesis of new vessels was not detected. Laser irradiation, however, promoted angiogenesis. The area covered by new vessels was 1,9±0,29 mm^2 and the maximal length of vessels was 0,75 ± 0,10 mm. No statistical difference was discovered between laser irradiation and VEGF application. After a combined influence of VEGF and laser light irradiation, the area covered by new vessels was 6,98 ± 0,88 mm^2 and the maximal length of vessels was 1,7 ± 0,23 mm.

The aim of a study by Tuby [1730] was to investigate the effect of LPT on the expression of vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS). Myocardial infarction was induced by occlusion of the left descending artery in 87 rats. Laser was applied to intact and post-infarction hearts. VEGF, iNOS, and angiogenesis were determined. Both the laser-irradiated rat hearts post-infarction and the intact hearts demonstrated a significant increase in VEGF and iNOS expression compared to non-laser-irradiated hearts. LPT also caused a significant elevation in angiogenesis

The possible molecular mechanism of HeNe laser irradiation on endothelial cells was proposed in the study by Chen [1845]. HeNe laser was used to stimulate human umbilical vein endothelial cell (HUVEC), and its effect on cell proliferation, nitric oxide secretion, and cell migration was determined. Irradiation enhanced endothelial nitric oxidase synthase (eNOS) protein expression, and irradiation of less than 0.26 J/cm^2 enhanced eNOS gene expression in HUVEC. The cell migration ability promoted HUVEC when irradiated with 0.26 J/cm^2. This agreed with the vinculin protein expression induced by irradiation. In addition, the angiogenesis was promoted. The induced eNOS expression was inhibited by LY294002, indicating that the effect of laser on EC could be attributed to the up-regulation of eNOS expression through the PI3K pathway at the cellular and molecular levels as a result of the HeNe laser. The study has shown that LPT increased endothelial cell proliferation, migration, NO secretion, and identified that *activation of the PI3K/Akt pathway was a critical step in elevating the eNOS expression upon LPT.*

As LPT seems to induce vasodilation besides many other known biological effects, LPT has been increasingly used in therapy of medical conditions with various irradiation parameters. The aim of a study by Plass [2196] was to investigate the effect of LPT on photorelaxation of human coronary and internal thoracic arteries (ITA). Thirty vessel segments of ITA used for routine coronary artery bypass grafting as well as left anterior descending coronary arteries (LAD) of patients undergoing cardiac transplantation were cut into 4-mm rings stored in a modified Krebs-Henseleit solution and evaluated in a myograph. Both types of vessel segments were irradiated by a laser operating at a wavelength of 680 nm. After precontraction with thromboxane agonist U44619, respective relaxation responses were evaluated and compared to pharmacological dilatation induced by substance P. Mean pharmacological vasodilation by substance P was 22.6 +/- 3.3%, 12.8 +/- 1.4%, and 20.4 +/- 3.2% in macroscopic healthy LAD, LAD with atheromatous plaque, and ITA, respectively. Average photorelaxation induced by LPT was 16.5 +/- 2.0%, 1.9 +/- 1.7%, and 6.8 +/- 4.7%, accordingly. Vasodilatatory responses induced either by substance P or administration of LPT were significantly decreased in LAD with atheromatous plaque. Vasospasms of ITA segments occurring during experiments could be abandoned when LPT was administered. Macroscopic healthy LAD exposed to LPT revealed significant photorelaxation. With the administration of LPT, 73% of the maximal obtainable effect by an endothelium-dependent vasodilator could be reached. Furthermore, LPT has the potential to overcome vasospasms of ITA.

Animal studies

Kubota [479] used the laser speckle flowgraphy to measure the microcirculation in rodent flaps. The blood flow rate was reduced immediately following one minute of irradiation at 830 nm. Thirty minutes later, the flap perfusion was greater than in the control flap.

In an animal study by Kobayashi [666], the effect of GaAlAs laser on the blood flow in flaps was studied through laser speckle flowgraphy (LSF). Forty rats were divided into four groups. Two groups had random pattern flaps, two had axillary pattern flaps with the dominant vessels intact. Flaps were raised and peripheral blood flow assessed through LSF. Laser irradiation was performed in two groups, either directly on the dominant vessel or at one point on the distal part of the flap. The blood flow directly after irradiation was higher than before irradiation. On day five, there was a clear difference between the irradiated and the non-irradiated flaps. The flaps irradiated at the dominant vessels had a slightly better outcome than those irradiated at the centre of the flap.

In the experiment performed by Pinfildi [1603], 48 rats were used, weighed and divided into four groups with 12 rats each. A skin flap was per-

formed, measuring 10 x 4 cm, with a plastic sheet interposed between the flap and the donor site. Group 1 (control) underwent sham irradiation with HeNe laser. Group 2 was submitted to laser irradiation, using the punctual contact technique on the skin flap surface. Group 3 was submitted to laser irradiation surrounding the skin flap, and Group 4 was submitted to laser irradiation both on the skin flap surface and around it. The experimental groups were submitted to HeNe laser irradiation with a 3 J/cm^2 energy density immediately after surgery and for four subsequent days. The percentage of necrotic area in the four groups was calculated on the seventh post-operative day, through a paper-template method. Group 1 reached an average necrotic area of 48.86%; Group 2, 38.67%; Group 3, 35.34%; and Group 4, 22.61%.

Studies by Bibikova [667, 587] conclude that during skeletal muscle regeneration in the toad, HeNe laser irradiation markedly promotes the process of neoformation of blood vessels and young myofibres in the injured zone.

Thirty-four adult rabbits were used in a study by Ihsan [1720]. Two of the rabbits were considered 0-h reading group, while the rest were divided into two equal groups, with 16 rabbits each: control and those treated with laser. Each rabbit underwent two surgical operations; the medial aspect of each thigh was slit, the skin incised and the femoral artery exposed and ligated. The site of the operation in the treated group was irradiated directly following the operation and for three days thereafter, one session daily for 10 min/session. The laser system used was a GaAs laser with a wavelength of 904 nm and a power output of 10 mW. Blood samples collected from the femoral artery above the site of the ligation were sent for examination with high-performance liquid chromatography (HPLC) to determine the levels of adenosine, growth hormone (GH) and fibroblast growth factor (FGF). Tissue specimens collected from the site of the operation, consisting of the artery and its surrounding muscle fibres, were sent for histopathological examination to determine the fibre/capillary (F/C) ratio and capillary diameter. Blood samples and tissue specimens were collected at 4, 8, 12, 16, 20, 24, 48 and 72 h postoperatively from the animals of both groups, control and treated. Rapid increases in the level of adenosine, GH, and FGF occurred. The F/C ratio and capillary diameter peaked at 12-16 h, after which their levels declined gradually, reaching normal values 72 h after irradiation in the treated group. Numerous collateral blood vessels proliferated the area, with marked increases in the diameters of the original blood vessels.

Maegawa [1030] used a 30 mW GaAlAs laser to irradiate the rat's mesenteric microcirculation in vivo, with a power density of 38.2 mW/mm^2. The irradiation caused a potent dilatation in the irradiated arteriole, which led to a marked increase in the arteriolar blood flow. The irradiation also caused a power-dependent decrease in [Ca^{2+}] in the vascular smooth muscle cells.

Núñez [1441] performed a rodent study where an injury was provoked in 15 rats and blood flow was measured periodically over a period of 21 days. Control groups were established to evaluate Laser Doppler Flowmetry and HeNe laser effects on microcirculation. A 1 J/cm² dose was utilised, with a 6 mW/cm² irradiance. The results demonstrated flow alterations provoked by lesion, and an inflammatory response. There were no statistical differences between groups.The results did not show a significant effect on microcirculation with this HeNe dose.

The influence of HeNe laser radiation on the formation of new blood vessels in the bone marrow compartment of a regenerating area of the mid-cortical diaphysis of the tibiae of young adult rats was studied by Garavello [1544]. A small hole was surgically made with a dentistry burr in the tibia and the injured area received a daily LPT over 7 or 14 days transcutaneously starting 24 h after surgery. Incident energy density dosages of 31.5 and 94.5 J/cm² were applied during the period of the tibia wound healing being investigated. Light microscopic examinations of histological sections of the injured area and quantifications of the newly-formed blood vessels were undertaken. LPT accelerated the deposition of bone matrix and histological characteristics compatible with an active recovery of the injured tissue. HeNe LPT significantly increased the number of blood vessels after 7 days of irradiation at an energy density of 94.5 J/cm², but significantly decreased the number of vessels in the 14- day irradiated tibiae, independent of the dosage. These effects were attributed to laser treatment, since no significant increase in blood vessel numbers was detected between 8 and 15 non-irradiated control tibiae.

Salate [1624] divided ninety-six rats into three groups subject to treatment for 3, 5, and 7 days post-lesion. Thirty-two animals were used in each group. The groups were further divided into four subgroups with eight animals in each, receiving InGaAlP laser, 660 nm, treatment at (1) a mean output of 10 mW, or (2) 40 mW during 10 sec, (3) a sham subgroup, and (4) a non-treatment subgroup. Each animal was subjected to a lesion of the Achilles tendon by dropping a 186-g weight from a 20-cm height over the tendon. Treatment was initiated six hours post-injury for all the groups. Blood vessels were coloured by an India ink injection and were examined in a video microscope. Laser exposure promoted an increase in blood vessel count when compared to controls. The 40-mW group showed early neovascularisation, with the greatest number of microvessels after three laser applications. The 10-mW subgroup showed angiogenesis activity around the same time as the sham laser group did, but the net number of vessels was significantly higher in the former than in the controls. After seven irradiations, the subgroup receiving 40 mW experienced a drop in microvessel numbers, but it was still higher than in the control groups.

The aim of a study by Corazza [1865] was to compare the angiogenic effects of laser and light-emitting diode (LED) illumination on wounds induced in rats, with varying fluences. The LED is an alternative light source *that accelerates wound healing, and its efficiency concerning the angiogenic effect was compared to LPT. The experimental model consisted of a circular wound inflicted on the quadriceps of 120 rats, using a 15-mm-diameter "punch." Animals were divided randomly into five groups: two groups of laser, with dosages of 5 and 20 J/cm², respectively, two groups of LED, also with dosages of 5 and 20 J/cm², and a control group. Six hours after wound infliction, the treated groups received the diverse applications accordingly and were irradiated every 24 h. Angiogenesis was studied through histomorphometry on days 3, 7, 14 and 21 after the wounds were inflicted. On days 3, 7 and 14, the proliferation of blood vessels in all irradiated groups was superior in comparison to those of the control group. Treatment with a fluence of 5 J/cm² was better than for the group treated with 20 J/cm² on day 21. Red LPT and LED demonstrated expressive results in angiogenesis. Light coherence was shown not to be essential to angiogenesis under these circumstances.*

The study by Ribeiro [1899] was carried out to evaluate the effects of LPT, 660 nm, in rat's burned skin with two different dose regimens by histomorphometry. The number of new blood vessels was quantified by appropriate software. The findings suggest that laser may accelerate angiogenesis compared to the control group, but no significant differences were observed between laser groups using fractionated or single doses during the entire experimental period.

Nitric oxide (NO) is a crucial mediator of hindlimb collateralisation and angiogenesis. Within tissues there are nitrosyl-heme proteins which have the potential to generate NO under conditions of hypoxia or low pH. Low level irradiation of blood and muscle with light in the far red/near infrared spectrum (670nm, R/NIR) facilitates NO release. Therefore, Lohr [2233] assessed the impact of red light exposure on the stimulation of femoral artery collateralisation. Rabbits and mice underwent unilateral resection of the femoral artery and chronic R/NIR treatment. The direct NO scavenger carboxy-PTIO and the nitric oxide synthase (NOS) inhibitor L-NAME were also administered in the presence of R/NIR. DAF fluorescence assessed R/NIR changes in NO levels within endothelial cells. In vitro measures of R/NIR induced angiogenesis were assessed by endothelial cell proliferation and migration. R/NIR significantly increased collateral vessel number which could not be attenuated with L-NAME. R/NIR induced collateralisation was abolished with c-PTIO. In vitro, NO production increased in endothelial cells with R/NIR exposure, and this finding was independent of NOS inhibition. Similarly R/NIR induced proliferation and tube formation in a NO dependent manner. Finally, nitrite supplementation accelerated R/NIR collateralisation in wild type C57Bl/6 mice. In an eNOS deficient transgenic mouse model, R/NIR restores collateral development. In conclusion, R/NIR increases NO levels independent of NOS activity, and leads to the observed enhancement of hindlimb collateralisation.

The study by Zaidi [2298] shows that LPT stimulates angiogenesis by increasing angiomotin and decreasing angiostatin expression in the ischemic hindlimb of mice.

Cury [2348] investigated the effects of 660 and 780 nm lasers at fluences of 30 and 40 J/cm² on three important mediators activated during angiogenesis. Sixty male Wistar rats were used and randomly divided into five groups with twelve animals each. Groups were distributed as follows: skin flap surgery non-irradiated group as a control; skin flap surgery irradiated with 660 nm laser at a fluence of 30 or 40 J/cm² and skin flap surgery irradiated with 780 nm laser at a fluence of 30 or 40 J/cm² . The random skin flap was performed measuring 10x4cm, with a plastic sheet interposed between the flap and the donor site. Laser irradiation was performed on 24 points covering the flap and surrounding skin immediately after the surgery and for 7 consecutive days thereafter. Tissues were collected, and the number of vessels, angiogenesis markers (vascular endothelial growth factor, VEGF and hypoxia inducible factor, HIF-1alpha) and a tissue remodelling marker (matrix metalloproteinase, MMP-2) were analysed. LPT increased an angiogenesis, HIF-1alpha and VEGF expression and decrease MMP-2 activity. These phenomena were dependent on the fluences, and wavelengths used. In this study it was shown that LPT may improve the healing of skin flaps by enhancing the amount of new vessels formed in the tissue. Both 660 nm and 780 nm lasers were able to modulate VEGF secretion, MMP-2 activity and HIF-1alpha expression in a dose dependent manner.

Gorshkova [2486] reports that the responses of rat pial vessels to red laser irradiation can be mediated by NO. NO mainly affected major arteries and did not contribute to reactivity of small pial arteries and precortical arterioles.

Clinical studies

Podelinskaia [571] used a computer-aided analytical system of TV images to study the microcirculation in the anterior segment of the eye. Exposure to 890 nm LPT had a favourable impact on blood aggregation.

Saito [630] studied the effect of GaAlAs laser on the blood flow of 15 healthy male subjects. The upper side of the foot was irradiated for one minute (60 mW). Laser speckle flowmetry was performed at the start of irradiation, as well as 30 and 60 minutes post irradiation. During the period of irradiation, blood flow was reduced significantly but increased immediately after the treatment, remaining at this level for 60 minutes. The laser speckle flowmetry method itself has a potential of influencing the outcome in both groups.

Schaffer [904] explored the effect of a diode laser (780 nm) on normal skin tissue. Time-dependent contrast enhancement was determined by magnetic resonance imaging (MRI). In the examinations, six healthy volunteers were irradiated on their right planta pedis (sole of foot) with 5 J/cm² at a power density of 100 mW/cm². T1-weighted magnetic resonance imaging was *used to quantify the time-dependent local accumulation of Gadolinium-DPTA; its actual content in the local current blood volume, as well as its distribution to the extracellular space. Images were obtained before and after the application of laser light. When laser light was applied, the signal to noise ratio increased by more than 0.35 ± 0.15 (range 0.23-0.63) after irradiation according to contrast-enhanced MRT. According to the authors: "it can be observed that after biomodulation with light of low energy and low power, wound healing improves and pain is reduced. This effect might be explained by an increased blood flow in this area. Therefore, the use of this kind of laser treatment might improve the outcome of other therapeutic modalities such as tumour ionising radiation therapy and local chemotherapy".*

Schindl [145] treated three cases of Bürger's Disease, which is characterised by reduced microcirculation in the extremities. In practice, this always leads to amputation, often up to and past the knee/elbow. The illness has a very poor prognosis, and patients suffer from acute ischaemic pain. The three patients in the study refused to undergo further amputations and discharged themselves from hospital at their own risk. They remained on antibiotics during the entire treatment, but other than that, HeNe laser light was the only treatment they received. All three patients avoided further amputations, began healing and could return to work. The intense pain also disappeared. Bearing in mind these encouraging results, HeNe laser should be tested more on diabetics, in whom peripheral circulation can fall, rendering amputation necessary.

In a case report by Sasaki [913], a patient with thromboangitis obliterans (Bürger's disease) was treated with a 60 mW, 830 nm laser and a defocused 20 W, Nd:YAG laser. Ulcers were remarkably improved. Agonising pain and ischemia were relieved. In the MRA findings, sudden arterial obliteration disappeared. In the thermographical findings, skin temperature increased to normal.

Schindl [674] treated a chronic radiation ulcer with HeNe laser, 30 J/cm^2. A video measuring system was used to determine the number of dermal vessels in the ulcer before and after the laser treatment. After seven irradiations, the ulcer had healed completely. Light microscopy in combination with the video measuring system showed a significant increase in the number of dermal capillaries after laser treatment.

Koslov [566] used laser dopplerography, TV capillaroscopy, and polarography of transcutaneous oxygen tension to study microcirculation. Patients with stage II and III arterial ischemia in the feet were studied. LPT at 890 nm increased microcirculation.

The pilot study by Al-Awami [1200] was performed to evaluate the efficacy of LPT as a new non-drug, non-invasive treatment for patients with primary and secondary Raynaud's disease. Altogether 40 patients (29 female, 11 male, mean age 51 years) with active primary (28%) and secondary (72%) Raynaud's phenomenon received 10 sessions of LPT distant irra-

diation during the winter months. Assessments of subjective and objective parameters were performed at baseline one week after the last session and three months later. Variations of subjective parameters, such as the number of daily acute episodes and the severity of discomfort, were assessed by a coloured Visual Analogue Scale. A standardised cold challenge test using computed thermography of continuous temperature recordings by means of infrared telethermography was used to assess the digital blood flow. A significant improvement was noticed clinically and thermographically after six weeks and three months, respectively.

The effect of LPT on Raynaud's disease has also been investigated by Hirschl [1265]. Absolute and relative frequency and intensity of vasospastic attacks during three weeks of either LPT or placebo, and the results of infrared thermography before onset and at the end of both therapy sequences, were evaluated in 15 patients with primary Raynaud's phenomenon. The frequency of attacks was not significantly affected, but the intensity of the attacks was reduced. The mean temperature gradient after cold exposure was reduced after irradiation, but the number of fingers showing prolonged rewarming was unaffected.

Silveira [1907] did not find any change in vessel dilatation after LPT on excised hypertrophic human gingiva, but as the authors suspect, there was no time for such changes since the excised samples were formaline-fixed immediately after irradiation and excision.

Mitchell [2277] conducted a single-blind, placebo-controlled, randomised clinical trial to measure NO, by its metabolites nitrite and nitrate, in venous blood draining from tissue receiving LPT. Fifteen healthy subjects received LPT to the forearm, and blood samples were taken immediately before treatment; at 1, 5, 15, and 30 mins; as well as 15 mins after the treatment to check for NO content. The investigators found a significant treatment effect. A post hoc test showed that minutes 1, 5, and 15 were different compared with the baseline measures. The area under the treatment curve was significantly larger than the area under the sham treatment curve. A limitation of this study was that the data were collected from healthy subjects. LPT increased NO levels in venous blood draining from the treatment site in healthy subjects. The peak increase in NO occurred 5 m into the treatment, after which it slowly waned.

The objective of the study by Saied [2463] was to examine skin blood flow in diabetic patients having disease-related skin lesions, and to evaluate possible improvement imposed by LPT as a new treatment modality. Thirty patients (in addition to 15 controls receiving conventional treatment = group II and 15 others receiving no treatment = group III) having diabetes-related skin lesions were tested for skin blood flow by laser Doppler flowmetry. Group I patients received LPT by a specified dosimetry. This was by combined uniform HeNe and infrared lasers delivered by a scanner over the affected area. This study used a paired t test to determine the significance of blood flow recovery after treatment within each group while Independent t *test compared results between the three groups. The most frequently detected diabetes specific skin lesions were dryness, nail changes, hair loss, infections, itching, and frank eczema-like reactions, mostly in combinations (76%). This pattern appears specific for Egyptians as it is different from data registered in foreign literature. The minimum perfusion flow improved from 16.45 before LPT to 25.94 after, while maximum flow recovered from 32.91 to 48.47 and basal perfusion changed from 24.68 to 34.84 blood perfusion units. The percentage change in perfusion values was 23.17. All these were statistically significant. The study demonstrates that diabetes-linked skin lesions have a special pattern in Egyptians and are apparently caused by deranged skin blood flow. The deficit is measurable by laser flowmetry and can be partially reversed by LPT.*

For additional studies on microcirculation, see chapter 4.1.18 "Diabetes" on page 254.

Further literature: [145, 308, 1015, 1075, 1082,1442, 1464, 1472, 1482, 1486, 1592, 2013]

4.1.35 Morbus Sluder

Literature:

Mb Sluder is a painful condition originating in the spheno-palatinal ganglion. Parascandalo [1071] used a GaAs laser on three patients for 12 sessions, irradiating the maxillary nerve apertures. Total pain relief was obtained after five sessions, difficulties in swallowing improved after three sessions, reduction of high tear flow after several sessions. Full recovery after nine sessions.

Further literature: [1070]

4.1.36 Mucositis

Mucositis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer [1]. Mucositis can occur anywhere along the gastrointestinal (GI) tract, but oral mucositis refers to the particular inflammation and ulceration that occurs in the mouth. Oral mucositis is a common and often debilitating complication of cancer treatment.

Oral and gastrointestinal (GI) mucositis affects almost all patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT), 80% of patients with malignancies of the head and neck receiving radiotherapy, and a wide range of patients receiving chemotherapy. Alimentary tract mucositis increases mortality and morbidity and contributes to rising health care costs.

For most cancer treatment, about 5-15% of patients get mucositis. However, with 5-fluorouracil (5-FU), up to 40% get mucositis, and 10-15% get grade 3-4 oral mucositis.[4] Irinotecan is associated with severe GI mucositis in over 20% of patients. 75-85% of bone marrow transplantation recipients experience mucositis, of which oral mucositis is the most common and most debilitating, especially when melphalan is used. In grade 3 oral mucositis, the patient is unable to eat solid food, and in grade 4, the patient is unable to consume liquids as well.

Radiotherapy to the head and neck or to the pelvis or abdomen is associated with Grade 3 and Grade 4 oral or GI mucositis, respectively, often exceeding 50% of patients. Among patients undergoing head and neck radiotherapy, pain and decreased oral function may persist long after the conclusion of therapy. Fractionated radiation dosage increases the risk of mucositis to > 70% of patients in most trials. Oral mucositis is particularly profound and prolonged among HSCT recipients who receive total-body irradiation. [Text from Wikipedia].

Figure 4.17 Mucositis in the lip before and after LPT, performed during the radiation period. Courtesy: Alyne Simões.

Clinical studies

Skobelkin [2] compared the effect of HeNe and infrared 890 nm irradiation in 60 oncologic patients. The irradiation was delivered during the immediate preoperative period. Parameters analysed were cell components of the blood: behaviour of T-lymphocyte fractions and immunoglobulin activity. The total immunoresponse increased following LPT, with no visible increase in the tumoural remnant size. The 890 nm laser was more effective.

Podolskaya [366] has used HeNe lasers on post-radiation reactions and injuries in lip skin and mucous membranes (post-radiation heilitis). The method has been more successful than previously used medical treatments. There were no complications in the laser group, while the traditionally treated group had several allergic reactions and reoperations. The pace of epithelialisation was 7 mm/week in the HeNe group, as compared with 4.1 mm/week in the control group.

Pourreau-Schneider [46] used a HeNe laser to reduce the oral side-effects of fluorouracil. The drug causes painful mucositis, which in turn causes eating problems. The mucositis dictates the limit for the dosage of fluorouracil (dose limiting factor). The use of a HeNe laser was shown to *reduce discomfort to a great extent, and administering LPT prophylactically before the treatment could also alleviate the problems.*

Cowen [575] used a HeNe laser in the prevention of oral mucositis in patients undergoing bone marrow transplant in a double-blind randomised trial. Significant reduction of the radiation-induced oral mucositis was reported using a 60 mW HeNe laser.

Barasch [611] treated 20 patients subjected to bone marrow transplantation and receiving mucositis-inducing medications. One side of the mouth received HeNe laser irradiation, the other one sham irradiation. Oral mucositis and pain scores were significantly lower for the treated side compared with the untreated side.

In a double-blind phase III study by Bensadoun [929], 30 patients were about to receive radiotherapy for head and neck neoplasms. With conventional fractionation (2 Gy/day, 5 fractions per week), mucositis becomes evident in the third week of irradiation and progresses to confluent mucositis. The severity of mucositis is a major problem in head and neck radiotherapy. In this study, patients in the laser group received HeNe laser irradiation daily (Monday to Friday) during the seven weeks of radiotherapy, prior to each fraction. Nine points in the oropharyngeal area were irradiated, 2 J/cm^2. Except for the first week of treatment, daily grade of mucositis was higher in the non-laser group, the difference being statistically significant for weeks four, five, six and seven. In particular, the number of weeks in which patients had grade 3 mucositis was reduced. Pain was also reduced in the laser group and the ability to swallow improved.

The phase III randomised double-blind placebo-controlled study by Schubert [1805] was designed to compare the ability of 2 different wavelengths (650 nm and 780 nm) to prevent oral mucositis in HCT patients conditioned with chemotherapy or chemoradiotherapy. A total of 70 patients were enrolled and randomised into one of three treatment groups: 650 nm laser, 780 nm laser, or placebo. All active laser treatment patients received daily direct laser treatment to the lower labial mucosa, right and left buccal mucosa, lateral and ventral surfaces of the tongue, and floor of the mouth with energy densities of 2 J/cm^2. Study treatment began on the first day of conditioning and continued through the day +2 post HCT. Mucositis and oral pain were measured on days 0, 4, 7, 11, 14, 18, and 21 post HCT. The 650 nm wavelength reduced the severity of oral mucositis and pain scores, whereas the 780 nm laser group was less effective. LPT was well-tolerated and no adverse events were noted.

Antunes [1782] investigated the clinical effects of LPT on the prevention and reduction of severity of conditioning-induced oral mucositis (OM) for hematopoietic stem cell transplantation (HSCT). Altogether 38 patients who underwent autologous (AT) or allogeneic (AL) HSCT were randomised into groups. A laser at 660 nm, 50 mW, and 4 J/cm^2, measured at the fibreoptic end with 0.196 /cm^2 of section area was used. The evaluation of OM was done using the Oral Assessment Scale (OMAS) and the World Health Organ-

isation (WHO) scale. In the LPT group, 94.7% of the patients had an OM grade (WHO) lower than or equal to grade 2, including 63.2% with grade 0 and 1, whereas in the control group, 31.5% of the patients had an OM grade lower than or equal to grade 2 . Remarkably, the hazard ratio (HR) for grades 2, 3 and 4 OM was 0.41, and for grades 3 and 4 it was 0.07. By using OMAS to calculate the ulcerous area, 5.3% of the laser group presented ulcers from 9.1 /cm^2 to 18 cm^2, whereas 73.6% of the control group presented ulcers from 9.1 cm^2 to 18 cm^2.

It is interesting to compare the relatively modest result in the Schubert study to the results in the studies by Bensadoun and Antunes. Bensadoun used HeNe 2 J/cm^2, which was also the dose in the Schubert study. However, we believe that red diodes need higher dosage than HeNe, because of the short coherence length of the diodes. This assumption seems to be confirmed by Antunes, also using a red diode but at double the Bensadoun dose and with better results. [See ref. 1634, Qadri et al.]

A study by Cruz [1746] assessed the use of therapeutic laser in the prevention or reduction of the severity of oral mucositis. A randomised clinical trial was carried out. Patients from 3 to 18 years of age treated with chemotherapy or hematopoietic stem-cell transplantation were eligible. The intervention group received laser application (780 nm, 60 mW, 4 J//cm^2) for 5 days following the start of chemotherapy: Sixty patients were included for analysis; thirty-nine were males, 35 (58%) patients had a diagnosis of leukemia or lymphoma, and 25 had solid tumours. Twenty-nine patients were randomised in the laser group and 31 in the control group. On day 1, no patients presented mucositis. On day 8, out of the 20 patients who had developed mucositis, 13 of them were from the laser group and 7 from the control group. On day 15, a total of 24 patients had developed mucositis, 13 of them were from the laser group and 11 from the control group. There was no significant difference between groups concerning the grades of mucositis on day 8 or on day 15.

Although the dose of 4 J/cm^2 appears to be within the therapeutic window, it is not. The energy per point was only 0.18 J. The seemingly reasonable dose is achieved by using a very thin fibre.

In a study by Arun Maiya [1727], patients with carcinoma of the oral cavity with stages II-IV, being uniformly treated with a curative total tumour dose of 66 Gy in 33 fractions over six weeks, were selected for the study. The patients were divided based on computer generated randomisation into laser (study group) and control groups, with 25 patients in each group. Both study and control groups were comparable in terms of the site of the lesion, the stage of the cancer and the histology. The study group's patients were treated with HeNe laser, output of 10mW, and the control group's patients were given oral analgesics, local application of anaesthetics, 0.9% saline and povidine wash during the course of radiotherapy. All patients tolerated the laser treatment without any adverse effects or reactions. The result showed a significant difference in pain and mucositis between the two groups. At the end of *radiotherapy (after six weeks), mean pain score and mucositis grade were significantly lower in the study group compared to the control group.*

Migliorati [1195] used 780 nm 60 mW, 2 J/cm² in a group of 11 patients receiving high-dose chemotherapy and could confirm the pain relieving effect of LPT for this indication.

Figure 4.18 Typical mucositis
Courtesy: René-Jean Bensadoun

da Cuhna [1334] compared the effect of visible and infrared laser in patients who were undergoing radiotherapy. With 15 patients in each group, the effects of the two wavelengths were almost identical.

A study by Balakirev [1212] suggests that the application of LPT makes it possible to reduce the time needed for the management of radiation injuries and chemotherapy complications in paediatric patients 1.5-2-fold. It was shown that exposure to LPT caused mononuclear levels of donors' blood to rise, which in turn led to a release, in higher concentrations, of IL-1 and FNO cytokins, which are major factors of the immune response development.

A study by Durnov [1213] outlines the outcomes of treatment for complications associated with chemo- and radiation therapy in children with malignant neoplasms by using laser irradiation. The use of this therapy may reduce the duration of the treatment of these complications by 1.5-2 times. The use of therapeutic laser radiation in the treatment of other complications that are common in paediatric oncological care is briefly described.

In a study by Arora [1823], 24 hospitalised patients with oral cancer, scheduled to undergo radiotherapy were enrolled in the study and assigned to laser (Group I)/control group (Group II). They were treated using HeNe laser (10 mW, 1.8 J/cm²). Patients were subjected to treatment using a laser scanner for eight days and were subsequently treated using a laser probe at six anatomic sites in the oral cavity for five minutes each. The patients were evaluated on each day of treatment for pain severity (NRS), functional impairment (FIS), and oral mucositis (RTOG) and were followed until the end of cancer treatment. Statistical analysis was done using SPSS version 10. LPT applied prophylactically during radiotherapy could reduce the severity of oral mucositis, severity of pain, and functional impairment.

In a study by Abramoff [1472] patients undergoing chemotherapy (22 cycles) without mucositis were randomised into a group receiving prophylactic laser irradiation (group 1), and a group receiving placebo light treatment (group 2). Patients who already presented mucositis were placed in a group receiving irradiation for therapeutic purposes (group 3, with 10 cycles of chemotherapy). Serum granulocyte levels were taken and compared to the progression of mucositis. In group 1, most patients (73%) presented mucosi-

tis of grade 0 when compared with the placebo group, and 18% presented grade 1. In group 2, 27% had no mucositis and did not require therapy. In group 3, the patients experienced a marked pain relief (as assessed by a Visual Analogue Scale), and a decrease in the severity of mucositis, even when they had severe granulocytopenia.

In a study by Jaguar [1986], 24 patients received prophylactic laser therapy (L+ group). The applications started from the beginning of the conditioning regimen up to day +2. The oral assessment was performed daily until day +30. This group was compared with historical controls, namely 25 patients, who did not receive laser therapy (L- group). All patients developed some grade of mucositis. However, the L- group presented initial mucositis by 4.36 days, whereas the L+ group presented it in 6.12 days. The maximum mucositis occurred between day +2 and day +6 with healing by day +25 in the L- group, and between day +2 and day +7 with healing by day +14 for the L+ group. Laser therapy also reduced the time of oral pain from 5.64 to 2.45 days and decreased the consumption of morphine.

The study by Nes [1985] was performed as a clinical test with a sample consisting of 13 adult patients receiving oncology treatment. The patients were treated during a five-day period, and the pain was measured before and after each laser application. A 830 nm 250 mW laser was used. The energy given was 35 J/cm². There was a 67% decrease in the daily average experience of pain felt before and after each treatment, confirming that LPT can relieve pain among patients who have developed mucositis. The low number of COM patients at the hospital did not allow a control group to be included in the study, and therefore the results contain a potential placebo effect.

The study by Zanin [2037] included a total of 84 patients, divided into two groups: group (L): 43 patients with laser, group (C): 41 patients without laser. Area of irradiated tissue was considered as 1cm² per application point, in a contact mode. Irradiated regions were: three points in the jugal mucosa, three points in the internal mucosa of the inferior lip, three points on the soft palate, two points on the palatine folds, two points on the sublingual caruncles and five points on the tongue. Applications were given twice weekly, before or after radiotherapy sessions. Statistically significant differences were observed between the two studied groups (NCI scale). Patients in group (L) usually did not present OM. However, all patients in group (C) presented OM levels I to III. Patients in group (C) presented growing indexes of pain from the first week of Rt treatment. Patients in group (L) reported absence of pain during the whole radiotherapy treatment. LPT was effective in preventing and treating severe oral effects induced by radio and chemotherapy, controlling inflammation, maintaining mucosal integrity, bringing more comfort to patients, thus improving their quality of life.

A placebo-controlled randomised trial was carried out by Kuhn [2101], using LPT or placebo (sham treatment). Children and adolescents with cancer receiving chemotherapy or hematopoietic stem-cell transplantation were eligible as soon as they developed OM. Patients received interven-

tion for 5 days. The LPT group was treated with 830 nm, 100 mW, 4 J/cm^2, and the placebo group underwent sham treatment. The grade of OM was clinically assessed by the National Cancer Institute, Common Toxicity Criteria scale. Twenty-one patients developed OM and were evaluable for analysis; 18 (86%) patients had a diagnosis of leukemia or lymphoma and 3 (14%) had solid tumours. The mean age was 8.2 (+/-3.1) years. Nine patients were randomised in the laser group and 12 in the placebo-control group. Once OM was diagnosed, the patients had daily OM grading assessments before laser or sham application and thereafter until complete healing of the lesions. On day 7 after OM diagnosis, 1/9 of patients remained with lesions in laser group and 9/12 of patients in the placebo-control group. In the laser group, the mean of OM duration was 5.8+/-2 days and in the placebo group was 8.9+/-2.4 days.

The aim of a study by Simões [2120] was to verify how LPT used for oral mucositis could influence xerostomia symptoms and hyposalivation of patients undergiong RT. Patients were divided into two groups: 12 individuals receiving three laser irradiations per week (G1) and 10 patients receiving one laser irradiation per week (G2). A diode laser (660 nm, 6 J/cm(2), 0.24 J, 40 mW) was used until completely healing of the lesions or the end of the RT. At the first and last laser sessions, whole resting and stimulated saliva were collected, and questionnaires were administered. According to Wilcoxon and Student statistical test, xerostomia for G1 was lower than for G2, and salivary flow rate was no different before and after RT, except for stimulated collection of G2, which was lower. These results suggest that LPT can be beneficial as an auxiliary therapy for hypofunction of salivary glands.

In a review of the literature, Bjordal [2094] comes to the following conclusion:

1. There is moderate evidence of a dose-dependent LPT effect which is significantly better than placebo in relieving pain and severity of oral mucositis.

2. The use of J/cm^2 causes confusion and should be substituted with energy doses in Joules. Wavelengths of 632-685 nm and 810-830 nm should be preferred.

3. Optimal procedures should cover all of the oral lesions with irradiation exceeding 30 seconds/1-4 Joules per point, placed 1-2 cm apart. Treament sessions should be performed 3-5 days per week before, or during chemotherapy.

A literature review [2115] revealed 33 potentially relevant papers. Of these, nine studies were reviews and six studies were case studies, while another three were animal studies. Three controlled studies were excluded for lack of randomisation, while one study lacked a placebo-control group. The final sample consisted of 11 randomised placebo-controlled trials published from 1997 until 2009 with a total of 415 patients. The analysed papers confirm that there is moderate to strong scientific evidence for the use of LPT to treat mucositis.

The study by Arbabi-Kalati [2247] was undertaken to evaluate the effect of LPT on the prevention of mucositis, xerostomia and pain as a result of chemotherapy. The subjects in this double-blind randomised controlled study were 24 adult patients who underwent chemotherapy. The results showed that LPT was able to decrease the effect of chemotherapy on oral mucositis, xerostomia and pain in a variety of malignancies.

In a review article Zimin [2125] writes: Although low-power visible (VIS) and near infrared (nIR) radiation emitted from lasers, photodiodes, and other sources does not cause neoplastic transformation of the tissue, these phototherapeutic techniques are looked at with a great deal of caution for fear of their stimulatory effect on tumour growth. This apprehension arises in the first place from the reports on the possibility that the proliferative activity of tumour cells may increase after their in vitro exposure to light. Much less is known that these phototherapeutic modalities have been successfully used for the prevention and management of complications developing after surgery, chemo- and radiotherapy. The objective of the present review is to summarise the results of applications of low-power visible and near infrared radiation for the treatment of patients with oncological diseases during the last 20-25 years. It should be emphasised that 2-4 year-long follow-up observations have not revealed any increase in the frequency of tumour recurrence and metastasis.

A triple blinded study by Gautam [2285] randomised 220 HNC patients scheduled for CRT into laser (110) and placebo (110) groups. The laser group received LPT (HeNe, 24 mW/cm^2, energy = 3.0 J at each point, total dose/session=36-40 J, spot size 1 cm^2, irradiation time/point 125 s) before each radiation session, while the placebo group did not receive laser therapy. Results analysis revealed that OMWQ-HN and FACT-HN scores were significantly lower in LPT than placebo group patients. Also, a significant reduction in incidence of severe OM, need for opioid analgesics, and total parenteral nutrition was observed.

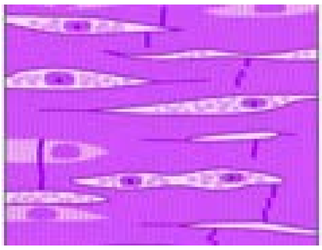
No negative side effects of LPT for this indications are reported, but as pointed out by Mourão e Lima [2338], there are on the other hand no studies confirming the absolute safety.

A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology [2384]. The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. Based on the evidence level, one of the following three guideline determinations was possible: recommendation, suggestion, and no guideline possible. A new recommendation was made for low-level laser (wavelength at 650 nm, power of 40 mW, and each square centimetre treated with the required time to a tissue energy dose of 2 J/cm^2 (2 s/point) for the prevention of oral mucositis in adult patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation. A new suggestion was made for low-level laser (wavelength around 632.8 nm) for *the prevention of oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer. No guideline was possible in other populations and for other light sources due to insufficient evidence. The increasing evidence in favour of LPT allowed for the development of two new guidelines supporting this modality in the populations listed above. Evidence for other populations was also generally encouraging over a range of wavelengths and intensities.*

The study by Ottaviano [2437] shows that a "Class IV laser", i.e. a 970 nm laser of 5 W can treat oral mucositis. ***So far so good, but the presentation is clearly very biased, implying that high powered lasers are more effective for oral mucositis than "Class 3B" lasers. The authors claim to have been using a "standard 3B laser protocol" for comparison. In fact, they have not. The "standard" laser used is a 635 nm diode of 2.5 mW, delivering 0.45 J per point and delivered from a distance of 1 - 3 cm, further reducing the power density and for some reason pulsed. In spite of this, the authors refer to the review by Bjordal [2115] where 10 - 60 mW and 3 J per point is recommended. This is clearly a study to distrust. Where were the reviewers?***

Further literature: [2, 3, 47, 371, 564, 978, 979, 980, 1072, 1073, 1076, 1133, 1176, 1483, 1485, 1728, 2432]

4.1.37 Muscle regeneration



LPT has the ability to stimulate muscular regeneration in areas of trauma, even in cases of snake bites. The therapy can also improve muscular strength [1468] and reduce muscular fatigue.

Literature:

In vitro studies

Schwartz [626] found a transient elevation of intracellular calcium in the myotubes immediately after irradiation, using HeNe laser light at 3-10 J/cm^2. These findings suggest the hypothesis that transient changes in calcium may accelerate the release of cytokines from the myotubes.

Shefer [1243] has demonstrated that HeNe laser can stimulate cell cycle entry and the accumulation of satellite cells around isolated single fibres, grown under serum-free conditions. It is demonstrated that LPT promotes the survival of muscle fibres and their adjacent cells, as well as cultured myogenic cells, under serum-free conditions that normally lead to apoptosis.

Animal studies

Lievens [521] summarises a study on the effects of LPT on muscle regeneration as follows: The effect of GaAs, 904 nm, laser irradiation on the process of skeletal muscle regeneration after simple injuries to the tibialis anterior muscle of mice is studied histologically and statistically. The right-hand side injured zones in the experimental mice were subjected to one direct nuclear magnetic resonance technique laser irradiation for three minutes daily, starting on the first day post injury. The left-hand side injuries were left untreated and served as a control. Morphometric analysis was performed on histological sections of injured areas on days 7 and 18 post injury. On day 7 post injury, mononucleated cells populated most of the injured area. Thereafter, their proportion decreased gradually but more rapidly in the laser-irradiated muscles than in those on the control side. The early myotubes were evident in the control side, while they were less evident in the experimental side. The injured area was populated by myotubes in the experimental muscles, while they were less evident in the control side. On day 18 post injury, the process of muscle regeneration was almost completed in the laser-irradiated muscles. In the untreated muscles, myotubes still populated a large part of the injured zone, and there were less regenerated myofibres. It is concluded that the process of muscle regeneration is promoted when the injured area is exposed to GaAs-laser irradiation, following injury to the tibialis anterior muscle of mice.

In a study by Amaral [665], 15 mice received a single muscular injection of myotoxin in the tibialis anterior muscle of both legs. One group received HeNe laser irradiation with a dose of 2.6 J/cm^2, another 8.4 J/cm^2 and a third 25 J/cm^2 on one leg, while the other was sham irradiated. The 2.6 J group showed a significant difference, with evidence of a greater concentration of mitochondria in the treated muscle, whereas the higher doses did not produce this effect. The laser treated mice showed an increase of the cross-section area of the muscle fibres.

Popova [147] studied the effects of a HeNe laser on the healing of muscle tissue after irradiation with 10 Gy X-ray. The muscle tissue of rats was removed, irradiated with X-rays and re-transplanted. Improved healing compared with the control group was observed whether laser light was administered before or after the transplant.

Weiss [276] and Bibikova [277], in experiments on rats and toads respectively, observed improved muscle regeneration as a result of the use of HeNe and GaAs lasers.

Oliveira [1186] failed to find such regeneration in a rodent experiment using GaAs, 1.5 mW, with 3 or10 J/cm^2 daily irradiations over intact skin. Although there was no effect on the muscular regeneration, the body weight of the mice was increased in the 10 J/cm^2 group.

Buliakova [570] found that HeNe laser indeed accelerated the regenerative process in crosscut gastrocnemius muscles of adult guinea pigs. However, the regenerating muscle tissue did not connect the two muscle stumps; a narrow connective tissue scar being formed instead. The same *experiment on rats was more successful, so it is likely that the regenerative ability of LPT depends on the species' peculiarities.*

Ramos [1477] treated four groups of rats with HeNe laser. The constriction potential of the anterior tibial muscle was recorded. Only animals with atrophic muscles showed any effect of the therapy.

The aim of a study by Avni [1601] was to investigate the effect of LPT on ischemic-reperfusion (I-R) injury in the gastrocnemius muscles of rats. Ischemic injury in skeletal muscles is initiated during hypoxia and aggravated by reoxygenation during blood reperfusion and accumulation of cytotoxic reactive oxygen superoxides. The injury was induced in the gastrocnemius muscles of 106 rats by complete occlusion of the blood supply for three hours, followed by reperfusion. Another group of intact rats served to investigate the effect of LPT on intact non-ischemic muscles. Creatine phosphokinase, acid phosphatase, and heat shock protein were determined seven days after I-R injury and antioxidant levels two hours after reperfusion. Laser irradiation (810 nm) was applied to the muscles immediately and one hour following blood supply occlusion. It was found that laser irradiation markedly protects skeletal muscles from degeneration following acute I-R injury. This was evident by a significantly higher content of creatine phosphokinase activity and lower activity of acid phosphatase in the laser-treated muscles, relative to the injured non-irradiated ones. The content of antioxidants and heat shock proteins was also higher in the laser-treated muscles, relative to that of injured non-irradiated muscles. The present study describes for the first time the ability of LPT to significantly prevent degeneration following ischemia/reperfusion injury in skeletal muscles, probably by induction of synthesis of antioxidants and other cytoprotective proteins, such as hsp-70i. The elevation of antioxidants was also evident in intact muscles following laser irradiation. The above phenomenon may also be of clinical relevance in scheduled surgery or microsurgery requiring extended tourniquet applications to skeletal muscles followed by reperfusion.

The purpose of the study by Rizzi [1731] was to investigate the effects of LPT on nuclear factor kappa B (NF-kappaB) activation and inducible nitric oxide synthase (iNOS) expression in an experimental model of muscle trauma. The injury to the gastrocnemius muscle in the rat was produced by a single impact blunt trauma. A GaAs laser, 45 mW, and 5 J/cm^2 was applied for 35 seconds continuously. Histological abnormalities with an increase in collagen concentration, and oxidative stress, were observed after trauma. This was accompanied by activation of NF-kappaB and upregulation of iNOS expression, whereas protein concentration of I kappa B alpha decreased. These effects were blocked by LPT. The associated reduction of iNOS overexpression and collagen production suggest that the NF-kappaB pathway may be a signalling route involved in the pathogenesis of muscle trauma.

The purpose of a study by Prado [1732] was to develop an experimental model to be used in the study of low LPT on viability of random skin flaps *in rats. The sample was 24 rats. The random skin flap measured 10 x 4 cm and a plastic sheet was interposed between the flap and donor site. Group 1 (control) underwent sham irradiation. Group 2 was submitted to laser irradiation with a diode laser (830 nm). The animals were submitted to LPT with a 36 J/cm^2 energy density (72 seconds) immediately after surgery and on four subsequent days. The probe was usually held in contact with the skin flap surface on a point at 2.5 cm cranial from the flap base. On the seventh post-operative day, the percentage of necrotic area was measured and calculated. Group 1 reached an average necrotic area of 48.86%, Group 2 - 23.14%.*

A study by Cressoni [2012] aimed to investigate the effects of LPT on muscle regeneration. For this purpose, the anterior tibialis muscle of 48 male Wistar rats received treatment (785 nm) after a surgically-induced injury. The animals were randomised into four groups: uninjured rats (UN); uninjured and laser-irradiated rats (ULI); injured rats (IN); and injured and laser-irradiated rats (ILI). The direct contact laser treatment started 24 h after surgery. A laser emitting 75 mW of continuous power at 785 nm was used for irradiation. The laser probe was placed at three treatment points to deliver 0.9 J per point, for a total dose of 2.7 J per treatment session. The animals were euthanised after treatment sessions one, two and four. Mounted sections were stained with hematoxylin and eosin and used for quantitative morphological analysis, in which the number of leukocytes and fibroblasts were counted over an area of 4480 mum2. Quantitative data showed that the number of both polymorphonuclear and mononuclear leukocytes in the inflammatory infiltrate at the injury site was smaller in the ILI(1), ILI(2), and ILI(4) subgroups compared with their respective control subgroups (IN(1), IN(2), and IN(4)) for sessions one, two and four, respectively. On the other hand, the number of fibroblasts increased after the fourth treatment session. With regard to the regeneration of muscle fibres following injury, only after the fourth treatment session was it possible to find muscle precursor cells such as myoblasts and some myotubes in the ILI(4) subgroup. Thus, in the acute inflammatory phase, the laser treatment was found to have anti-inflammatory effects, reducing the number of leukocytes at the injury site and accelerating the regeneration of connective tissue.

The sciatic nerve-gastrocnemius muscles of 35 frogs were prepared in an experiment by Komatsu [1941]. In Experiment 1, continuous stimulation for gastrocnemius contraction was delivered to the sciatic nerve (10 minutes); the experimental group simultaneously received LPT. In Experiment 2, two sets of stimulation and cessation (2 minutes each) were repeated after the initial stimulation period (2 minutes); the experimental group received LPT during the resting period. In Experiment 1, 60 mW significantly facilitated an attenuation of AMP and maintained a smaller prolongation of CP, whereas 100 mW significantly influenced a retardation of AMP attenuation and LAT prolongation. In Experiment 2, 100 mW significantly influenced AMP attenuation and LAT prolongation by retardation; almost no effects were obtained in the case of 60 mW. These results suggest that 808 nm LPT *influences both synaptic signal transmission at the neuromuscular junction and excitation-contraction coupling in the muscle fibres, but not the relaxation process. The authors conclude that LPT at relatively high doses can influence muscles by retarding AMP attenuation and LAT prolongation.*

Elderly people suffer from skeletal muscle disorders that undermine their daily activity and quality of life; some of these problems can be listed as but not limited to: sarcopenia, changes in central and peripheral nervous system, blood hypoperfusion, regenerative changes contributing to atrophy, and muscle weakness. Determination, proliferation and differentiation of satellite cells in the regenerative process are regulated by specific transcription factors, known as myogenic regulatory factors (MRFs). In the elderly, the activation of MRFs is inefficient which hampers the regenerative process. Recent studies found that LPT has a stimulatory effect in the muscle regeneration process. However, the effects of this therapy when associated with aging are still unknown. The study by Vatansever [2312] aimed to evaluate the effects of 830 nm on the tibialis anterior (TA) muscle of aged rats. The total of 56 male Wistar rats formed two population sets: old and young, with 28 animals in each set. Each of these sets were randomly divided into four groups of young rats (3 months of age) with n=7 per group and four groups of aged rats (10 months of age) with n=7 per group. These groups were submitted to cryoinjury + laser irradiation, cryoinjury only, laser irradiation only and the control group (no cryoinjury/no laser irradiation). The laser treatment was performed for 5 consecutive days. The first laser application was done 24 h after the injury (on day 2) and on the seventh day, the TA muscle was dissected and removed under anesthesia. After this the animals were euthanised. Histological analyses with toluidine blue as well as hematoxylin-eosin staining (for counting the blood capillaries) were performed for the lesion areas. In addition, MyoD and VEGF mRNA was assessed by quantitative polymerase chain reaction. The results showed significant elevation in MyoD and VEGF genes expression levels. Moreover, capillary blood count was more prominent in elderly rats in laser irradiated groups when compared to young animals. In conclusion, LPT increased the maturation of satellite cells into myoblasts.

The aim of the study by Paiva-Oliveira [2426] was to investigate the effects of 904 nm in the repair process of skeletal muscle tissue. Swiss mice were submitted to cryoinjury and divided in test (LPT-treated) and control groups. Histological sections were stained with hematoxylin-eosin to assess general morphology and inflammatory influx, and Picrossirus to quantify collagen fibres deposition. The results showed significant reduction in inflammatory infiltrated in irradiated mice after 4 days of treatment compared to control. After 8 days, the irradiated group showed high levels at regenerating myofibres with significant statistically differences in relation at control group. Collagen deposition was significantly increased in the final stages of regeneration at test group, when compared with control group.

Satellite cells, angiogenesis and growth factors play important roles in the regeneration of muscle. The objective of the study by Nagano [2455] was to examine the effect of LPT on rat gastrocnemius muscle recovering from disuse muscle atrophy. Eight-week-old rats were subjected to hindlimb suspension for 2 weeks, after which they were released and recovered. During the recovery period, rats underwent daily irradiation (830 nm; 60 mW; total 180 s) to the right gastrocnemius muscle through the skin. The untreated left gastrocnemius muscle served as the control. In conjunction with LLL irradiation, 5-bromo-2-deoxyuridine (BrdU) was injected subcutaneously to label the nuclei of proliferating cells. After 2 weeks, myofibre diameters of irradiated muscle increased in comparison with those of untreated muscle, but did not recover back to normal levels. Additionally, in the superficial region of the irradiated muscle, the number of capillaries and fibroblast growth factor levels exhibited significant elevation relative to those of untreated muscle. In the deep region of irradiated muscle, BrdU-positive nuclei of satellite cells and/or myofibres increased significantly relative to those of the untreated muscle. The results of this study suggest that LLL irradiation can promote recovery from disuse muscle atrophy in association with proliferation of satellite cells and angiogenesis.

A study by Rochkind [2469] was designed to assess the status of skeletal muscles after laser treatment during long-term denervation processes, by investigating changes in the level of acetylcholine receptors (AChR) and creatine kinase (CK) activity in the denervated gastrocnemius muscle of the rat. The study was conducted on 96 rats: 48 that received laser treatment and 48 untreated controls. The gastrocnemius muscle was denervated by removing a 10 mm segment of the sciatic nerve. Low power laser irradiation was delivered transcutaneously to the right gastrocnemius muscle (HeNe, 30 mW, 30 min) for 14 consecutive days. Under general anaesthesia, the rats were euthanised at seven time points: day 7 (n=10), day 14 (n=10), day 21 (n=10), day 30 (n=5), day 60 (n=4), day 120 (n=5), and day 210 (n=4), with and without laser treatment, respectively. Laser treatment had a significant therapeutic effect on the denervated muscle during the first 21 days for AChR and the first 30 days for CK activity. In the early stages of muscle atrophy, laser phototherapy may preserve the denervated muscle by maintaining CK activity and the amount of AChR.

Yonezu [2475] examined in an in vivo animal model whether LPT affects both muscle tension and muscle hardness in a wavelength-dependent manner, using the rat gastrocnemius muscle. Forty adult rats were used. Under pentobarbital sodium anaesthesia, their gastrocnemius muscle and tibial nerve were exteriorised. Diode systems delivering 3 wavelengths (405, 532, and 808 nm; 100 mW output) were used. Ten sets of tetanus (tetanic contractions) were delivered to the tibial nerve followed by a brief rest or LPT for 15 s and an additional 7 sets of tetanus with an inter-stimulus interval of 5 min. The muscle tension and muscle hardness were measured with a tension transducer and hardness meter, respectively. 405 nm did not influ-

ence either muscle tension or hardness. 532 nm significantly improved the maintenance of muscle tension compared with the 808 nm group. In contrast, 808 nm significantly improved the recovery from muscle hardness compared with the other groups. It is concluded that LPT has wavelength-dependent effects on the gastrocnemius muscle and at appropriate wavelengths and dosimetry offers potential in the treatment to relieve muscle tension or stiffness.

Clinical studies

Leal Junior [2006] investigated if the development of skeletal muscle fatigue during repeated voluntary biceps contractions could be attenuated by LPT. Twelve male professional volleyball players were entered into a randomised double-blind placebo-controlled trial for two sessions (on day one and day eight) at a one-week interval, with both groups performing as many voluntary biceps contractions as possible, with a load of 75% of the maximal voluntary contraction force (MVC). At the second session on day eight, the groups were either given LPT (655 nm) of 5 J at an energy density of 500 J/cm^{2,} administered to each of four points along the middle of the biceps muscle belly, or placebo LPT in the same manner immediately before the exercise session. The number of muscle contractions with 75% of MVC was counted by a blinded observer and the blood lactate concentration was measured. Compared to the first session (on day one), the mean number of repetitions increased significantly by 8.5 repetitions (+/- 1.9) in the active LPT group at the second session (on day eight), while in the placebo LPT group the increase was only 2.7 repetitions (+/- 2.9) (p=0.0001). At the second session, blood lactate levels increased from a pre-exercise mean of 2.4 mmol/L to 3.6 mmol/L in the placebo group, and to 3.8 mmol/L in the active LPT group after exercise, but this difference between groups was not statistically significant. It is concluded that LPT appears to delay the onset of muscle fatigue and exhaustion by a local mechanism in spite of increased blood lactate levels.

The study by Leal Junior [2428] aimed at investigating if LPT can affect biceps muscle performance, fatigue development, and biochemical markers of postexercise recovery. Nine healthy male volleyball players participated in the study. They received either active LPT (cluster probe with 5 laser diodes; 810 nm; 200 mW; 30 seconds of irradiation, applied in 2 locations over the biceps of the nondominant arm; 60 J of total energy) or placebo LPT using an identical cluster probe. The intervention or placebo were applied 3 minutes before the performance of exercise. All subjects performed voluntary elbow flexion repetitions with a workload of 75% of their maximal voluntary contraction force until exhaustion. Active LPT increased the number of repetitions by 14.5% and the elapsed time before exhaustion by 8.0% when compared to the placebo treatment. The biochemical markers also indicated that recovery may be positively affected by LPT, as indicated by postexercise blood lactate levels, creatine kinase activity and C-reactive pro-

tein levels, showing a faster recovery with LPT application prior to the exercise. It is concluded that pre-exercise irradiation of the biceps with an LPT dose of 6 J per application location, applied in 2 locations, increased endurance for repeated elbow flexion against resistance and decreased postexercise levels of blood lactate, creatine kinase, and C-reactiveprotein.

The aim of the study by Dos Santos Maciel [2474] was to investigate the effect of LPT on the tibialis anterior muscle of regular physical activity practitioners by electromyographic, biomechanical, and biochemical (lactate) analysis. Double-blind controlled clinical trials were conducted with 12 healthy females, regular physical activity practitioners, between 18 and 30 years. The LPT application (780 nm, 30 mW, 0.81 J/point, beam area of 0.2 cm^2 , 27 s, approximately 29 points) in the tibialis anterior muscle occurred after the delimitation of the points on every 4 cm2 was held. It was observed that (a) a significant torque increase post-LPT compared to the values after placebo therapy at the beginning of resistance exercise, (b) both muscle torque (isokinetic) and median frequency (EMG) showed a faster decay of the signals collected after placebo and laser treatment when compared to control values, (c) no significant change in torque in the strength test of five repetitions, (d) a significant muscle activity decrease after laser therapy compared to control values, and (e) an increase in lactate levels post-LPT after 30 min of exercise. It is concluded that the LPT increased the muscle torque at the beginning of the exercise and maintained the levels of lactate after resistance exercise. Therefore, the LPT with the parameters used in this study can be utilised in rehabilitation to improve muscle performance in elite athletes.

Leal-Junior [2475] performed a systematic review with meta-analysis to investigate the effects of phototherapy applied before, during and after exercises. A literature search was performed in Pubmed/Medline database for randomised controlled trials (RCTs) published from 2000 through 2012. Trial quality was assessed with the ten-item PEDro scale. Main outcome measures were selected as: number of repetitions and time until exhaustion for muscle performance, and creatine kinase (CK) activity to evaluate risk for exercise-induced muscle damage. The literature search resulted in 16 RCTs, and three articles were excluded due to poor quality assessment scores. From 13 RCTs with acceptable methodological quality (>/=6 of 10 items), 12 RCTs irradiated phototherapy before exercise, and 10 RCTs reported significant improvement for the main outcome measures related to performance. The time until exhaustion increased significantly compared to placebo by 4.12 s and the number of repetitions increased by 5.47 after phototherapy. Heterogeneity in trial design and results precluded meta-analyses for biochemical markers, but a quantitative analysis showed positive results in 13 out of 16 comparisons. The most significant and consistent results were found with red or infrared wavelengths and phototherapy application before exercises, power outputs between 50 and 200 mW and doses of 5 and 6 J per point (spot). The analysis concludes that phototherapy (with lasers and

LEDs) improves muscular performance and accelerate recovery mainly when applied before exercise.

A review article on photoengineering of tissue repair in skeletal and cardiac muscles is written by Oron [1682].

Further reading: chapter 4.1.49 "Snake bites" on page 386, chapter 4.1.16 "Delayed onset muscular soreness (DOMS)" on page 249.

Further literature: [356, 533, 587, 616, 702, 916, 1327]

4.1.38 Mycosis

Literature:

Paracoccidioidomycosis (PCM) is the most prevalent human mycosis in Latin America. The infection is thought to take place firstly in the lungs and then possibly disseminate to other organs and tissues. Treatment by currently available antifungals is lengthy, the drugs may have undesirable side effects, and some are costly. Occasional resistant strains of Paracoccidioides brasiliensis, the causative agent of PCM, have been reported. Therefore, the search for more efficient treatments or adjuvant therapies has to be continued. In the work by Ferreira [1848], the author evaluated the effects of HeNe laser irradiation on cutaneous inflammatory lesions caused by the inoculation of 5 × 106/0.1 ml yeasts cells into the back footpad of Balb/c mice. HeNe irradiation (3 mW, 3 J/cm^2) was applied on days seven, eight and nine post-infection, and histological and immunohistochemical analyses were done. Un-irradiated animals were used as controls. The results showed that laser-treated mice presented a reduction of footpad oedema, faster cutaneous wound healing, confluent granuloma, diffuse- and more loosely distributed immunolabeling of TNF-alpha, enhanced labeling of IFN-gamma and any P. brasiliensis form detected, whereas multiple viable fungi were seen in diffuse widespread granulomas obtained from non-treated mice foot-pads. Fungi that was harvested from laser-treated animals presented no capability of growth in vitro as compared to those obtained from non-treated mice. The authors conclude that HeNe laser irradiation was able to inhibit the progress of inflammatory local reaction produced by P. brasiliensis infection and influence local cytokines production. It is suggested that this treatment modality can be a useful coadjuvant tool to be combined with antifungal agents in the treatment of PCM ulcerations.

Further literature: [1909]

4.1.39 Nerve conduction

Literature:

Wakabayashi [190] demonstrated that C-fibres play a part in the analgesic effect of LPT. A small hole was drilled in the mandibular incisor of a rat through which a probe made contact with the dental pulp. The incisor was stimulated electrically and the subsequent action potential was registered through a probe from the ipsilateral trigeminal caudal neurons. A 830 *nm laser was used to irradiate the incisor's cervical surface. The rate of firing discharges and the number of spikes evoked in the caudal neurons before and after laser treatment were compared. LPT suppressed the late discharges in the response of the caudal neurons which were evoked by excitatory inputs from C-fibre afferents, but did not suppress the early discharges evoked by inputs from A-delta-fibre afferents. This indicates that GaAlAs irradiation inhibited the excitation of unmyelinated fibres of the pulp without affecting fine myelinated fibres. It is suggested that LPT has a suppressive effect on injured tissue by blocking the depolarisation of the afferent C-fibres.*

Ohno [719] demonstrated that laser irradiation suppresses the excitation of the unmyelinated C-fibres in the afferent sensory pathway. Substance P in the rat spinal dorsal root ganglion was measured after electrical stimulation of the sciatic nerve.

The involvement of afferent unmyelinated A-delta fibres in LPT pain attenuation has been demonstrated by Kasai [488]. High threshold evoked responses were reduced by 9% to 19% during LPT irradiation in experimental animals. The data in this study suggest that low-power laser acts as a reversible direct suppressor of neuronal activity

In a study by Tsuchiya [519], a GaAlAs laser reduced the action potentials in the dorsal roots elicited from the saphenous nerve of a rat. The amplitude of slower conduction parts of action potentials (velocity <12 m/s) was suppressed. The suppression was time-dependent. After three minutes of irradiation, the slowest velocity group (<1.3 m/s) was totally diminished and the 1.3-12 m/s group was reduced by 12-67%. In contrast, faster components (>12 m/s) were unaffected.

Balaban [650] concludes that HeNe laser does not affect silent neurons. However, when the spontaneously active neurons, generating spikes every 7-10 minutes, were irradiated in between their spontaneous spikes, the depolarisation of membrane and the generation of action potentials occurred as a function of light intensity.

Walsh [977] irradiated the skin overlying the human right superficial radial nerve in healthy individuals at three points (1.2 J per point, energy density 9.55 J/cm^2, 830 nm, 50 mW). Antidromic action potentials were recorded from the nerve prior to irradiation and at 5, 10 and 15 minutes after irradiation. There were no differences between the placebo laser group, the control group or the active laser groups regarding negative peak latency or skin temperature. Pulsing at 8, 12 or 73 Hz made no difference.

4.1.40 Nerve regeneration and function

The regeneration of damaged nerves is one of the most promising indications for LPT. Studies on Bell´s palsy are difficult to evaluate, bearing in mind the high spontaneous remission rate. However, the rapid pain relief is a good verification of the laser effect. The swelling and the neuritis in the bony fallopian canal is believed to be influenced. This intrabony region is the major target for LPT in this indication. The suspected association with herpes viruses also supports the use of LPT. See also 4.1.47 Trigeminal neuralgia.

Literature:

In vitro studies:

van Breugel [353] investigated HeNe laser irradiation effects on proliferation and laminin production of rat Schwann cells in vitro. Schwann cell (SwC) proliferation is an essential part of Wallerian degeneration after nerve damage, and thus a prerequisite for regeneration. HeNe irradiation in vitro showed a dose-related stimulation of SwC proliferation. Laminin production was not affected.

Mulligan [354] investigated the effect of HeNe laser irradiation on neurite elongation in vitro. Doses around 1.5 J/cm^2 were given to a rat neuronal clonal cell line for 5, 15, 30, 45 and 60 minutes. Neurite outgrowth was greater than that in the control for all groups, but only the 15 and 30 minute groups were statistically different from the control values.

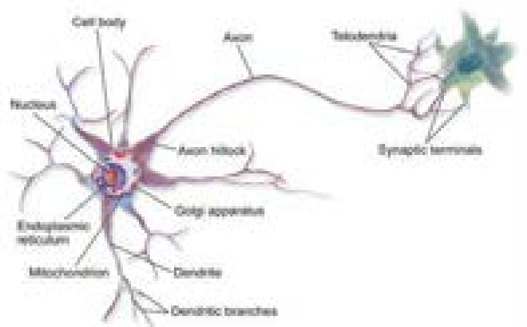
Wollman [537] irradiated foetal brain cells in vitro using a HeNe laser. One single dose enhanced the appearance of brain cells around the treated aggregates. Two and three doses were correlated with 97% and 142% increases respectively. Rhodamine-labelled antibodies bound to receptors on cells indicated a massive neurite sprouting and an outgrowth of migrating brain cells in culture.

In a study by Rochkind [1236], embryonal spinal cord nerve cells dissociated from rat fetuses, cultured in biodegradable microcarriers and embedded in hyaluronic acid, were implanted in the completely transsected spinal cords of 24 adult rats. Altogether 15 rats underwent 14 days of consecutive laser irradiation (780 nm, 250 mW, 30 minutes daily), while 7 rats received the same treatment but without laser. Out of the 15 laser treated rats, 11showed different degrees of active leg movements and gait performance compared to 4 of the 9 rats with implantation alone. In a control group of 7 rats with no therapy after the transsection of the spinal cord, 6 remained completely paralysed. Intensive axonal sprouting occurred in the laser group. In the control group, the transsected area contained proliferating fibroblasts and blood capillaries only.

In a study by Jimbo [835], the effects of 830 nm, 16.2 mW laser irradiation on the distal portion of the processes of cultured murine dorsal root ganglion (DRG) neurons associated with C-fibres was studied by patch-clamp whole-cell recording of membrane potentials at the cell body. The chemical as well as the laser light stimulation were limited to the processes of the neuron isolated from the cell body by a separator. The action potentials elicited by bradykinin (BK) in the cell body were reversibly suppressed by the irradiation of laser light. The laser irradiation may block the conduction of nociceptive signals in primary afferent neurons.

The aim of a study by Oron [1872] was to investigate whether GaAs laser irradiation can enhance adenosine triphosphate (ATP) production in *normal human neural progenitor (NHNP) cells in culture. NHNP cells were grown in tissue cultures and treated by a GaAs laser (808 nm, 50 mW/cm^2, 0.05 J/cm^2), and ATP was determined 10 min after laser application. The quantity of ATP in laser-treated cells was 7513 ± 970 units, which was significantly higher than in the non-treated cells, which comprised 3808 ± 539 ATP units. Laser application to NHNP cells significantly increases ATP production in these cells.*

Previously, Anders [2040] reported that 810 nm light was the optimal wavelength in the differentiation of normal human neural progenitor cells (NHNPC). Various combinations of dosimetry and power density for 810 nm were evaluated using in vitro NHNPC. NHNPC were placed into one of three treatment groups, two slides per group: 1) Control (no factors, no light); 2) Factors (no light); and 3) 810 nm Light Treated (spot size 0.78cm^2). The 810 nm Light Treated group consisted of four subgroups: 1) 0.01 J/cm^2 dose: 1, 5 and 19 mW/cm^2; 2) 0.05 J/cm^2 dose: 1, 5, 15, 19, 25, and 50 mW/cm^2; 3) 0.2 J/cm^2 dose: 1, 5, 15, 19, 25, and 50 mW/cm^2; and 4) 1 J/cm^2 dose: 1, 5, 15, 19, 25, and 50 mW/cm^2. NHNPC were treated for three consecutive days and the cells were killed on day seven with 4% paraformaldehyde. Images of 20 random neurospheres per group were captured digitally and assayed for differentiation by determining neurite numbers and length. The total neurite length for all neurites per neurosphere was determined and averaged per group. The data was analysed using one way ANOVA with Tukey Post tests. Based on this data, the total neurite length per neurosphere increased as power densities (19-50 mW/cm^2) and dosages (0.05-1J/cm^2) increased. A low power density (1-15 mW/cm^2) did not have an effect on the total neurite length. These data suggest that there is not one optimal combination of dose and power density, but rather an optimal window of effective combinations of dose and power density for a given wavelength. The same combinations of dosimetry and power density are currently being evaluated for other wavelengths (both continuous wave and pulsed).



Animal studies

The aim of a study by Bae [1489] was to determine if GaAs laser treatment stimulates the regeneration process of damaged nerves. A standardised crush to the sciatic nerve was applied to cause extensive axonal degeneration. After this procedure, low-power infrared laser irradiation was administered transcutaneously to the injured sciatic nerve, three minutes daily to each of four treatment groups for one, three, five and seven weeks, respectively. A nerve conduction study was done, and a morphological assessment was performed using both light and electron microscopy. With a trauma to the nerve, both the amplitude of the compound motor action potential and the nerve conduction velocity decreased significantly compared to the pre-trauma state. Morphologically, the numbers of myelinated axons and degenerated axons decreased and increased, respectively, compared with the control. Typical aspects were an onion skin-type lamellation, fragmentation,oedematous swelling and rarefaction in the myelin sheath. All these parameters recovered almost to the level of the pre-trauma state with laser irradiation, in direct proportion to the time spent for treatment.

Walker [89] and Tsai [90] achieved results which indicate that the central nervous system is photosensitive. Wu [187] conducted Walker's experiment again on a larger scale, but was unable to confirm the results.

Rochkind [32] has carried out extensive studies on the effects of HeNe laser light on nerve damage. In one experiment, the sciatic nerves of rats were exposed and crushed in a standardised fashion. After suturing, HeNe laser light was administered transcutaneously. The effects were monitored at intervals of 1 to 360 days. In the experimental group, action potential was at a high level, while in the control group (no laser treatment) it was very low. This effect was only achieved if the laser treatment was administered immediately after the injury - when it was given 3 and 7 days afterwards, there was no difference as compared to the control group.

In another rodent study [1131], the sciatic nerves in rats were crushed in a standardised fashion and HeNe laser irradiation was performed directly after suturing. The irradiation was performed over the corresponding segment of the spinal cord and not over the crushed area. LPT was performed for 30 minutes daily for 21 consecutive days. The electrophysiological activity of the injured nerves (compound muscle action potentials – CMAPs) was found to be approximatively 90% of the normal precrush value, and remained so for a long time. In the control group, the CMAPs dropped to about 20% on day 21 and showed the first signs of slow recovery 30 days after surgery.

Anders [387] found that laser irradiation with certain wavelengths alters the rate of regeneration of the rat facial nerve. The facial nerve of rats was crushed unilaterally and transcutaneously irradiated with a laser beam directed at the area of the crush injury daily for seven, eight or nine days. The wavelengths examined were 361, 457, 514, 633, 720 and 1064 nm. Power ranged from 8.5 to 40 mW, length of irradiation from 13 to 120 minutes. The most effective wavelength was 633 nm and 45.9 J.

The double-blind randomised study by Shamir [1182] evaluated the effect of LPT on peripheral nerve regeneration after complete transection and direct anastomosis of the rat sciatic nerve. All in all 13 of 24 rats received postoperative LPT, 780 nm, applied transcutaneously, 30 min daily for 21 consecutive days, to corresponding segments of the spinal cord and to the injured sciatic nerve. Positive somatosensory evoked responses were found in 69.2% of the irradiated rats compared to 18.2% of the non-irradiated rats. Immunohistochemical staining in the laser-treated group showed an increased total number of axons and better quality of the regeneration process, due to an increased number of large-diameter axons compared to the non-irradiated control group.

In the study by Shin [1500] the authors verified the therapeutic effect on neuronal regeneration by finding elevated immunoreactivities (IRs) of growth-associated protein-43 (GAP-43), which is upregulated during neuronal regeneration. Twenty rats received a standardised crush injury of the sciatic nerve, mimicking the clinical situations accompanying partial axonotmesis. The injured nerve received calculated LPT immediately after injury and for four consecutive days thereafter. The walking movements of the animals were scored using the sciatic functional index (SFI). In the laser treated rats, the SFI level was higher in the laser treated animals at three to four weeks while the SFIs of the laser treated and untreated rats reached normal levels at five weeks after surgery. In an immunocytochemical study, although GAP-43 IRs increased both in the untreated control and the laser treated groups after injury, the number of GAP-43 IR nerve fibres was much more increased in the laser group than those in the control group. The elevated numbers of GAP-43 IR nerve fibres reached a peak three weeks after injury, and then declined in both the untreated control and the laser groups at five weeks, with no differences in the numbers of GAP-43 IR nerve fibres of the two groups at this stage. This immunocytochemical study using a GAP-43 antibody study shows for the first time that laser has an effect on the early stages of the nerve recovery process following sciatic nerve injury.

Bagis [1565] evaluated the electrophysiological and histopathological effects of gallium arsenide (904 nm) laser irradiation on the intact skin injured rat sciatic nerve. Twenty-four male rats were divided into three groups (n=8 each) and the sciatic nerve situated at a level approximately one-third of the length of the femur was crushed bilaterally with an aneursym clip for half a second. A gallium arsenide laser (wavelength 904 nm, pulse duration 220 ns, peak power per pulse 27 W, spot size 0.28 cm², pulse repetition rate 16, 128 and 1000 Hz; total applied energy density of 0.31, 2.48 and 19 J/cm²) was applied to the right sciatic nerve for 15 min daily at the same time on 7 consecutive days. The same procedure was performed on the left sciatic nerve on the same animal, but without radiation emission, and this was accepted as a control. Compound muscle action potentials (CMAP) were recorded from the right and left sides in all three groups before surgery, immediately after the injury was inflicted, at the 24th hour and on the 14th *and 21st day in all rats. The rats were sacrificed 21 days after injury. The sciatic nerves of the operated parts were harvested from the right and left sides. Histopathological evaluation was performed by light microscopy. Statistical evaluation was done using analysis of variance for two factors (right and left sides), repeated-measures (CMAP variables within groups), and the Tukey-Kramer Honestly Significant Difference test (CMAP variables between laser groups). No statistically significant difference was found regarding the amplitude, area, or duration and conduction velocity of CMAP for each applied dose (0.31, 2.48 and 19 J/cm^2) on the irradiated (right) side and the control (left) side, or between irradiated groups. There were no qualitative differences 21 days after injury in the morphological pattern of the regenerated nerve fibres in either irradiated (0.31, 2.48 and 19 J/cm^2) or control nerves when evaluated by light microscopy.*

In a rat experiment by Byrnes [1222, 1527], the spinal cord was hemisected at vertebral level T9. The light from a 810 nm, 150 mW laser was applied immediately after hemisection and daily for 14 days, with a dosage of 1.589 J/cm^2. Control rats received identical treatment, but without laser. The results indicate that LPT initially blocks cell invasion and activation of the injured spinal cord. Once LPT ceases 14 days post-injury (the time point at which lesioned axons are reported to begin to sprout), there is a rebound increase in non-inflammatory cell invasion and activation that is visible 16 days post-injury. These alterations in the spinal cord environment may contribute to the ability of lesioned axons to regenerate following injury.

The objective of a study by Gigo-Benato [1562] was to investigate the effects of postoperative lasertherapy on nerve regeneration after end-to-side neurorrhaphy, an innovative technique for peripheral nerve repair. After complete transection, the left median nerve was repaired by end-to-side neurorrhaphy on the ulnar donor nerve. The animals were then divided into four groups: one placebo group, and three laser-treated groups that received LPT three times a week for 3 weeks starting on the first postoperative day. Three different types of laser emission were used: continuous (808 nm), pulsed (905 nm), and a combination of the two. Functional testing was carried out every 2 weeks after surgery by means of the grasping test. At the time of withdrawal 16 weeks postoperative, muscle mass recovery was assessed by weighing the muscles innervated by the median nerve. Finally, the repaired nerves were withdrawn, embedded in resin and analysed by light and electron microscopy. Results showed that laser biostimulation induces: (1) a statistically significant faster recovery of the lesioned function; (2) a statistically significant faster recovery of muscle mass; (3) a statistically significant faster myelination of the regenerated nerve fibres. From comparison of the three different types of laser emissions, it turned out that the best functional outcome was obtained by means of pulsed-continuous-combined laser biostimulation.

Both LPT and olfactory ensheathing cells (OECs) transplantation improve recovery following spinal cord injury. However, neither the combi-

nation of these two therapies nor the effect of light on OECs have been reported. The purpose of a study by Byrnes [1587] was to determine the effect of light on OEC activity in vitro. OECs were purified from adult rat olfactory bulbs and exposed to 810 nm light (150 mW; 0.2 or 68 J/cm²). After 7-21 days in vitro, cells underwent immunocytochemistry or RNA extraction and RT-PCR. Analysis of immunolabeling revealed a significant decrease in fibronectin expression in the cultures receiving 68 J/cm². Analysis of gene expression revealed a significant increase in brain derived neurotrophic factor (BDNF), glial derived neurotrophic factor (GDNF), and collagen expression in the 0.2 J/cm² group in comparison to the non-irradiated and 68 J/cm² groups. OEC proliferation was also found to significantly increase in both light treated groups in comparison to the control group. These results demonstrate that low and high dosages of LPT alter OEC activity, including an upregulation of a number of neurotrophic growth factors and extracellular matrix proteins known to support neurite outgrowth.

A persistent increase in calcitonin gene-related peptide (CGRP) immunoreactivity in motoneurons may serve as an indicator for regeneration after peripheral nerve injury. Snyder [1719] examined the effects of laser treatment (633 nm) on axotomy-induced changes in alpha-CGRP mRNA and long-term neuronal survival in facial motoneurons. A quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) assay for alpha-CGRP mRNA was used to detect changes in the response to axotomy and laser irradiation. Cell counts of neurons in injured and non-injured facial motor nuclei of laser-treated and non-treated rats were done to estimate neuronal survival. A 10-fold increase in mRNA for alpha-CGRP on day 11 post-transection and an almost 3-fold increase in neuronal survival at six to nine months post-transection were found in 633 nm light treated rats. These findings demonstrate that 633 nm laser light upregulates CGRP mRNA and support the theory that laser irradiation increases the rate of regeneration, target reinnervation, and neuronal survival of the axotomised neuron.

In a study by Ihsan [1866], 24 adult male rabbits were randomly assigned to two equal groups (control and laser-treated). General anesthesia was administered intramuscularly, and an exploration of the peroneal nerve was done in the lateral aspect of the left leg. Complete section of the nerve was performed, which was followed by suturing of the neural sheath (epineurium). Irradiation was carried out directly after the operation and for 10 consecutive days. The laser used was a diode with a wavelength of 901 nm (pulsed) and a power of 10 mW. It was a square-shaped window type (16 cm²), and its energy was applied by direct contact of the instrument's window to the site of the operation. Three rabbits from each group were sacrificed at the end of weeks two, four, six and eight, and specimens were collected from the site of nerve suturing and sent for histopathological examination. Two important factors were examined via histopathology: diameter of the nerve fibres and individual internodal length. Compared to the control group, significant variations in regeneration were observed, including thicker nerve *fibres, more regular myelin layers, and clearer nodes of Ranvier with an absence of short nodes in the treated group. Variations between the two groups for diameter were significant for the second week, highly significant for the fourth and sixth week, respectively, and very highly significant for the 8th week. Variations between the two groups for internodal length were highly significant for the second and fourth week and very highly significant for the sixth and eighth week.*

A pilot double-blind randomised study by Rochkind [1867] evaluated the efficacy of 780 nm laser phototherapy on the acceleration of axonal growth and regeneration after peripheral nerve reconstruction by polyglycolic acid (PGA) neurotube. The right sciatic nerve was transected, and a 0.5 cm nerve segment was removed in 20 rats. A neurotube was placed between the proximal and the distal parts of the nerve for reconnection of the nerve defect. Altogether 10 of 20 rats received post-operative, transcutaneous, 200 mW, 780 nm laser irradiation for 14 consecutive days to the corresponding segments of the spinal cord (15 min) and to the reconstructed nerve (15 min). At three months after surgery, positive somato-sensory evoked responses were found in 70% of the irradiated rats, compared to 30% of the non-irradiated rats. The Sciatic Functional Index in the irradiated group was higher than in the non-irradiated group. Morphologically, the nerves were completely reconnected in both groups, but the laser-treated group showed an increased total number of myelinated axons.

The purpose of a study by Chen [2003] was to determine whether low-power pulsed laser irradiation could affect the regeneration of a 10-mm gap in the rat sciatic nerve created between the proximal and distal nerve stumps, which were sutured into silicone rubber tubes. After eight weeks of recovery, pulsed laser-irradiated groups at frequencies of 5 kHz and 20 kHz both had significantly lower success percentages of regeneration (50% and 44%, respectively) compared to sham-irradiated controls (100%). In addition, qualitative and quantitative histology of the regenerated nerves revealed a less mature ultrastructural organisation with a smaller cross-sectional area and a lower number of myelinated axons in both pulsed laser-irradiated groups than in the controls. These results suggest that superpulsed laser irradiation could elicit suppressing effects on neural growth.

However, the conclusion in the above study has been questioned by Tunér [2004]. The references used by Chen are all from studies using continuous lasers. In a paper by Rochkind [2005], several wavelengths were compared, even 980 nm, and all had some effect, except for 904 nm. So it is probably not the wavelength per se but the superpulsing mode that makes the difference. GaAs is known to require a much lower dosage than continuous lasers [8]. The correct conclusion would be that the wavelength and doses used were inhibitory. Apart from a questionable conclusion, the study by Chen is valuable.

Spinal cord injury (SCI) is a severe central nervous system trauma with no restorative therapies. Previously, Anders [1898] demonstrated that

LPT improves axonal regeneration and functional recovery in a dorsal hemisection rodent SCI model. Weight-drop contusion SCI rodent models are widely used since this model is comparable to human SCI. The comparative effectiveness of laser on these two SCI models was studied. The light treated groups were transcutaneously irradiated at the injury site with a 810 nm diode laser (150 mW, 1.589 J/cm^2) for 14 consecutive days. All rats were euthanised 3 weeks after injury. Axonal regeneration and functional recovery were assessed. The laser-treated groups had a significantly longer average axon growth and a higher total axon number in both the contusion and hemisection models compared to the control groups. In both models, the laser groups showed a significant functional improvement compared to the control groups.

The aim of a study by Ribeiro [2007] was to evaluate the action of an anti-COX-2 selective drug (celecoxib) on bone repair associated with LPT. A total of 64 rats underwent surgical bone defects in their tibias, being randomly distributed into four groups: Group 1) negative control; Group 2) animals treated with celecoxib; Group 3) animals treated with LPT, and Group 4) animals treated with celecoxib and LPT. The animals were killed after 48 h, and 7, 14 and 21 days. The tibias were removed for morphological, morphometric and immunohistochemistry analysis for COX-2. Statistically significant differences were observed in the quality of bone repair and quantity of formed bone between groups 3 and 4 on day 14 after surgery. COX-2 immunoreactivity was more intense in bone cells in the intermediate periods evaluated in the laser-exposed groups. Taken together, such results suggest that LPT is able to improve bone repair in the tibia of rats as a result of an upregulation of the cyclooxygenase-2 expression in bone cells.

The aim of a study by dos Reis [2008] was to analyse the influence of 660 nm laser light on the myelin sheath and functional recovery of the sciatic nerve in rats. The sciatic nerves of 12 Wistar rats were subjected to injury through neurotmesis and epineural anastomosis, and the animals were divided into two groups: group 1 was the control, and group 2 underwent LPT. After the injury, a 660 nm, 4 J/cm^2 , 26.3 mW laser with a beam area of 0.63 cm^2 was administered to three equidistant points on the injury for 20 consecutive days. In the control group, the mean area of the myelin impairment was 0.51 on day 21 after the operation, whereas this value was 1.31 in the LPT group. Comparison of the sciatic functional index (SFI) showed that there was no significant difference between the pre-lesion value in the laser therapy group and the control group. The use of 660 nm LPT provided significant changes to the morphometrically assessed area of the myelin sheath, but it did not culminate in any positive results for the functional recovery of the sciatic nerve in the rats after injury caused by neurotmesis.

The aim of a study by Akgul [2231] was to analyse the differences between early and delayed use of LPT in functional and morphological recovery of the peripheral nerve. Thirty male Wistar rats were divided into three groups after the sciatic nerve was crushed: (1) control group without *laser treatment, (2) early group with laser treatment started immediately after surgery and lasted 14 days, and (3) delayed group with laser treatment starting on the postoperative day 7 and lasted until day 21. A 650 nm laser with an output power of 25 mW exposed transcutaneously at three equidistant points on the surgical mark corresponding to the crushed nerve. The length of the laser application was calculated as 57 s to satisfy approximately 10 J/cm^2. A Sciatic Functional Index (SFI) was used to evaluate functional improvement in groups at pre- and post-surgery (on days 7, 14, and 21). Compound action potential (CAP) was measured after the sacrifice and histological examination was performed for all groups. SFI results showed that there was no significant difference between groups at different days On the other hand, the latency of CAP decreased significantly in the delayed group. Histological examination confirmed that the number of mononuclear cells was lower in both early and delayed groups. In conclusion, results supported the hypothesis that LPT could accelerate the rate of recovery of injured peripheral nerves in this animal model. Though both laser groups had positive outcomes, delayed group showed better recovery.*

The aim of a study by Alcantara [2261] was to evaluate the effects of LPT (660 nm, 60 J/cm^2, 40 mW/cm^2) on acute sciatic nerve injury. Thirty Wistar male rats were divided into three groups: (1) Normal, intact nerves; (2) I3d, crushed nerves evaluated on Day-3 post-injury; (3) I + L3d, crushed nerves submitted to two sessions of LPT and investigated at 3 days post-injury. Sciatic nerves were removed and processed for gene expression analysis (real-time PCR) of the pro-inflammatory factors TWEAK, Fn14 and TNF-alpha and extracellular matrix remodelling and axonal growth markers, such as TIMP-1, MMP-2, and MMP-9. Zymography was used to determine levels of MMP-2 and MMP-9 activity and Western blotting was used to evaluate TNF-alpha protein content. Shapiro-Wilk and Levene's tests were applied to evaluate data normality and homogeneity, respectively. An increase in TNF-alpha protein level was found in I + L3 compared to Normal and I3d. Zymography showed an increase in proMMP-9 activity, in both I3d and I + L3d groups. The increase was more evident in I + L3d (p=0.02 compared to I3d). Active-MMP-9 isoform activity was increased in I + L3d compared to Normal and I3d groups. Furthermore, the activity of active-MMP-2 isoform was increased in I3d and I + L3. An increase in TIMP-1 expression was observed in both I3d and I + L3d groups. The study showed that LPT increased MMPs activity, mainly MMP-9, and TNF-alpha protein level during the acute phase of nerve injury, modulating inflammation. Based on these results, it is recommended that LPT should be started as soon as possible after peripheral nerve injury. A study by Shen [2306] proposes a novel combination of neural regeneration techniques for the repair of damaged peripheral nerves. A biodegradable nerve conduit containing genipin-cross-linked gelatin was annexed using beta-tricalcium phosphate (TCP) ceramic particles (genipin-gelatin-TCP, GGT) to bridge the transection of a 15 mm sciatic nerve in rats. Two trigger points were irradiated transcutaneously using 660 *nm via laser diodes for 2 min daily over 10 consecutive days. Walking track analysis showed a significant improvement in sciatic functional index (SFI) and pronounced improvement in the toe spreading ability of rats undergoing laser stimulation. Electrophysiological measurements (peak amplitude and area) illustrated by compound muscle action potential (CMAP) curves demonstrated that laser stimulation significantly improved nerve function and reduced muscular atrophy. Histomorphometric assessments revealed that laser stimulation accelerated nerve regeneration over a larger area of neural tissue, resulting in axons of greater diameter and myelin sheaths of greater thickness than that observed in rats treated with nerve conduits alone. Motor function, electrophysiological reactions, muscular reinnervation, and histomorphometric assessments all demonstrate that the proposed therapy accelerated the repair of transected peripheral nerves bridged using a GGT nerve conduit.*

The objective of a study by Führer-Valdivia [2527] was to observe the effect on the application of LPT in patients that have been previously intervened with a sagittal ramus split osteotomy and present neurosensory impairment due to this surgery, compared with placebo. This preliminary study is a randomised clinical trial, with an experimental group (n=17) which received laser light and a control group (n=14), placebo. All participants received laser applications, divided after surgery in days 1, 2, 3, 5, 10, 14, 21 and 28. Neurosensory impairment was evaluated clinically with 5 tests; VAS for pain and sensitivity, directional and 2 point discrimination, thermal discrimination, each one of them performed before and after surgery on day 1, and 1, 2 and 6 months. Participants and results evaluator were blinded to intervention. Variables were described with absolute frequencies, percentages and medians. Results demonstrate clinical improvement in time, as well as in magnitude of neurosensory return for laser group; VAS for sensitivity reached 5 (normal), 10 participants recovered initial values for 2 point discrimination (62,5%) and 87,5% recovered directional discrimination at 6 months after surgery. General VAS for sensitivity showed 68,75% for laser group, compared with placebo 21,43%. Left side sensitivity (VAS) showed 3.25 and 4 medians for placebo and laser at 2 months, respectively.

Patient with facial paresis following an ear operation 15 years ago. The second photo shows the situation after two laser sessions per week for one month.

Figure 4.19 Long standing facial paresis after four session of LPT. Courtesy: Per Hugo Christensen

Clinical studies

The studies by Khullar [361, 900, 901, 902, 939, 1037] on the effects of LPT on long-standing paraesthesiae in the orofacial region found, in summary:

- A course of 20 LPT treatment sessions using 820 nm on an area of long-standing paraesthesiae in the orofacial region induced an objectively evaluated significant improvement in fine mechanosensory perception and a decrease in the area of paraesthesiae.

- The significant improvement in mechanosensory perception was also perceived as a subjective improvement by the patients.

- A course of 20 LPT treatment sessions with 820 nm induced no change in thermoperception in an area of paraesthesiae.

- Daily LPT treatment over a 28 day period with a GaAlAs laser accelerated motor nerve reinnervation as assessed by a return of motor function subsequent to a standardised axonotmesis injury in the rat sciatic nerve.

- Treatment with 820 nm enhanced sensory reinnervation of peripheral target tissues subsequent to an IAN axotomy injury in the rat model. The findings are demonstrated immunohisto-chemically by the presence of CGRP positive neurones

A study by Miloro [899] examined the potential benefit of perioperative and short-term postoperative LPT on objective and subjective neurosensory recovery after bilateral sagittal split osteotomy surgery. Six consecutive patients undergoing bilateral sagittal split osteotomy procedures were enrolled in this prospective study. A complete preoperative clinical neurosensory test, consisting of brush stroke directional discrimination, 2-point discrimination, contact detection, pin prick nociception, and thermal discrimination, was performed on each patient; and a subjective assessment of neurosensory function was made by using a Visual Analogue Scale (VAS). The protocol for LPT treatment con-

sisted of 6 J per point along the distribution of the inferior alveolar nerve at four sites for a total of seven sessions delivered immediately before surgery; at 6 and 24 hours after surgery; and on postoperative days 2, 3, 4 and 7. The clinical neurosensory test and VAS were completed just before each of the treatment sessions and on days 14 and 28 by one examiner. When the results of the patients treated with LPT were compared with published values for neurosensory recovery after orthognathic surgery, there was a significant acceleration in the time, as well as in the magnitude, of neurosensory return. Brush stroke directional discrimination approached normal values by 14 days, whereas 2-point discrimination and contact detection showed significant improvement on day 14 and returned to near-normal values by two months. The results of thermal discrimination and pinprick nociception revealed few neurosensory deficits; however, those patients who were affected showed a slower recovery trend and remained neurosensory-deficient for up to two months. The VAS analysis revealed a rapidly progressive improvement in subjective assessment, showing a 50% deficit on day 2 and only a 15% subjective deficit at two months.

In an investigation by Martins [2200], the authors used an experimental IAN injury in rats to which was associated with LPT to assess how laser stimulates nerve repair in experimental animals. The investigators also studied the nociceptive behavior (allodynia von Frey test) before and after the injury and the behavioral effects of treatment with laser therapy. Since neurotrophins are essential for the process of nerve regeneration, immunoblotting techniques were used to approach the effects of laser therapy upon the expression of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). The injured animals treated with laser had an improved nociceptive behavior. In irradiated animals there was an enhanced expression of NGF (53%) and a decrease of BDNF expression (40%) after LPT. These results indicate that BDNF plays a locally crucial role in pain-related behavior development after IAN injury, increasing after lesions (in parallel to the installation of pain behavior) and decreasing with LPT (in parallel to the improvement of pain behavior), whereas NGF probably contributes for the repair of nerve tissue and acts by improving the pain-related behavior, thus increasing after laser therapy.

González [1552] reports that 26 ortognathic surgery patients were operated by one and the same surgeon and with laser applied to the right side only. The irradiation was carried out postop for 10 sessions. At four and eight weeks postop, biopsies were taken in five patients and sent for blinded histological evaluation. At six weeks, X-rays confirmed a better bone condensation on the irradiated side. The biopsies showed higher fibroblastic activity, dense collagenisation and less inflammation on the irradiated side.

The study by Prazeres [2226] aimed at evaluating the effect of 830 nm in the prevention and treatment of paresthesias after orthognathic surgery. Six patients underwent orthognathic surgery: the experimental group composed of 4 patients and the control group that did not receive laser therapy *composed of 2 patients. The experimental group received laser applications during the transoperative and 12 postoperative sessions. Tests for mechanical (deep and shallow) and thermal (cold) sensitivity were performed in the preoperative and postoperative period (during 12 sessions) in the lip and chin areas by the same operator. The paresthesia was classified into 1, strong; 2, moderate; 3, mild; and 4, absent, through the patient's response to stimuli. The results showed that all patients had no disturbance of sensitivity in the preoperative period, but paresthesia was presented at various levels in the postoperative period. Both groups showed recovery of deep mechanical sensitivity within a shorter time interval compared with the superficial mechanical and thermal sensitivity. However, at the 12th assessment, patients who underwent the laser therapy showed better reduction in the level of paresthesia or even complete regression of this. The laser, therefore, brought benefits to the treatment of paresthesia, accelerating the return of neurosensorial sensitivity.*

The paper by Ozen [1635] reports on the effects of LPT in four patients with longstanding sensory nerve impairment following mandibular third molar surgery. Four female patients had complaints of paresthesia and dysesthesia of the lip, chin and gingiva, and buccal regions. Each patient had undergone mandibular third molar surgery at least one year earlier. The unit had a contact probe with a laser beam diameter of 0.5 cm. The system delivers a 70 mW output that emits a wavelength of 830 nm. The irradiance used was 6.0 J per treatment site, which was delivered by applying the laser for approximately 90 seconds. Each patient received a total of 20 laser treatment sessions. The patients were treated at 2-day intervals, three times a week until all sessions were completed. The laser probe was applied directly to the treatment sites. The patients experienced no sensation when the laser treatments were being carried out. The treatment time per point was 90 seconds. Thus, one treatment session, consisting of five treatment sites, took approximately eight minutes. The treatment sites were as follows: extraorally: the lower lip, chin and the region of mental foramen; intraorally: the mental foramen region, buccally in the region of the apicies of the first molar, and lingually in the region of the mandibular foramen. Clinical neurosensory tests (the brush stroke directional discrimination test, 2-point discrimination test, and a subjective assessment of neurosensory function using a Visual Analogue Scale) were used before and after treatment, and the responses were plotted over time. When the neurosensory assessment scores after treatment with LPT were compared with the baseline values prior to treatment, there was a significant acceleration in the time course, as well as in the magnitude, of neurosensory return. The VAS analysis revealed progressive improvement over time.

The study by Führer-Valdivia [2503] on patients with neurosensory impairment of mandibular nerve after sagittal split ramus osteotomy is a randomised clinical trial, with an experimental group (n=17) which received laser light and a control group (n=14), placebo. All participants received *laser applications, divided after surgery in days 1, 2, 3, 5, 10, 14, 21 and 28. Neurosensory impairment was evaluated clinically with 5 tests; Visual Analogue Scale (VAS) for pain and sensitivity, directional and 2 point discrimination, thermal discrimination, each one of them performed before and after surgery on day 1, and 1, 2 and 6 months. Participants and results evaluator were blinded to intervention. Variables were described with absolute frequencies, percentages and medians. Results demonstrate clinical improvement in time, as well as in magnitude of neurosensory return for laser group; VAS for sensitivity reached 5 (normal), 10 participants recovered initial values for 2 point discrimination (62,5%) and 87,5% recovered directional discrimination at 6 months after surgery. General VAS for sensitivity showed 68.7 % for laser group, compared with placebo 21.4 3%. Left side sensitivity (VAS) showed 3.25 and 4 medians for placebo and laser at 2 months, respectively.*

Yamada [1054] has compared corticosteroids, LPT and a combination of the two in a study comprising seven patients in each group. The effect of LPT was comparable to that of corticosteroids but the combined therapy showed the best outcome. The laser was a 150 mW GaAlAs laser and the LPT was performed over the area of paralysis (36 J per session), the stylomastoid foramen (10.8 J) and the stellate ganglion (63.7 J). The number of sessions in the laser group ranged from 21 to 66, 5-12 weeks. In the combination group, success was achieved within 14-31 sessions, 3-10 weeks.

Paolini [960] treated 40 patients with Bell's paralysis. One group received only prednison (corticosteroid) 60 mg/day. The other group was treated with GaAs laser on points along the nerve, followed by an array of GaAs/HeNe five days a week for three weeks, then every second day, 30 sessions in all. The outcome in the laser group was significantly better than in the pharmacological group.

Figure 4.20 Ideopathic parasthesia after delivery resolved by LPT. Courtesy: Per Hugo Christensen

The aim of a study by Alayat [2222] was to investigate and compare the effects of high intensity laser therapy (HILT) and LPT on the treatment of patients with Bell's palsy. Forty-eight patients participated in and completed this study. The mean age was 43 +/- 9.8 years. They were randomly assigned into three groups: HILT group, LPT group, and exercise group. All patients were treated with facial massage and exercises, but the HILT and LPT groups received the respective laser therapy. The grade of facial recovery was assessed by the facial disability scale (FDI) and the House-Brackmann scale (HBS). Evaluation was carried out 3 and 6 weeks after treatment for all patients. Laser treatments included eight points on the affected side of the face three times a week for 6 successive weeks. FDI and HBS were used to assess the grade of recovery. The scores of both FDI and HBS were taken before as well as 3 and 6 weeks after treatment. The result showed that both HILT and LPT significantly improved the recovery of patients with Bell's palsy. Moreover, HILT was the most effective treatment modality compared to LPT and massage with exercises. Thus, both HILT and LPT are effective physical therapy modalities for the recovery of patients with Bell's palsy, with HILT showing a slightly greater improvement than LPT.

Brugnera [970] treated two groups of patients with lesions to the inferior alveolar and mental nerves. The laser used was a 830 nm 40 mW, spot size 3 mm^2. All paraesthesias were due to surgical interventions. The first group was identified as immediate and was treated within 2-15 days after the injury. In this group, 72.7% achieved absolute recovery, 18.3% a relative improvement and 9% did not respond to treatment. In the latter group, the history of injury was 30-365 days. In this group, only 27.7% reached an absolute improvement.

Bernal [156] presented six years of experience of patients with facial paralysis on whom HeNe and GaAs lasers had been used. If the laser treatment was begun within two days of the occurrence of the injury, treatment with LPT was successful in 100% of cases and a maximum of 15 treatment sessions were required. If the patient was treated later, Meticorten (40 mg/day) was administered for seven days as a supplement. Up to 30 doses could be administered to the latter group. The degree of healing in this latter group varied, but complete rehabilitation was achieved by some of the patients.

Murakami [186] treated 52 people with idiopathic facial paralysis or Bell's paralysis; 26 were treated with stellate ganglion block (SGB), 11 received 830 nm LPT and 15 a combination of the two. The patients who received LPT or a combination of LPT and SGB showed a similar picture of recovery from paralysis, in contrast to the group which received SGB only. The group that received only LPT also showed a better initial improvement.

Rochkind [1867] conducted a clinical pilot study to prospectively investigate the effectiveness of laser irradiation (780 nm) in the treatment of patients suffering from incomplete peripheral nerve and brachial plexus injuries for six months up to several years. Injury to a major nerve trunk frequently results in considerable disability associated with loss of sensory and *motor functions. Spontaneous recovery of long-term severe incomplete peripheral nerve injury is often unsatisfactory. A randomised, double-blind, placebo-controlled trial was performed on 18 patients who were randomly assigned to placebo (non-active light: diffused LED lamp) or laser irradiation (wavelength, 780 nm; power, 250 mW). Twenty-one consecutive daily sessions of laser or placebo irradiation were applied transcutaneously for three hours to the injured peripheral nerve (energy density 450 J/cm^2) and for two hours to the corresponding segments of the spinal cord (energy density 300 J/cm^2). Clinical and electrophysiological assessments were done at baseline, at the end of the 21 days of treatment, and three and six months thereafter. The laser-irradiated and placebo groups were in clinically similar conditions at baseline. The analysis of motor function during the six-month follow-up period compared to baseline showed a statistically significant improvement in the laser-treated group compared to the placebo group. No statistically significant difference was found in sensory function. Electrophysiological analysis also showed a statistically significant improvement in recruitment of voluntary muscle activity in the laser-irradiated group compared to the placebo group.*

Rochkind [2175] summarises: Posttraumatic nerve repair and prevention of muscle atrophy represent a major challenge of restorative medicine. Considerable interest exists in the potential therapeutic value of laser phototherapy for restoring or temporarily preventing denervated muscle atrophy as well as enhancing regeneration of severely injured peripheral nerves. LPT was applied for treatment of rat denervated muscle in order to estimate biochemical transformation on cellular and tissue levels, as well as on rat sciatic nerve model after crush injury, direct or side-to-end anastomosis, and neurotube reconstruction. Nerve cells' growth and axonal sprouting were investigated in embryonic rat brain cultures. The animal outcome allowed clinical double-blind, placebo-controlled randomised study that measured the effectiveness of 780 nm laser phototherapy on patients suffering from incomplete peripheral nerve injuries for 6 months up to several years. In denervated muscles, animal study suggests that the function of denervated muscles can be partially preserved by temporary prevention of denervation-induced biochemical changes. The function of denervated muscles can be restored, not completely but to a very substantial degree, by laser treatment initiated at the earliest possible stage post injury. In peripheral nerve injury, laser phototherapy has an immediate protective effect. It maintains functional activity of the injured nerve for a long period, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord, and significantly increases axonal growth and myelinisation. In cell cultures, laser irradiation accelerates migration, nerve cell growth, and fibre sprouting. In a pilot, clinical, double-blind, placebo-controlled randomised study in patients with incomplete long-term peripheral nerve injury, 780 nm laser irradiation can progressively improve peripheral nerve function, which leads to significant functional recovery. A

780 nm laser phototherapy temporarily preserves the function of a denervated muscle, and accelerates and enhances axonal growth and regeneration after peripheral nerve injury or reconstructive procedures. Laser activation of nerve cells, their growth, and axonal sprouting can be considered as potential treatment for neural injury. Animal and clinical studies show the promoting action of phototherapy on peripheral nerve regeneration, which makes it possible to suggest that the time for broader clinical trials has come.

The objective of a study by Fontana [2193] was to apply LPT to accelerate the recovery process of a child patient with Bell's palsy (BP). The subject was a 3-year-old boy with a sudden onset of facial asymmetry due to an unknown cause. The laser sources used were 660 nm and 780 nm. No steroids or other medications were given to the child. The laser beam with a 0.04 cm^2 spot area, and an aperture with approximately 1 mm diameter, was applied in a continuous emission mode in direct contact with the facial area. The duration of a laser session was between 15 and 30 minutes, depending on the chosen points and the area being treated. Light was applied 10 seconds per point on a maximum number of 80 points, when the entire affected (right) side of the face was irradiated, based on the small laser beam spot size. According to the acupuncture literature, this treatment could also be carried out using 10-20 Chinese acupuncture points, located unilaterally on the face. In this case study, more points were used because the entire affected side of the face (a large area) was irradiated instead of using acupuncture points. The House-Brackmann grading system was used to monitor the evolution of facial nerve motor function. Photographs were taken after every session, always using the same camera and the same magnitude. The 3-year-old boy recovered completely from BP after 11 sessions of LPT. There were 4 sessions a week for the first 2 weeks, and the total treatment time was 3 weeks. The result of this study was the improvement of facial movement and facial symmetry, with complete reestablishment to normality.

Further literature: [375, 218, 493, 646, 933, 1038, 1113, 1469, 1669, 1670]

The following case is contributed by Daiane Thais Meneguzzo, Brazil:

Female, 48 years old.
Diagnosis: bilateral facial paralysis right side (2006) and left side (December 2008).
Probable causes:

right side - thermal shock (she worked with solder components of cell phones)

left side - vascular problem caused by high blood pressure after a nervous breakdown

Familiar history: aunt, nephew and sister have had facial paralysis.
Lesions history: In 2006 she worked with welding equipment and mobile phones one day she realised her face swollen, her eye was odd. The next day

her face was paralysed, searched a hospital and was prescribed Meticorten (1 box, 20 days), Benerva (30 days) and Propranolol (to control high blood pressure). She did 6 months of physical therapy (25 min once a week) without significant clinical improvement. She was off work for 5 months and soon after was fired. After this has become an antidepressant consumer and after a nervous breakdown in December 2008 the other side of the face (left) was paralysed. Medical treatments: is currently on anti-depressant (clonazepan), takes medication for high blood pressure (propanolol) and for thyroid hormone replacement (T4).

Figure 4.21 Laser treatment of bilateral facial paralysis

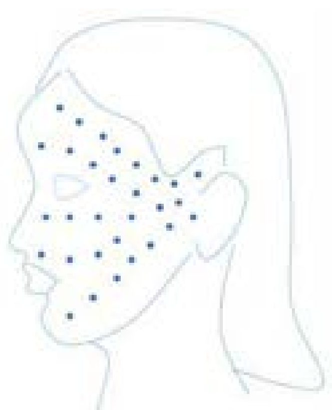


Figure 4.22 Face irradiation points

Laser treatment:
Spot area: 0,028 cm² (2 mm away from the target) or 0,0028 cm² in contact. Power output: 100 mW, 660 nm and 810 nm, energy: from 2 J to 3.4 J, energy density: from 70 J/cm² to 120 J/cm² Time of irradiation per point: 20 s to 34 s. Number of points: 30 per face. Distance between points: 1,5 to 2,5 cm. Number of sessions: 15 (7 sessions once a week, February and March), 2 session in May, 1 June, 3 August, 1 September, 1 November.

4.1.41 Oedema

A more or less pronounced oedema always appears after a surgical intervention. The anti-oedematous effect is based on a dilatation of lymphatic vessels and a reduction in the permeability of blood vessels. Large doses are required if the oedema is already established - even 1-2 J/cm^2 with a GaAs laser or 10-15 J/cm^2 with a GaAlAs laser are on the low side after an operation. An established oedema may or may not be filled with blood, and haemoglobin is one of the most powerful chromophores in the organism. Penetration of the cases containing blood is therefore shallow, particularly with a HeNe laser.

Laser energy has a regenerative effect on lymphatic vessels, as it also has on veins. As can be seen in [92] and [299] below, LPT can probably not be used as an oedematic prophylaxis ahead of operation unless the oedema is already present before the operation.

When treating peripheral oedemas, the proximal sites of the body should always be irradiated first. Opening the blood flow at a peripheral site could be followed by a circulatory obstruction at the proximal site, thus causing pain.

Literature:

In vitro studies

Kiyoizumi [95] reported that a GaAlAs laser has two different effects on oedema. The laser stimulated the synthesis of PGI_2 (prostacyclin), which has a strong vasodilating effect, and counteracted the aggregation of platelets. The accumulation of PGI_2 in the tissue reduced the oedema tendency. Laser light was also shown to counteract the occurrence of fibrin networks, which were studied with radioactive iodine. Kiyoizumi's clinical experience of skin transplants is that LPT reduces oedema.

The aim of an investigation by Powell [2039] was to compare the cell proliferative effects of a range of doses of LPT at wavelengths of 780, 830 and 904 nm on human breast and immortalised human mammary epithelial cell lines in vitro. LPT is used in the clinical treatment of post-mastectomy lymphoedema, despite safety information being limited and circumstantial. This research was the first step in systematically developing guidelines for the safe clinical use of LPT in the management of post-mastectomy lymphoedema. Human breast adenocarcinoma (MCF-7), human breast ductal carcinoma (MDA-MB-435S), and immortalised human mammary epithelial (SVCT and Bre80hTERT) cell lines were irradiated with a single exposure of laser at 0.5, 1, 2, 3, 4, 10 and 12 J/cm^2 (780 nm) and at 0.5, 1, 2, 3, 4, 10 and 15 J/cm^2 (830 and 904 nm). MCF-7 cells were further irradiated with two and three exposures of all three laser wavelengths. XTT colourimetric assays were utilised to assess cell proliferation 24 hours after irradiation. SVCT *cell proliferation significantly increased after exposure to a range of doses at 780 and 904 nm irradiation. MDA-MB-435S and Bre80hTERT cell lines showed negligible effects after one exposure from all three wavelengths, and no dose response relationships were noted. MCF-7 cells irradiated with 780 nm laser demonstrated an increasing dose response relationship after one exposure and a decreasing dose response relationship after three exposures. The MCF-7 cells irradiated with 904 nm laser demonstrated a decreasing dose response relationship after two and three exposures. Despite certain doses of laser increasing MCF-7 cell proliferation, multiple exposures had no effect or a decreasing effect on dose response relationships. Before a definitive conclusion can be made regarding the safety of LPT for post-mastectomy lymphoedema, further in vivo research must be conducted.*

Animal studies

Labajos [300] noted that the flow of water and electrolytes through the intestinal wall was retarded by LPT, 1 J/cm^2.

Lievens [92, 298] studied the effects of GaAs laser light on the vasomotricity of the lymphatic system. The everted skin of mice was observed microscopically under a cold light source. The lymph vessels were visualised by an injection of a physiological dye. The vessels did not dilate after laser treatment if the tissue had not been subjected to trauma, but did dilate as a result of laser treatment when in an oedematous condition.

In another study of the regeneration of the lymphatic system, Lievens [299] used a combined GaAs/HeNe laser. A median incision along the linea alba was made on 600 white mice. The skin was turned back and pinned on a cork plate. The lymph vessels were visualised by means of an injection of Patent V Blue into an inguinal lymph node. There were 100 animals in the laser group and 500 in the control group. The results were as follows:

1. *Adhesion of the wound to the underlying tissue was present in 100% of the animals in the control group after day 4. The adhesion gradually disappeared after day 10. Adhesion hardly ever occurred in the laser group.*
2. *The regeneration of the veins was faster in the laser group.*
3. *In the control group, the lymphatic vessels regenerated through a network of small vessels. In the laser group, the lymph vessels regenerated into their original shape. Regeneration was much quicker in the laser group, in particular during the initial healing stage.*
4. *The network-regenerated vessels in the non-irradiated group were very permeable. This increased permeability could be seen in 50% of the cases even after six months. The vessels in the laser group showed hardly any increased permeability after the first few days.*

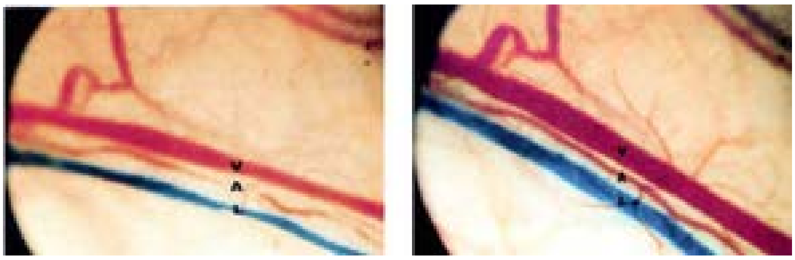


Figure 4.23 Vein, artery and lymph vessels before and after LPT. Courtesy: Pierre Lievens

Honmura [96] studied the effects of a GaAlAs laser on experimentally produced inflammation in rats. In all cases in the laser group, the degree of inflammation was reduced by 20-30%. LPT also reduced the extent of the oedema in the acute inflammation phase. LPT was effective if administered within two hours after the inflammation-causing substance was given to the rats; if it was administered later, a poorer effect on the oedema was observed. In a comparison using the inflammation-reducing substance indomethacin, LPT was better in one experimental model, not so good in another, but effective in both cases. LPT also impeded the vessels' permeability in cases of acute inflammation and thereby reduced the acute oedema.

Prokofeva [1217] evaluated the doses of infrared laser exposure on the structure of the eye in rabbit experiments, and the potentials of such lasers in ophthalmology were assessed. Wavelength was 890 nm and doses varied from 0.0001 to 1.0 J/cm^2, corresponding to an exposure duration of 0.3 seconds to 45 min. Experiments were carried out on 20 animals. The right eyes were exposed, and the left ones were used as controls. An increase of intraocular pressure was recorded at a dose of 0.1 J/cm^2 (4.5 min) and higher. Morphological examination showed dilatated, well filled and newly formed vessels in the ciliary body and iris, as well as oedema and a destruction of the external layers of the retina. Exposure to a dose of 0.05 J/cm^2 and lower did not lead to the destruction of any ocular structures or to an increase of intraocular pressure. The maximal dose causing no side effects for the organ of vision was established at 0.05 J/cm^2.

The aim of a study by Aimbire [1800] was to investigate if LPT can modulate formation of hemorrhagic lesions induced by immune complex, since there is a lack of information on LPT effects in hemorrhagic injuries of high perfusion organs, and the relative efficacy of LPT compared to anti-inflammatory drugs. A controlled animal study was undertaken with 49 rats, randomly divided into seven groups. Bovine serum albumin i.v. was injected through the trachea to induce an immune complex lung injury. The study compared the effect of irradiation by a 650 nm laser with doses of 2.6 J/cm^2 to celecoxib, dexamethasone, and control groups for hemorrhagic index (HI) *and myeloperoxide activity (MPO) at 24 h after injury. The HI for the control group was 4.0. Celecoxib, laser, and dexamethasone all induced significantly lower HI than in the control animals at 2.5, 1.8 and 1.5, respectively. Dexamethasone, but not celecoxib, induced a slightly, but significantly lower HI than laser (p=0.04). MPO activity was significantly decreased at 1.6 in groups receiving celecoxib at 0.87, dexamethasone at 0.50, and laser at 0.7 when compared to the control group, but there were no significant differences between any of the active treatments. In conclusion, LPT at a dose of 2.6 J/cm^2 induces a reduction of HI levels and MPO activity in hemorrhagic injury, which is not significantly different from that obtained by celecoxib. Dexamethasone is slightly more effective than LPT in reducing HI, but not MPO activity.*

Clinical studies

Røynesdal [93] studied the effects of GaAlAs in the surgical removal of impacted wisdom teeth. 6 J was administered before and after the operation. The same person operated on 25 people with bilaterally impacted wisdom teeth. The study showed that laser with these parameters had no effect on oedema, trismus or pain alleviation as compared with placebo laser. ***The dose appears to be too low.***

The study by Ozkan [1431] was performed in a total of 25 patients with 41 digital flexor tendon injuries in five anatomical zones. In Group I (21 digits in 13 patients), whirlpool and infrared GaAs diode laser with a pulse repetition rate of 100 Hz. was applied between the 8th and 21st day postoperatively and all patients were given the Washington rehabilitation programme until the end of the 12th week. In Group II (20 digits in 12 patients), the same treatment protocol was given, but the laser instrument was switched off during applications. The results of the study showed a significant improvement in the laser-treated group only for the parameter of oedema reduction; the difference between the two groups was non-significant for pain reduction, hand grip strength, and functional evaluation performed according to the Strickland and Buck-Gramcko systems using total active motion and fingertip-to distal palmar crease distance parameters. The significant improvement obtained in oedema reduction both immediately and 12 weeks after supplementary GaAs laser application in our study has been interpreted as an important contribution to the rehabilitation of human flexor tendon injuries, because oedema is known to have a detrimental effect on functional recovery during both early and late stages of tendon healing. However, this study failed to show a significant positive effect of supplementary GaAs laser application on the other functional parameters.

The aim of a study by Markovic [1911] was to compare the effectiveness of LPT and dexamethasone after surgical removal of impacted lower third molars under local anaesthesia. There were 120 healthy patients divided into four groups of 30 patients each. Group 1 received LPT irradiation immediately after operation (4 J/cm^2, 50 mW, 637 nm); group 2 also received an intramuscular injection of 4 mg dexamethasone into the internal *pterygoid muscle; group 3 received LPT irradiation supplemented by systemic dexamethasone 4 mg i.m. in the deltoid region, followed by 4 mg of dexamethasone intraorally six hours postoperatively; and the 4th (control) group received only the usual postoperative recommendations (cold packs, soft diet, etc.). Laser irradiation with local use of dexamethasone (group 2) resulted in a statistically significant reduction of postoperative oedema in comparison to the other groups. No adverse effects of the procedure or medication were observed.*

Piller [928] has since 1993 treated over 700 patients with chronic secondary arm and leg lymphoedemas with GaAs scanning. LPT had no effect on any parameter on normal arms and legs. In the affected arms there was a significant reduction of volume, average 233 ml. There was also a significant effect on the level of fibrotically indurated tissues in the lymphatic territories of the upper arm and forearm. Average volume reduction in legs was 199 ml, which was not statistically significant. However, as with the arms, there were significant reductions in the level of free extra cellular fluids in the whole limb, and reductions in the level of fibrotic induration in the lymphatic territories of the lower posterior leg and the upper anterior leg. These results correlated strongly with the patients' subjective indications of feelings of tension, heaviness and aching.

Carati [1337] performed a randomised, double-blind study on the effect of GaAs laser on postmastectomy lymphoedema. There was no immediate effect of the irradiation, but at the one and three month follow-up after two cycles of laser treatment, about 30% of the patients had a clinically significant reduction of the arm volume and there was a significant softening of the tissue. Treatment did not appear to improve range of movement of the affected arm.

Similar, but not quite as positive results are reported by Kaviani [1692], using 890 nm, 1.5 J/cm² over the arm and axillary areas.

In a three-group, pilot, randomised clinical trial by Ridner [2305], 46 breast cancer survivors with treatment-related lymphedema to examine the impact of advanced practice nurse (APN)-administered LPT as both a stand-alone and complementary treatment for arm volume, symptoms, and quality of life (QOL) in women with breast cancer-related lymphedema. Patients were screened for eligibility and then randomised to either manual lymphatic drainage (MLD) for 40 minutes, LPT for 20 minutes, or 20 minutes of MLD followed by 20 minutes of LPT. Compression bandaging was applied after each treatment. Data were collected pre-treatment, daily, weekly, and at the end of treatment. Independent variables consisted of three types of APN-administered lymphedema treatment. Outcome variables included limb volume, extracellular fluid, psychological and physical symptoms, and QOL. No statistically significant between-group differences were found in volume reduction; however, all groups had clinically and statistically significant reduction in volume. No group differences were noted in psychological and physical symptoms or QOL; however, treatment-related improvements were *noted in symptom burden within all groups. Skin improvement was noted in each group that received LPT. LPT with bandaging may offer a time-saving therapeutic option to conventional MLD. Alternatively, compression bandaging alone could account for the demonstrated volume reduction. APNs can effectively treat lymphedema. APNs in private healthcare practices can serve as valuable research collaborators. Lasers may provide effective, less burdensome treatment for lymphedema. APNs with lymphedema certification can effectively treat this patient population with the use of LPT.*

The aim of a study by Omar [2373] was to evaluate the effect of LPT on limb volume, shoulder mobility, and hand grip strength. Fifty women with breast cancer-related lymphedema were enrolled in a double-blind, placebo controlled trial. Patients were randomly assigned to active laser (n=25) and placebo (n=25) groups and received irradiation with 904 nm, 5 mW, spot size of 0.2 cm² over the axillary and arm areas, three times a week for 12 wk. The total energy applied at each point was 300 mjoules over seven points, giving a dosage of 1.5 J/cm² in the active group. The placebo group received placebo therapy in which the laser had been disabled without affecting its apparent function. Limb circumference, shoulder mobility, and grip strength were measured before treatment and at 4, 8, and 12 wk. The two groups had similar parameters at baseline. The reduction of limb volume tended to decline in both groups. The trend being more significantly pronounced in active LPT group than placebo at 8 and 12 wk, respectively. Goniometric data for shoulder mobility and hand grip strength were statistically significance for LPT group than for placebo. Laser treatment was found to be effective in reducing the limb volume, increase shoulder mobility, and hand grip strength in approximately 93% of patients with postmastectomy lymphedema.

Seventeen breast-cancer-related lymphedema (BCRL) patients referred to a lymphedema programme between 2007 and 2009 were enrolled in a study by Dirican [2374]. All patients had experienced at least one conventional treatment modality such as complex physical therapy, manual lymphatic drainage, and/or pneumatic pump therapy. LPT was added to patients' ongoing therapeutic regimen. All patients completed the full course of LPT consisting of two cycles. The difference between sums of the circumferences of both affected and unaffected arms (DeltaC), pain score, scar mobility, and range of motion were measured before and after first and second cycles of LPT sequentially. All patients were female with a median age of 51.8 (44-64) years. DeltaC decreased 54% (15-85%) and 73% (33-100%), after the first and second cycles of LPT, respectively. Fourteen out of seventeen experienced decreased pain with motion by an average of 40% (0-85%) and 62.7% (0-100%) after the first and second cycle of LPT, respectively. Three patients had no improvement in pain after LPT. Scar mobility increased in 13 (76.4%) and shoulder range of motion improved in 14 (82.3%) patients after LPT. One patient developed cellulitis during LPT. Patients with BCRL received additional benefits from LPT when used in conjunction with standard lymphedema treatment. These benefits included *reduction in limb circumference, pain, increase in range of motion and scar mobility. Additionally, two cycles of LPT were found to be superior to one in this study.*

A prospective, single-blinded, controlled clinical trial was conducted to examine the effectiveness of LPT on managing postmastectomy lymphedema (PML) was carried out by Lau [2375]. Twenty-one women suffering from unilateral PML were randomly allocated to receive either 12 sessions of LPT in 4 wk (the laser group) or no laser irradiation (the control group). Volumetry and tonometry were used to monitor arm volume and tissue resistance; the Disabilities of Arm, Shoulder, and Hand (DASH) questionnaire was used for measuring subjective symptoms. Outcome measures were assessed before and after the treatment period and at the 4 wk follow-up. Reduction in arm volume and increase in tissue softening was found in the laser group only. At the follow-up session, significant between-group differences were found in arm volume and tissue resistance at the anterior torso and forearm region. The laser group had a 16% reduction in the arm volume at the end of the treatment period, which dropped to 28% in the follow-up. Moreover, the laser group demonstrated a cumulative increase from 15% to 33% in the tonometry readings over the forearm and anterior torso. The DASH score of the laser group showed progressive improvement over time.

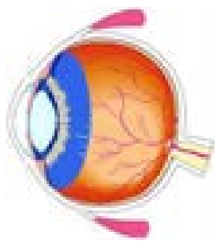
The objective of the study by Kozanoglu [2376] was to compare the long-term efficacy of pneumatic compression and LPT in the management of postmastectomy lymphedema in a randomised controlled trial. Forty-seven patients with postmastectomy lymphoedema were enrolled in the study. Patients were randomly allocated to pneumatic compression (group I, n=24) and LPT (group II, n=23) groups. Group I received 2 hours of compression therapy and group II received 20 minutes of LPT for four weeks. All patients were advised to perform daily limb exercises. Demographic features, difference between sum of the circumferences of affected and unaffected limbs (delta C), pain with Visual Analogue Scale and grip strength were recorded. Mean age of the patients was 48.3 (10.4) years. Delta C decreased significantly at one, three and six months within both groups, and the decrease was still significant at month 12 only in group II. Improvement of group II was greater than that of group I post treatment and at month 12 after 12 months. Pain was significantly reduced in group I only at posttreatment evaluation, whereas in group II it was significant post treatment and at follow-up visits. No significant difference was detected in pain scores between the two groups. Grip strength was improved in both groups, but the differences between groups were not significant. Patients in both groups improved after the interventions. Group II had better long-term results than group I.

The study of Gasperini [2511] verified the efficacy of an LPT protocol to reduce swelling and pain after orthognathic surgery. Ten healthy patients who underwent a bilateral sagittal split with Le Fort I osteotomy were randomly selected for this study. The LPT protocol consisted of intraoral and extraoral application to one side of the face after surgery (irradiated side);

application to the other side was simulated (non-irradiated side). The irradiated and non-irradiated sides were compared regarding the swelling coefficient and were assessed for pain using a Visual Analogue Scale. There were no significant differences between the irradiated and non-irradiated sides regarding swelling and pain in the immediate postoperative assessment. Swelling decreased significantly on the irradiated side in the postoperative assessments on days 3, 7, 15, and 30. Self-reported pain was less intense on the irradiated side at the 24-h (1.2 vs. 3.4) and 3-day (0.6 vs. 2.1) assessments, but at 7 days after surgery neither side showed pain. This LPT protocol can improve the tissue response and reduce the pain and swelling resulting from orthognathic surgery.

Further literature: [222, 485, 664, 769, 1696]

4.1.42 Ophthalmic problems



Treatment of the eye with LPT has been controversial, stemming from the early days of LPT and the hard-to-kill misconception that lasers in the low-milliwatt range could damage the eye. Patient and operator were recommended to use protective goggles even when treating a foot, using a laser of a couple of milliwatts.

Treating the unprotected eye is still the sole province of specialists. However, any reasonably trained person can carry out eye treatment through the eyelid. Closing the eye comes naturally when it is treated with a visible beam such as a HeNe laser. When a collimated invisible laser is used, one must make sure that the patient keeps his eyes closed. If the treatment probe is close to the eye and the beam is highly divergent, the light will not be focused onto a small point, even if the eye is open. Therefore, the risk in this case is small, and even negligible. We therefore recommend a visible beam in this context. High-powered non-visible beams should only be used by a qualified therapist.

Treating a

on the eyelid, for instance, is quite effective. Maeno [129] reported as early as 1989 that HeNe was effective in treating keratoconjunctivitis.

Literature:

Belkin and Schwartz [599] have presented a thorough review of the literature on LPT in ophthalmology. The majority of the studies are from Russia. The conclusion of the review is "that many studies must be looked at with skepticism because of lack of statistical evaluation, adequate inclusion and exclusion criteria, masking procedures etc. Nevertheless, the basic science experiments described in the earlier parts of the review and the demonstrable bioeffects of low-energy irradiation measured in various body systems leave us no option but to conclude that low-energy laser irradiation does exert some effects on ocular tissues in health and disease, and that *these effects exhibit definite dose-response curves. Energy concentrations less than 1 J/cm² are generally ineffective and those over 5 J/cm² can be injurious. The precise dosage, however, depends on the specific laser/tissue combination. The clinical reports surveyed here are thus not theoretically impossible, but will have to be reconfirmed".*

In a report by Inkova [903], 82 patients with severe post-traumatic uveitis (eye inflammation), which could not be treated by traditional anti-inflammatory therapy, were exposed to LPT. The patients were divided into three groups: infrared laser exposure semiconductor pulsed laser, intravenous exposure of the blood to a He-Ne laser, and both treatments combined. The treatment efficacy was monitored by measuring lipid per-oxides and superoxide dismutase in the lacrimal fluid. The treatment proved to be effective. The best results were attained by applying both methods of exposure, as shown by an earlier normalisation of the content of lipid peroxidation products and activity of superoxide dismutase.

Figure 4.24 Stye day one and two, following HeNe LPT.

A review of Russian LPT studies in ophthalmology is presented by Pankov [1122]. The first studies appeared as early as 1976. HeNe lasers of a low output are used; some examples of which are 0.25 mW/cm and 0.05 mW/cm. Some indications treated are amotio retinae, functional amplyopia, post-traumatic iridocyclitis, endothelial-epithelial dystrophy, burn accidents, acute inflammatory and allergic diseases of the cornea, conjunctiva, iris and ciliary body. HeNe laser has also been shown to increase the lymphocirculation of the eye.

The study by Desmettre [1819] was performed with exposures shorter than 60 seconds to assess a choroidal heat shock protein hyperexpression after transpupillary thermotherapy (TTT). Male pigmented rabbits were anesthetised and TTT was performed on their right eyes with a 810 nm laser (spot size: 1.3 mm). Three exposure durations (60, 30, or 15 seconds) were used with three ranges of power for each duration ("high," "mild," or "low"). A series of laser impacts were delivered to the posterior pole of the retina. Left eyes were used as controls. Twenty-four hours after laser irradiation, the animals were killed and a histological study was performed on chorioret-

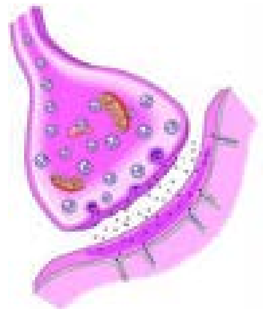
inal layers. Tissue samples were fixed in formalin and embedded in paraffin. A monoclonal antibody was used to detect Hsp70 immunoreactivity followed by a biotinylated goat anti-mouse antibody revealed by the avidin-biotin complex and the AEC chromogen. Retinal structures were further identified by HES colouration. During the experiments, the laser spots were not visible except for the strongest "high" powers for each exposure duration, where whitening was discernable at the end of the laser exposures. A strong HSP70 immunoreactivity was detected in choroidal, non-pigmented cells for laser exposures lasting 60, 30, or 15 seconds with "mild" laser powers. On the contrary, rare HSP hyperexpression was detected with "high" or "low" laser powers lasting 60, 30, or 15 seconds. HSP-70 immunoreactivity was neither detected in control eyes nor outside the irradiated zones of treated eyes. Transpupillary laser irradiation lasting 15, 30, or 60 seconds induces a hyperexpression of HSP on choroidal layers.

Age-related macular degeneration (AMD) is an eye condition that affects a tiny part of the retina at the back of your eye, which is called the macula. AMD causes problems with your central vision, but does not lead to total loss of sight and is not painful. AMD affects the vision you use when you're looking directly at something, for example when you are reading, looking at photos or watching television. AMD may make this central vision distorted or blurry and, over a period of time, it may cause a blank patch in the centre of your vision. A total of 203 patients (90 men and 113 women; mean age 63.4 ±5.3 y) with beginning ("dry") or advanced ("wet") forms of AMD (n=348 eyes) were included in a study by Ivandic [1850]. Altogether 193 (mean age 64. ± 4.3 y; n=328 eyes) with cataracts (n=182 eyes) or without cataracts (n =146 eyes) were treated four times using LPT (twice per week). A laser diode (780 nm, 7.5 mW, continuous emission) was used for transconjunctival irradiation of the macula for 40 sec (0.3 J/cm^2) resulting in a total dose of 1.2 J/cm^2. All in all 10 patients (n =20 eyes) with AMD received mock treatment and served as controls. Visual acuity was measured at each visit. LPT significantly improved visual acuity in 162/182 (95%) of eyes with cataracts and in 142/146 (97%) of eyes without cataracts. The prevalence of metamorphopsia, scotoma, and dyschromatopsia was reduced. In patients with wet AMD, the oedema improved and the bleeding was reduced. The improved vision was maintained for 3-36 months after treatment. Visual acuity in the control group remained unchanged. No adverse effects were observed in those undergoing therapy. Monthly injections of ranibizumab into the eye has given promising results but the method is very expensive and invasive. In relation to this situation, the above study deserves attention.

Ivandic [2109] further investigated the potential use of LPT as a diagnostic tool for identifying hypertensive eyes at risk of glaucoma. The study of a case series included 123 healthy subjects with normal vision. The intraocular pressure (IOP) was determined before (baseline) and 30 min after a 30-sec irradiation of the limbus area with laser light (780 nm; 7.5 mW; 292 Hz *modulation). Baseline IOP was >21 mm Hg in 44 of 211 eyes (20.9%), consistent with ocular hypertension. LPT decreased the mean IOP by 6.2 mm Hg in these eyes. The remaining 167 eyes (79.1%) exhibited a normo-tensive IOP <or=21 mm Hg. LPT reduced the mean IOP by 2.9 mm Hg in these eyes, but there were different response patterns: 1) the IOP did not change (27.0%); 2) the IOP was reduced by the same extent in both eyes (32.3%); 3) initial IOP differences between left and right eyes became level and the absolute IOP was reduced to a lower level that was identical in both eyes (18.0%); and 4) the initial difference in IOP between the left and right eye persisted despite LILI (22.7%). In conclusion, LPT lowers IOP, even in normotensive eyes. This effect may be useful to determine the individual physiological IOP and to diagnose latent ocular hypertension in eyes with presumably normotensive IOP.*

A case report by Ivandic [2501] describes the effects of LPT in a single patient with retinitis pigmentosa (RP). RP is a heritable disorder of the retina, which eventually leads to blindness. No therapy is currently available. LPT was applied using a continuous wave laser diode (780 nm, 10 mW average output at 292 Hz, 50% pulse modulation). The complete retina of eyes was irradiated through the conjunctiva for 40 sec (0.4 J, 0.333 W/cm2) two times per week for 2 weeks (1.6 J). A 55-year-old male patient with advanced RP was treated and followed for 7 years. The patient had complained of nyctalopia and decreasing vision. At first presentation, best visual acuity was 20/50 in each eye. Visual fields were reduced to a central residual of 5 degrees. Tritan-dyschromatopsy was found. Retinal potential was absent in electroretinography. Biomicroscopy showed optic nerve atrophy, and narrow retinal vessels with a typical pattern of retinal pigmentation. After four initial treatments of LPT, visual acuity increased to 20/20 in each eye. Visual fields normalised except for a mid-peripheral absolute concentric scotoma. Five years after discontinuation of LPT, a relapse was observed. LPT was repeated (another four treatments) and restored the initial success. During the next 2 years, 17 additional treatments were performed on an "as needed" basis, to maintain the result. LPT was shown to improve and maintain vision in a patient with RP, and may thereby have contributed to slowing down blindness.

Further literature: [571, 600, 601, 602, 603, 622, 1217, 2315, 2340, 2341]



4.1.43 Pain

"Pain" could be the heading of almost any chapter in medicine. No step forward is appreciated more by the patients than the reduction of pain! The old exhortation "nil nocere" meshes well with the principles of LPT - lasers can prevent and reduce pain, as can be seen from much of the text above. A positive aspect of laser treatment is that pain can be alleviated as early as during the treatment session itself.

Large dosages are often required to achieve an immediate effect on acute pain since the pain relieving effect appears to be a matter of inhibition rather than of stimulation [1784]. A case of alveolitis can, for example, require as much as 20 J of GaAs laser light just to alleviate the pain. Less pronounced pain, such as a herpes sore or a decubital wound can require 3-4 J to achieve full relief from the symptoms. There is reason to believe that the large dosages used to alleviate severe pain also entail overdoses in the biostimulating range. The choice here is simple, however, and pain should be given priority. But care must be taken not to always give pain full priority. High doses over a knee, for instance, will soon reduce pain, but the stimulation of the chondrocytes may at the same time be inhibited. So the fine tuning can sometimes be delicate. Nonetheless, lowering the pain in an early phase can, on the other hand, allow the patient to go back to exercising, which in itself is positive.

Several mechanisms behind the pain relieving effect of LPT have been put forward, among them that the laser acts by inhibiting cyclooxygenase, interrupting the conversion of arachidonic acid into prostaglandin and also increases the production of ß-endorphin [872].

Pain can be more than just suffering for the patient. It can also be an obstacle to any kind of treatment, for instance in dental surgery. A painful sore means that soft tissue anaesthetic is required to enable the dentist to manipulate the patient's lips and cheeks. Pain from the maxillary joint means that the patient cannot open his mouth sufficiently for an adequate occlusal adjustment to be performed, and it may not even be possible to take an imprint for a bite splint. Pain in the neck and back can make it difficult for a patient to lie down. In all these cases, reducing pain means that one can go straight ahead with normal therapy. Pain is often part of a vicious circle where the pain itself prevents the patient from exercise, thus aggravating the existing damage. When lasers are used for wound healing, one of the first observed effects is the reduction of pain. This is an observation not recorded in animal wound healing studies.

Laser is not only able to reduce pain sensations after injury; it can also be used preoperatively to reduce the expected pain reaction. In the study by Zeredo [1588], the researchers tested the possible antinociceptive effect of laser irradiation when applied to normal tissue before the onset of a painful stimulus. Male rats were used. A 1.5% formalin solution was injected into the right upper lip of the test animals (n=9) immediately after 10 min of Er:YAG laser irradiation (energy: 0.1 J/cm^2 per pulse at 10 Hz). Control animals (n=9) were restrained for 10 min without laser application. The nociceptive response, i.e. the amount of time the rats spent rubbing the formalin injected area, was measured by an investigator blind to whether the animals had been laser irradiated or not. On laser irradiated rats, significantly less nociceptive behavior was observed only during the late phase (12-39 min) of the test. This result is similar to that reported for non-steroid antiinflammatory drugs (NSAIDs) and other peripherally acting antiinflammatory agents.

In a Meta analysis of the literature [872], there was a highly significant outcome for this kind of treatment of pain. The possible mechanisms and clinical effects found in randomised placebo controlled studies are presented in a review article by Bjordal [1681].

Literature:

In vitro studies

Chow [1784] reports the formation of 830 nm laser-induced, reversible axonal varicosities, using immunostaining with ß-tubulin, in small and medium diameter, TRPV-1 positive, cultured rat DRG neurons. Laser also induced a progressive and statistically significant decrease in MMP in mitochondria in and between static axonal varicosities. In cell bodies of the neuron, the decrease in MMP was also statistically significant, but the decrease occurred more slowly. Importantly we also report for the first time that 830 nm laser blocked fast axonal flow, imaged in real time using confocal laser microscopy and JC-1 as mitotracker. Control neurons in parallel cultures remained unaffected with no varicosity formation and no change in MMP. Mitochondrial movement was continuous and measured along the axons at a rate of 0.8 microm/s (range 0.5-2 microm/s), consistent with fast axonal flow. Photoacceptors in the mitochondrial membrane absorb laser and mediate the transduction of laser energy into electrochemical changes, initiating a secondary cascade of intracellular events. In neurons, this results in a decrease in MMP with a concurrent decrease in available ATP required for nerve function, including maintenance of microtubules and molecular motors, dyneins and kinesins, responsible for fast axonal flow. Laser-induced neural blockade is a consequence of such changes and provides a mechanism for a neural basis of laser-induced pain relief. The repeated application of laser in a clinical setting modulates nociception and reduces pain.

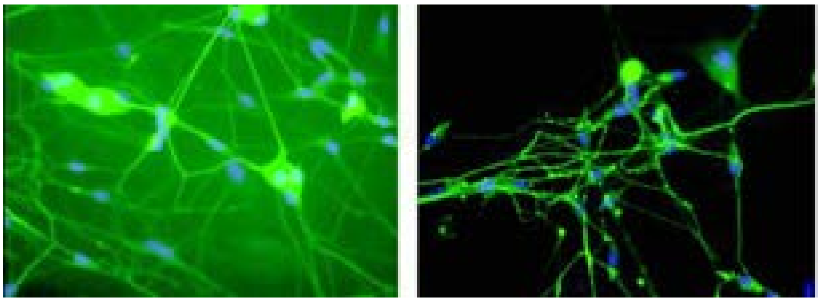


Figure 4.25 Formation of varicosities after 830 nm irradiation. Courtesy: Roberta Chow

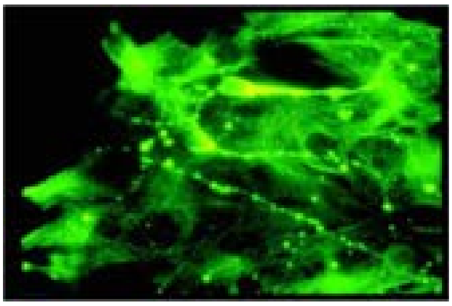


Figure 4.26 The same phenomenon observed with Nd:YAG laser. Courtesy: Ambrose Chan

The study by Hagiwara [2000] investigated whether LPT may enhance peripheral endogenous opioid analgesia. The effect of LPT on opioid analgesia and production was evaluated in vivo in a rat model of inflammation as well as in vitro in Jurkat cells, a human T-cell leukemia cell line. mRNA expression of the ß-endorphin precursors proopiomelanocortin and corticotrophin releasing factor was assessed by a reverse transcription polymerase chain reaction. LPT produced an analgesic effect in inflamed peripheral tissue which was transiently antagonised by naloxone. ß-endorphin precursor mRNA expression increased with LPT, both in vivo and in vitro. This study demonstrates that LPT produces analgesic effects in a rat model of peripheral inflammation. The researchers also revealed an additional mechanism of LPT-mediated analgesia via enhancement of peripheral endogenous opioids. These findings suggest that LPT induces analgesia in rats by enhancing peripheral endogenous opioid production in addition to previously reported mechanisms.

Animal studies

Montesinos [40] studied the blood concentration of various amino acids in rats after direct laser irradiation of the pituitary gland. The mean value in the control group was 4.57 µg/ml. In the laser group treated with HeNe, the mean level after day one was 47, day three 24, and day five 53. By day seven it had dropped to 0.8 and by day fifteen it had risen again to 24, then dropped once more to 22 by day twenty-one. In the GaAs group, the level was 44 after three days and 21 after seven days. Both lasers were thus effective but worked in different ways. The peptides studied build leukoencephalins and metencephalins, which affect the apprehension of pain.

Honmura [188], however, has conducted experiments which indicate that the pain-relieving effect of LPT is not only opiod-related. By injecting a substance which causes pain in the paws of rats (in accordance with a well-known experimental model), it was found that the analgesic effect was just as good whether indomethacin or LPT was used. In one group, a single dose of GaAlAs eliminated pain for 24 hours. Naloxone is a substance that counteracts the effects of opiates. When it was used, the effect of LPT was reduced but not eliminated. This experiment indicates that there are other possible explanations behind LPT's analgesic effects.

Katsuyama [662] studied the effect of 830 nm laser in a rat model of neuropathic pain. The left side's sciatic nerves of two groups of rats were ligated loosely to produce a neuropathic pain. The latency of the foot withdrawal reflex to noxious heat stimuli was measured before the ligation, immediately after laser/placebo radiation, and on day 14 after ligation. The laser group received 72 J through the dermis. This group showed a significant reduction in the left foot's withdrawal reflex immediately after irradiation and on day 14, the right foot remaining unchanged. Placebo irradiation did not change the latency either in the ligated group or in the non-ligated rats.

Giuliani [1515] used a red diode laser of 3 mW in experimental pain in rats. Acute inflammation was induced by an intraplantar injection of carrageenan, chronic inflammation was induced by a complete Freund's adjuvant (CFA), and neuropathic pain was produced by a sciatic nerve chronic constriction injury (CCI). In this study, laser was effective in reducing oedema and hyperalgesia in acute and chronic inflammation if administered at the points usually selected for acupuncture. Moreover, spontaneous pain and thermal hyperalgesia were reduced in CCI rats treated with LPT. In conclusion; laser reduced oedema and induced analgesia in experimental plantar pain in rats. The author suggests that the enkephalin mRNA level was strongly upregulated in the external layers of the dorsal horn of the spinal cord in CFA and CCI animals, and that laser further increased the mRNA level in single neurons.

In an animal study by Mrowiec [432], it is suggested that nitric oxide is involved in the mechanism of low-power laser-induced analgesia. The *injection of 1-NAME blocked the analgesic effect obtained by 904 nm irradiation of rat skulls.*

The purpose of a study by Aimbire [1560] was to investigate the effect of LPT on rat trachea hyperreactivity (RTHR), bronchoalveolar lavage (BAL) and lung neutrophils influx after Gram-negative bacteria lipopolysacharide (LPS) intravenous injections. The RTHR, BAL and lung neutrophils influx were measured over different intervals of time (90 min, 6 h, 24 h and 48 h). The energy density (ED) that produced an anti-inflammatory effect was 2.5 J/cm², reducing the maximal contractile response and the sensibility of trachea rings to methacholine after LPS. The same ED produced an anti-inflammatory effect on BAL and lung neutrophils influx. The Celecoxib COX-2 inhibitor reduced RTHR and the number of cells in BAL and lung neutrophils influx of rats treated with LPS. Celecoxib and laser reduced the PGE_2 and TXA2 levels in the BAL of LPS-treated rats. These results demonstrate that 685 nm LPT produced anti-inflammatory effects on RTHR, BAL and lung neutrophils influx in association with inhibition of COX-2-derived metabolites.

The purpose of another study by Albertini [1580] was to investigate the effect of LPT on the acute inflammatory process. Male rats were used. Paw oedema was induced by a sub-plantar injection of carrageenan, the paw volume was measured before and one, two, three and four hours after the injection, using a hydroplethysmometer. To investigate the mechanism action of the GaAlAs laser on inflammatory oedema, parallel studies were performed using adrenalectomised rats or rats treated with sodium diclofenac. Different laser irradiation protocols were employed for specific energy densities (EDs), exposure times and repetition rates. The rats were irradiated with laser for 80 s each hour. The EDs that produced an anti-inflammatory effect were 1 and 2.5 J/cm², reducing the oedema by 27% and 45.4%, respectively. The ED of 2.5 J/cm² produced anti-inflammatory effects similar to those produced by the cyclooxigenase inhibitor sodium diclofenac at a dose of 1 mg/kg. In adrenalectomised animals, the laser irradiation failed to inhibit the oedema. These results suggest that low-power laser irradiation possibly exerts its anti-inflammatory effects by stimulating the release of adrenal corticosteroid hormones.

The aim of the study by Ferreira [1733] was to evaluate the analgesic effect of the LPT with a HeNe laser on acute inflammatory pain, verifying the contribution of the peripheral opioid receptors and the action of LPT on the hyperalgesia produced by the release of hyperalgesic mediators of inflammation. Male rats were used. Three complementary experiments were done: (1) The inflammatory reaction was induced by the injection of carrageenin into one of the hind paws. Pain threshold and volume increase of the oedema were measured by a pressure gauge and plethysmography, respectively. (2) The involvement of peripheral opioid receptors on the analgesic effect of the laser was evaluated by simultaneous injections of carrageenin and naloxone into one hind paw. (3). Hyperalgesia was induced by injecting PGE_2 for the *study of the effect of the laser on the sensitisation increase of nociceptors. A HeNe laser of 2.5 J/cm² was used for irradiation. The researchers found that HeNe stimulation increased the pain threshold by a factor between 68% and 95% depending on the injected drug. They also observed a 54% reduction on the volume increase of the oedema when it was irradiated. The analgesic effect seems to involve hyperalgesic mediators instead of peripheral opioid receptors.*

Wedlock [1017] sought to establish dose dependency and time course for effects of cranial laser irradiation in two rodent models of pain. These were the hot plate and tail flick tests, which are both widely used to quantify analgesic drug effects. The laser used was GaAlAs, average power output 100 mW, pulse repetition rate 5 kHz. Irradiation was applied to shaved heads of rats above the midbrain. In the first experiment, four groups of 10 rats received doses of 0, 6, 12, 18, and 24 J/cm² in random order prior to hot plate testing either immediately, 30 min, 1 h or 24 h post laser. The second study employed three groups of 10 rats receiving 0, 12, and 18 J/cm² in random order prior to tail flick testing at the three shorter times above. Latency to lick hind paws on the hot plate was highly significantly prolonged by laser treatment across all doses and time periods. There was a clear dose dependency for immediate observations, but at 24 h 18 J/cm² was the most effective dose. Laser treatment also delayed tail flick responses at both doses and for all time periods, but 12 and 18 J/cm² doses were similar in efficacy.

In the study by Sato [1512], 830 nm, 40 mW was used for the treatment of many kinds of pain. The mechanism of action of the laser irradiation for analgesia was studied in anesthetised rats. The effect of laser irradiation of the saphenous nerve was studied by recording neuronal activity at the L4 dorsal root filaments after the injection of a chemical irritant, turpentine. Laser irradiation inhibited both the asynchronous firing that was induced by turpentine and increased part of the slow components of the action potentials. Thus, the laser irradiation selectively inhibited nociceptive signals at peripheral nerves.

The aim of the study by Pozza [1993] was to evaluate the analgesic effect of laser therapy on healthy tissue of mice. Forty-five animals were divided into three groups of fifteen each: A: infrared laser irradiation (830 nm), B: red laser irradiation (660 nm), and C: sham irradiation with the laser unit off. After laser application, the mice remained immobilised by injecting 30 microl of 2% formalin into the plantar pad of the irradiated hind paw. The time that the mouse kept the hind paw lifted was measured with 5 minute intervals for 30 minutes. Results showed statistically significant differences comparing the control group with the infrared laser group at 5, 20, 25 and 30 accumulated minutes, and with the red laser group at all time points. The analysis of partial times, for each 5 minutes, showed statistically significant differences between the control and the laser groups up to 20 minutes. Thus, laser irradiation had an analgesic effect and red laser had the best results.

To better understand the mechanisms of therapeutic lasers for treating human myofascial trigger points, Chen [1997] designed a blinded controlled study of the effects of a therapeutic laser on the prevalence of endplate noise (EPN) recorded from the myofascial trigger spot (MTrS) of rabbit skeletal muscle. In eight rabbits, one MTrS in each biceps femoris muscle was irradiated with a 660 nm at 9 J/cm^2. The contralateral side of the muscle was treated with a sham laser. Each rabbit received six treatments. The immediate and cumulative effects were assessed by the prevalence of EPN with electromyographic (EMG) recordings after the first and last treatments. Compared with pretreatment values, the percentages of EPN prevalence in the experimental side after the first and last treatments were significantly reduced. The change in EPN prevalence in the experimental side was significantly greater than in the control side immediately after the first and last treatments. However, no significant differences were noted between the first and last treatments. It seems that laser irradiation may inhibit the irritability of an MTrS in rabbit skeletal muscle. This effect may be a possible mechanism for myofascial pain relief with LPT.

Hagiwara [1999] investigated whether pre-irradiation of blood by LPT enhances peripheral endogenous opioid analgesia. The effect of LPT pretreatment of blood on peripheral endogenous opioid analgesia was evaluated in a rat model of inflammation. Additionally, the effect of LPT on opioid production was also investigated in vitro in rat blood cells. The expression of the ß-endorphin precursors, proopiomelanocortin and corticotrophin releasing factor, were investigated by a reverse transcription polymerase chain reaction. LPT pretreatment produced an analgesic effect in inflamed peripheral tissue, which was transiently antagonised by naloxone. Correspondingly, ß-endorphin precursor mRNA expression increased with LPT, both in vivo and in vitro. These findings suggest that LPT pretreatment of blood induces analgesia in rats by enhancing peripheral endogenous opioid production, in addition to previously reported mechanisms.

Neuropathic pain (NP) is one of the most suffered conditions in medical disciplines. The role of reactive oxygen species (ROS) and oxidative stress in the induction of NP was studied by many researchers. Neuropathies lead to medical, social, and economic isolation of the patient, so various therapies were used to treat or reduce it. Chronic constriction injury (CCI) is a well-known model for neuropathic pain studies. In order to find the effects of different wavelengths of LPT on the injured sciatic nerve, the present research was done by Masoumipoor [2506]. Thirty Wistar adult male rats were used in this study. The animals were randomly divided into three groups (n=10). To induce neuropathic pain for the sciatic nerve, the CCI technique was used. 660 and 980 nm were used for two consecutive weeks. Thermal and mechanical hyperalgesia was done before and after surgery on days 7 and 14, respectively. Paw withdrawal thresholds were also evaluated. CCI decreased the pain threshold, whereas both wavelengths of LPT for 2 weeks increased mechanical and thermal threshold significantly. A comparison of *the mechanical and thermal threshold showed a significant difference between the therapeutic effects of the two groups that received LPT. Based on these findings, the laser with a 660 nm wavelength had better therapeutic effects than the laser with a 980 nm wavelength, so the former one may be used for clinical application in neuropathic cases.*

Clinical studies

Laakso [253] wanted to study the possible relationship between LPT and opiods. In a double-blind study, 56 patients with chronic pain conditions were treated with a 820 nm, 25 mW; 670 nm, 10 mW and a LED 660 nm, 9.5 mW. ACTH and ß-endorphin levels were significantly elevated in the LPT groups but not in the LED group. Responses were dependent on dose and wavelength. The cumulative effect of LPT was confirmed.

Shiroto [53] carried out a retrospective interview-based study of patients who had received pain-relieving treatment with GaAlAs laser light. Of the 3635 patients treated over a period of 46 months, 82.8% regarded the treatment as effective. Of the 1300 patients who received more than 10 treatment applications, 76% regarded the treatment as effective. One single application could relieve pain for nine hours (16.5%) to three days (83.5%). This reference is obviously not a matter of a double-blind study or a controlled experiment, and the dropout rate is high, but the size of the group is such that the study should be taken seriously. Shiroto later [217] evaluated an extended patient group of 7700 patients and arrived at the same results. Recently, Shiroto published the results from 8844 patients and the results are consistent. The most recent publication on this long-term study is [1446].

Zhong [303] and Choi [496] have also demonstrated the role of endogenous opiate-like peptides and serotonin in laser acupuncture anaesthesia.

Mizokami [54] studied the effects of GaAlAs laser on pain conditions at a neurosurgical clinic. The number of cases where the result of treatment was "excellent" or "good" among patients with occipital neuralgia was 81%, among patients with pain in arms/shoulders/neck 79%, and for patients with pain in the back 50%.

Irradiation of the stellate ganglion can be used as an additional treatment in pain patients. Hashimoto and Kemmutso [691, 692] have shown that even irradiation of the stellate ganglion alone can have an effect on pain. In a double-blind study, patients with postherpetic neuralgia were treated with either a 150 mW GaAlAs, a 60 mW GaAlAs or a placebo laser. VAS pain scores and regional skin temperature were affected by laser, but there was no change in the placebo group. The pain reduction was dose dependent. It is suggested that laser irradiation of the stellate ganglion is a good alternative to traditional blocks.

Phantom pain after amputation is a severe problem. Taguchi [663] reports that LPT has been the most effective way of releasing the phantom pain of an amputee.

In a double-blind study by Mohktar [161], experimental pain was induced in human volunteers. The pain was similar to that of an acute fracture. This type of pain is unresponsive to 900 mg of paracetamol or 600 mg of aspirin. A GaAlAs laser, however, did have a significant pain reducing effect.

Hansen [55] treated 40 patients with various chronic oro-facial pain conditions. The majority of the patients (38 female, 2 male) suffered from dysaesthesia ("burning mouth syndrome"). The patients had had their symptoms for approximately five years and were resistant to therapy. The effect was measured on a Visual Analogue Scale (VAS) and by measuring 5-HIAA in urine. No positive effect was observed. ***It is interesting to note that the authors themselves state the origin of "burning mouth" as multifactor, psychosomatic or psychogenic. Thus, there would be no actual injury to the tissue, and laser, like any other modality, would have no effect. The negative 5-HIAA measurement may indeed confirm the inappropriate inclusion parameters in this study.***

Eckerdal [595] used 830 nm, 30 mW laser light for atypical facial pain. At the end of the trial, 76% of the patients were pain-free, and at the one-year check-up 44%, were free from pain.

Bradley [436] treated 100 cases of painful oral conditions with a GaAlAs laser. A good improvement was achieved in nearly 60%.

In a double-blind study, Cieslar [626] treated a group of 522 patients suffering from various overloading syndromes of the motional system. One group was given sham irradiation, one 904 nm, another 850 nm, and yet another 633 nm laser irradiation. The diagnoses were epicondylitis humeri (1), periarthritis humeroscapularis (2), periarthritis genu (3), and aponeurosis-sitis plantaris (4). Distinct pain relief was generally obtained after five to seven sessions. Regression of swelling and increased mobility were obtained after 10-20 irradiations. The best results were obtained in epicondylitis (87%), followed by (2), (3), and (4), the latter 61%. Indications (3) and (4) required more sessions than (1) and (2). The results obtained were significantly better by comparison with the control group, although the high percentage of improvement in the control group (39%) indicates that laser also is a strong placebo tool. There was no significant difference between the three wavelengths.

Ceccherelli [315] used a GaAs laser in a double-blind study on cervical myofascial pain. The patients were submitted to 12 sessions on alternate days, total dose per session 5 J. During each session, the four most painful muscular trigger points and five bilateral homometameric acupuncture points were irradiated. Pain relief was statistically significant both at the end of the treatment period and at a three-month follow-up examination.

Toya [255] performed a two-centre double-blind study on a group of 115 patients. The groups were: extremity joint pain, cervical pain and lumbar pain. A 830 nm 60 mW laser was used in the contact mode. All in all 82%

of those in the laser group reported effective pain relief, compared to 42% in the sham treatment group.

Maricic [56] tested a GaAs laser on 53 dental patients with various pain conditions. The diagnoses included pain after extraction, neuralgia, solitary aphtha, decubitus ulcer, dentitio dificilis and hyperaemic pulp. The average number of treatment sessions was 3.4 and each session took between 3 and 10 minutes. Full relief from pain was achieved in 69.8% of the cases, an obvious improvement in 20.7%, and some improvement in 9.4%. No patient reported a total lack of pain relief.

Taguchi [189] examined the effects of 780 nm on a group of 124 out-patients with various pain conditions. Treatment was administered one to three times a week for an average of seven weeks. The study was conducted double-blind. A high level of pain relief was achieved in 45 out of 63 members of the experimental group, and in 8 out of 61 of the control group. Thermography was carried out 92 times on 20 different patients. An increase in the skin's microcirculation was observed after LPT.

Nelson [1251] studied the effect on somatosensory trigeminal evoked potentials (STEP) and latencies by intraoral laser irradiation of the maxillary nerve. After electrical input at the left infraorbital foramen on 24 experimentally blinded, pain-free subjects, HeNe laser (1.7 mW, 50 Hz, 0.1 J) was performed on 12 of these subjects and sham irradiation on the other 12, at the left maxillary third molar area. Far-field STEP latencies and amplitudes were recorded; at baseline, immediately after intervention, 10 and 20 minutes after intervention. In the irradiated group an immediate average STEP amplitude decrease from baseline of 60% occurred, with a further reduction to 65 and 72% at the 10 and 20 minute intervals. No significant changes occurred in the sham irradiation group and no change in latencies was observed in either group.

The aim of the study by Schuhfried [1717] was to examine the effects of helium-neon laser irradiation on the mechanical (pressure algometry) and electrical (1 ms monophasic square-wave pulses, 50 Hz) pain threshold. Thirty-two pain-free subjects were randomly assigned to either the experimental group (helium-neon laser stimulation: 5 mW, 10 min) or the placebo group (sham stimulation). Laser or sham stimulation and pain threshold ascertainment were carried out on the dorsal aspect of the forearm area. The contra lateral arm served as an untreated control. The groups were compared with each other and with the control arm. No significant differences were found between the laser stimulation and the sham stimulation in changes of either the mechanical or the electrical pain threshold. There were no changes in the mechanical pain threshold through laser stimulation and sham stimulation with respect to the untreated contra lateral arm. After laser stimulation, electrical pain threshold was significantly higher in the treated arm than in the untreated contra lateral arm, because this threshold decreased in the contra lateral arm. This was not the case in sham treatment.

A prospective, double-blind, randomised, and controlled trial was conducted by Gür [1433] in patients with chronic myofascial pain syndrome (MPS) in the neck to evaluate the effects of infrared 904 nm Gallium-Arsenide LPT on clinical issues and quality of life (QoL).: The study group consisted of 60 MPS patients. Patients were randomly assigned to two treatment groups: Group I (actual laser; 30 patients) and Group II (placebo laser; 30 patients). LPT continued daily for 2 weeks except weekends. Follow-up measures were evaluated at baseline, and at week 2, 3 and 12. All patients were evaluated with respect to pain at rest, pain at movement, number of trigger points (TP), the Neck Pain and Disability Visual Analog Scale (NPAD), Beck Depression Inventory (BDI), and the Nottingham Health Profile (NHP). In the active laser group, statistically significant improvements were detected in all outcome measures compared with baseline, while in the placebo laser group, significant improvements were detected in only pain score at rest at 1 week after the end of treatment. The score for self-assessed improvement of pain was significantly different between the active and placebo laser groups (63 vs. 19%). This study revealed that short-period application of LPT is effective in pain relief and in the improvement of functional ability and QoL in patients with MPS.

The subjects of the investigation by Mizutani [1276] consisted of 83 female patients that were treated during the two-year period from January 1999 to December 2002. Laser irradiation was applied for three minutes either every day or every other day for a total of 10 times. A semi-conductor laser with a wavelength of 830 nm and a power of 1 W was used. Evaluations were performed before and after the series of 10 exposures to laser irradiation. The evaluation included the measurement of pain using the Visual Analogue Scale (VAS) and serum prostaglandin E_2 (pg/mL). The analgesic effects were observed in 67 of 83 cases. The VAS scores for the effective cases decreased after the irradiation series from 8.5 +/- 0.2, to 2.8 +/- 0.2. The post-irradiation PGE_2 levels were lower than the pre-irradiation PGE_2 levels in the effective cases, which were 5.8 +/- 0.3 and 7.1 +/- 0.4 pg/mL, respectively. The post irradiation PGE_2 levels for the effective cases were lower than those for the ineffective cases, which were 5.8 +/- 0.3 and 7.3 +/- 0.9 pg/mL, respectively.

The study by Chow [1478, 1702] was undertaken to test the efficacy of a 300 mW, 830 nm laser in a prospective double-blind, randomised, placebo-controlled trial in patients with chronic neck pain. Ninety patients were enrolled. Laser was applied using the contact method over tender areas in the neck musculature, twice a week for 7 weeks. The primary outcome measure was change in a 10 cm Visual Analogue Scale for pain. Other measures used included a Self-Reported Improvement in pain, measured by a VAS, Short-Form 36 Quality-of-Life Questionnaire, Northwick Park Neck Pain Questionnaire, Neck Pain and Disability Scale and the McGill Pain Questionnaire. Measurements were taken at baseline, at the end of 7 weeks of treatment and at 12 weeks from baseline. Patients in the treated group expe-

rienced a mean self-reported improvement of 48.5% compared with 3.99% in the placebo group.

Chow [2381] searched computerised databases comparing efficacy of LPT using any wavelength with placebo or with active control in acute or chronic neck pain. Effect size for the primary outcome, pain intensity, was defined as a pooled estimate of mean difference in change in mm on 100 mm Visual Analogue Scale. The research group identified 16 randomised controlled trials including a total of 820 patients. In acute neck pain, results of two trials showed a relative risk (RR) of 1.69 (95% CI 1.22-2.33) for pain improvement of LPT versus placebo. Five trials of chronic neck pain reporting categorical data showed an RR for pain improvement of 4.05 (2.74-5.98) of LPT. Patients in 11 trials reporting changes in Visual Analogue Scale had pain intensity reduced by 19.86 mm (10.04-29.68). Seven trials provided follow-up data for 1-22 weeks after completion of treatment, with short-term pain relief persisting in the medium term with a reduction of 22.07 mm (17.42-26.72). Side-effects from LPT were mild and not different from those of placebo. It was show that LPT reduces pain immediately after treatment in acute neck pain and up to 22 weeks after completion of treatment in patients with chronic neck pain.

A systematic review by Kadhim-Saleh [2268] provides inconclusive evidence because of significant between-study heterogeneity and potential risk of bias. The benefit seen in the use of LPT, although statistically significant, does not constitute the threshold of minimally important clinical difference. However, Bjordal [2470] has criticised this paper for lack of scientific rigour and challenges the interpretation.

Hurwitz [2326] systematically searched Medline and screened for relevance literature published from 1980 through 2006 on the use, effectiveness, and safety of non-invasive interventions for neck pain and associated disorders. Consensus decisions were made about the scientific merit of each article; those judged to have adequate internal validity were included in our best evidence synthesis. Of the 359 invasive and non-invasive intervention articles deemed relevant, 170 (47%) were accepted as scientifically admissible, and 139 of these related to non-invasive interventions (including health care utilisation, costs, and safety). For whiplash-associated disorders, there is evidence that educational videos, mobilisation, and exercises appear more beneficial than usual care or physical modalities. For other neck pain, the evidence suggests that manual and supervised exercise interventions, low-level laser therapy, and perhaps acupuncture are more effective than no treatment, sham, or alternative interventions; however, none of the active treatments was clearly superior to any other in either the short- or long-term. For both whiplash-associated disorders and other neck pain without radicular symptoms, interventions that focused on regaining function as soon as possible are relatively more effective than interventions that do not have such a focus.

Debilitating stump pain following amputation surgery (phantom pain) is a major problem when it affects the patient's quality of life, often making the patient totally dependent on others for their day-to-day care. Attempts have been made to treat those patients through pharmacological, psychological, and physical therapies, but in many cases these fail to relieve the pain. The paper by Santamaria [2169] focuses on three patients with chronic, intense, and debilitating stump pain who were previously treated with pain medications, but with little success. These patients underwent nine sessions of LPT to the stump. All patients reported a decrease in the intensity of their pain and increased ability to perform daily living activities during a 4-month follow-up.

Kannan [2170] aimed to study the effect of therapeutic ultrasound, LPT and ischemic compression in reducing pain and improving cervical range of motion among patients with MTPt. Experimental study comparing three groups was designed as a 5 days trial. VAS for pain, provocative pain test using "soft tissue tenderness grading scheme" and active cervical lateral flexion using inch tape. Patients were divided into 3 groups, Gr 1 underwent treatment using therapeutic ultrasound, Gr 2 with LPT and Gr 3 with ischemic compression. Assessments were done on day 1 and day 5 of treatment respectively. ANOVA revealed improvement among all 3 groups as statistically significant difference between the start and end of trial. Analysis using Chi square test shows a statistically significant difference in the improvement between laser and the other 2 groups. Mean difference in the change of scores between the assessments showed laser therapy to have a tendency towards progressive improvement over the treatment period and a better improvement than the other 2 groups.

Malliaropoulos [2190] performed a randomised, double-blinded, placebo-controlled study to assess the effectiveness of LPT in patients with meniscal pathology, including only symptomatic patients with tiny focus of grade 3 attenuation (seen only on 0.7 thickness sequences) or, intrasubstance tears with spot of grade 3 signal intensity approaching the articular surface. None of the patients in the study group underwent arthroscopy or new magnetic resonance imaging investigation. Pain was significantly improved for the LPT group than for the placebo group. Pain scores were significantly better after LPT. Four (12.5 %) patients did not respond to LPT. At baseline, the average Lysholm score was 77±4.6 for the LPT group and 77.2±2.6 for the placebo group. Four weeks after LPT or placebo therapy, the laser group reported an average Lysholm score of 82.5±4.6, and the placebo group scored 79.0±1.9. At 6 months, the laser group had an average Lysholm score of 82.2±5.7, and after 1 year, they scored 81.6±6.6. Treatment with LPT was associated with a significant decrease of symptoms compared to the placebo group: it should be considered in patients with meniscal tears who do not wish to undergo surgery.

After the literature search by Jang [2329], 22 LPT trials related to joint pain were selected. The average methodological quality score of the 22 *trials consisting of 1014 patients was 7.96 on the PEDro scale; 11 trials reported positive effects and 11 trials reported negative effects. The mean weighted difference in change of pain on VAS was 13.96 mm in favour of the active LPT groups. When only considering the clinical trials in which the energy dose was within the dose range suggested in the review by Bjordal et al. in 2003 and in World Association for Laser Therapy (WALT) dose recommendation, the mean effect sizes were 19.88 and 21.05 mm in favour of the true LPT groups, respectively. The review shows that laser therapy on the joint reduces pain in patients. Moreover, when restricting the energy doses of the laser therapy into the dose window suggested in the previous study, more reliable pain relief treatments can be expected.*

In 2009, the International Association for the Study of Pain published the following summary:

Management of myofascial trigger points is multimodal. The most commonly used interventions are:

- Massage, ischemic compression, pressure release, and other soft tissue interventions (such as muscle energy) have shown moderately strong evidence for immediate pain relief.

- Dry needling of trigger points has shown clinical benefits, but more studies are needed.

- Laser therapy shows strong evidence of effectiveness for pain relief.

- Transcutaneous electrical nerve stimulation and magnet therapy have shown moderate evidence for immediate effects over myofascial trigger points.

- Exercise has shown moderate benefit and can include stretching and range of motion, strengthening, endurance, or coordination exercises.

- Ultrasound therapy has weak evidence for effectiveness in management of trigger points.

Further literature: [222, 443, 1045, 1055, 1261, 1445, 1570, 1630]

4.1.44 Periostitis

Periostitis in the lower leg caused by overexercise is a universal problem in athletes and runners. LPT can be used as a prophylactic treatment as well as after training. The periost is superficial and low power densities are required not to overdose.

Literature:

The purpose of the study by Chang [2504] was to observe the functional improvement of the lower limbs upon rehabilitation LPT. A total of 54 patients underwent triple-phase bone scans using skeletal nuclear scintigraphy, which confirmed periostitis in their lower limbs. The patients were then randomly divided into two groups: one group received laser therapy (N=29) and the other group (N=25) received an equivalent placebo treatment (a drug or physical therapy). Treatment protocol commenced with rehabilitation intervention and LPT was performed three times daily for 5 days at a *dosage of 1.4 J/cm². A Likert-type pain scale was used to evaluate the severity of pain. Balance function, including postural stability testing (PST) and limits of stability (LOS), was also performed to evaluate the function outcome. Patients experienced a significant improvement in pain by day 2 or day 5 after starting LPT, but here was no significant difference in pain scale between the measurements before (baseline) and immediately after LPT. Comparing the PST, the group differences of dynamic vs. static testings ranged from -18.54 to -50.22 and the PST after LPT were 3.73 units lower than those of before LPT. Comparing the LOS, the group differences of dynamic vs. static testing were similar to those in PST, and the relationship between LOS and groups only varied with the direction control during dynamic testing in direction at backward/right vs. right. LPT had a positive effect on proprioception in patients with lower limb periostitis.*

4.1.45 Plantar fasciitis

Plantar fasciitis can be successfully treated with LPT. Infrared light is needed in view of the dense skin and the depth of the target (10-12 mm). A good knowledge of the anatomy is essential, since the area of the tendon defect is less than 1 cm². A total of 6-10 J over the tendon insertion, followed by 3-4 J per cm along the arch of the foot, is a reasonable dosage. Three to six sessions may be needed, depending on the initial condition of the patient.

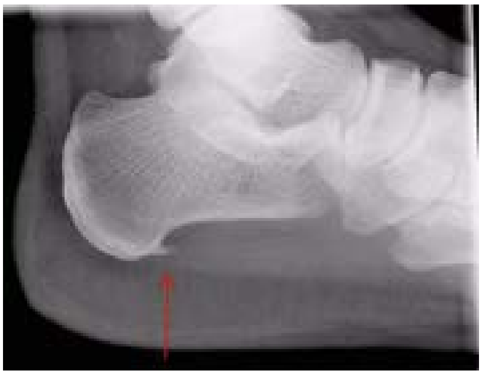


Figure 4.27 Plantar fasciitis
(Wikipedia)

Literature:

Basford [1028] treated 32 patients with plantar fasciitis during 12 sessions. The origin of the plantar fascia was given 1 J of 830 nm laser (30 mW) and the medial border of the fascia was swept with a total dose of 2 J. The outcome was negative, quite possibly due to the low dosage.

Hronková [949] irradiated the place of maximum pain with a 200 mW, 870 nm laser, energy density 9 J/cm², 10 sessions every other day. Sixty-one patients had this therapy while fifty-two patients had a non-active placebo *laser. In the laser group, 64% had a complete remission of pain, 26% experienced an improvement, and in 10% this therapy brought no effect at all. In the placebo group, 18% reported a full remission of pain, 42% reported an improvement and 40% felt no effect. In a separate study, ultrasound was used for 60 patients - 1 W/cm² applied for 5 minutes, 10 applications. All in all 50% of the patients had a complete remission of pain, 16.6% were improved and 33.3% reported no effect. Eight of the patients who had not experienced any effect from ultrasound were given LPT, no earlier than two weeks after ending the ultrasound treatment. Six of these patients evaluated their treatment as successful while the additional LPT had no effect in two patients.*

The aim of a study by Kiritsi [2118] was to investigate the effect of LPT on plantar fasciitis documented by the ultrasonographic appearance of the aponeurosis and by patients' pain scores. Thirty individuals with diagnosis of unilateral plantar fasciitis were enrolled in a randomised, double-blind, placebo-controlled trial, but 25 participants completed the therapeutic protocol. The contralateral asymptomatic fascia was used as control. After enrolment, symptomatic individuals were randomly assigned to receive LPT, or identical placebo, for 6 weeks. Ultrasonography was performed at baseline and after completion of therapy. The subjective subcalcaneal pain was recorded at baseline and after treatment on a Visual Analogue Analogue (VAS). After LPT, plantar fascia thickness in both groups showed significant change over the experimental period and there was a difference (before treatment and after treatment) in plantar fascia thickness between the two groups. However, plantar fascia thickness was insignificant (mean 3.627 +/- 0.977 mm) when compared with that in the placebo group (mean 4.380 +/- 1.0042 mm). Pain estimation on the Visual Analogue Analogue had improved significantly in all test situations (after night rest, daily activities) after LPT when compared with that of the placebo group. Additionally, when the difference in pain scores was compared between the two groups, the change was statistically significant. In summary, while ultrasound imaging is able to depict the morphologic changes related to plantar fasciitis, 904 nm gallium-arsenide (GaAs) infrared laser may contribute to healing and pain reduction in plantar fasciitis.

Plantar fasciitis affects nearly 1 million people annually in the United States. Traditional non-operative management is successful in about 90% of patients, usually within 10 months. Chronic plantar fasciitis develops in about 10% of patients and is a difficult clinical problem to treat. In a study by Jastifer [2500] thirty patients were administered LPT and completed 12 months of follow-up. Patients were treated twice a week for 3 weeks for a total of 6 treatments and were evaluated at baseline, 2 weeks post procedure, and 6 and 12 months post procedure. Patients completed the Visual Analogue Scale (VAS) and Foot Function Index (FFI) at study follow-up periods. Patients demonstrated a mean improvement in heel pain VAS from 67.8 out of 100 at baseline to 6.9 out of 100 at the 12-month follow-up period. Total FFI score improved from a mean of 106.2 at baseline to 32.3 at 12 months *post procedure. The laser was irradiating the heel area from three sides with 630 nm, 17 mW, during 10 minutes per session, delivering a total energy of about 30 J per session. Since few photons actually reached the inflamed tendon, this is a good example of a systemic effect.*

Further literature: [626]

4.1.46 Salivary glands

Mouth dryness is usually followed by inadequate mechanical cleaning of the mouth and decrease in the levels of salivary antimicrobial proteins (including secretory immunoglobulin A (sIgA)). It is accompanied by difficulties during speaking and food swallowing, with an unpleasant taste, burning sensations in the mouth and higher susceptibility to oral diseases. LPT can intensify cell metabolism and its application on salivary glands could improve salivation. Sjögren's syndrome is an RA-related condition characterised by low saliva and tear secretion, among other things. The treatment of Sjögren's syndrome with lasers is still in the experimental stage, although preliminary results show that the salivary glands do react quickly to local treatment. It has not yet been made clear whether LPT has a long-standing effect. All three wavelengths (HeNe, GaAlAs, GaAs) have been shown to stimulate the salivary glands.

Literature:

Animal studies

Takeda [113] examined the effects of a GaAs laser on the submandibular salivary glands of rats. The rats were divided into three groups: a control group, a group treated with GaAs laser irradiation at 760 pulses per second, and a group treated with GaAs laser irradiation at 190 pulses per second. The glands were uncovered and irradiated, after which they were sutured. The effects were studied histologically 1 hour and 24 hours after irradiation. Increased mitosis in the duct epithelium was observed in one laser group. The greatest increase was in the granular salivary ducts, while the effects in the striated salivary ducts and in the intercalated ducts were less pronounced. Interestingly, the 760 Hz group exhibited stimulated mitosis, while the 190 Hz group was no different from the control group. ***The report does not make clear whether the GaAs laser was pulse-train regulated (i.e. gave the same average power, regardless of pulse repetition rate), and the difference in response may thus be related to dosage.***

Plavnik [1109, 1493] found that HeNe LPT could elicit an acceleration of soluble proteins in hamster submandibular glands as a result of trophic cell stimulus.

The study by Simões [1796] aimed to investigate whether infrared LPT increased salivary flow rate and altered pH value, protein concentration, *and peroxidase and amylase activities in saliva of rats. Wistar rats were used and divided into three groups. Experimental groups (A and B) had their parotid, submandibular and sublingual glands submitted to a diode laser, 808 nm wavelength, on two consecutive days. The doses were 4 and 8 J/cm², respectively. A red guide light was used to visualise the irradiated area. Group C was irradiated only with a red pilot beam and served as a control group. The saliva samples were collected after each irradiation step (first and second day of collection) and one week after the first irradiation (seventh day). Statistical analysis was performed, and differences were observed according to different days of salivary collection. The results showed that the salivary flow rate for groups A and B was higher on the seventh day when compared to the data obtained for the first day.*

The aim of a study by Simões [1838] was to evaluate the effects of infrared LPT on tissues of the submandibular gland (SMG) and parotid gland (PG). Wistar rats were randomly divided into experimental (A and B) and control (C) groups. 808 nm in continuous wave mode was applied to the PG, SMG and sublingual gland in the experimental groups on two consecutive days. The doses were 4 J/cm² and 8 J/cm², and total energy was 7 J and 14 J, respectively. The power output (500 mW) and power density (277 mW/cm²) were the same for both experimental groups. In order to visualise the area irradiated by the infrared laser, the authors used a red pilot beam (650 nm) with 3 mW maximum power for the experimental groups. For the control group, the red pilot beam was the only device used. The SMG and PG were removed after 1 week of the first irradiation. Total protein concentration, amylase, peroxidase, catalase and lactate dehydrogenase assays were performed, as well as histological analysis. Statistical tests revealed significant increase in the total protein concentration for groups A and B in the parotid glands.

Onizawa [1824] investigated cell response, including cell proliferation and expression of heat stress protein and bcl-2, to clarify the influence of GaAlAs laser irradiation on Par-C10 cells derived from the acinar cells of rat parotid glands. Furthermore, the author also investigated amylase release and cell death from irradiation in acinar cells from rat parotid glands. The number of Par-C10 cells in the laser-irradiated groups was higher than that in the non-irradiated group on days 5 and 7, and the difference was statistically significant. Greater expression of heat shock protein (HSP)25 and bcl-2 was seen on days 1 and 3 in the irradiated group. Assay of the released amylase showed no significant difference statistically between the irradiated group and the non-irradiated group. Trypan blue exclusion assay revealed that there was no difference in the ratio of dead to live cells between the irradiated and the non-irradiated groups. These results suggest that laser irradiation promotes cell proliferation and expression of anti-apoptosis proteins in Par-C10 cells, but it does not significantly affect amylase secretion or induce rapid cell death in isolated acinar cells from rat parotid glands.

The aim of another study by Simões [2121] was to evaluate the effect of laser irradiation on the amylase and the antioxidant enzyme activities, as well as on the total protein concentration of submandibular glands (SMG) of diabetic and non-diabetic rats. Ninety-six female rats were divided into eight groups: D0, D5, D10, and D20 (diabetic animals), and C0, C5, C10, and C20 (non-diabetic animals), respectively. Diabetes was induced by administering streptozotocin and confirmed later by the glycemia results. Twenty-nine days after diabetes induction, the SMG of groups D5 and C5, D10 and C10, and D20 and C20 were irradiated with 5, 10, and 20 J/cm^2, respectively. A diode laser (660 nm/100 mW) was used. On the day after irradiation, the rats were euthanised and the SMG were removed. Catalase, peroxidase, and amylase activities, as well as protein concentration, were assayed. Results: Diabetic rats without irradiation (D0) showed higher catalase activity when compared to C0 (0.16 +/- 0.05 and 0.07 +/- 0.01 U/mg protein, respectively). However, laser irradiation of 5, 10, and 20 J/cm^2 reduced the catalase activity of diabetic groups (D5 and D20) to non-diabetic values . In conclusion, laser irradiation decreased catalase activity in diabetic rats' SMG.

The objective of yet another study by Simões [2122] was to evaluate the effect of LPT on the glycemic state and the histological and ionic parameters of the parotid and submandibular glands in rats with diabetes. One hundred twenty female rats were divided into eight groups. Diabetes was induced by administration of streptozotocin and confirmed later according to results of glycemia testing. Twenty-nine days after the induction, the parotid and submandibular glands of the rats were irradiated with 5, 10, and 20 J/cm^2 using a laser diode (660 nm/100 mW) without diabetes: C5, C10, and C20; with diabetes: D5, D10, and D20, respectively). On the following day, the rats were euthanised, and blood glucose determined. Histological and ionic analyses were performed. Rats with diabetes without irradiation (D0) showed lipid droplets accumulation in the parotid gland, but accumulation decreased after 5, 10, and 20 J/cm^2 of laser irradiation. A decrease in fasting glycemia level from 358.97+/-56.70 to 278.33+/-87.98 mg/dL for D5 and from 409.50+/-124.41 to 231.80+/-120.18 mg/dL for D20 was also observed. In conclusion, LPT could be explored as an auxiliary therapy for control of complications of diabetes because it can alter the carbohydrate and lipid metabolism of rats with diabetes.

Clinical studies

The first study of salivary stimulation was published in 1987 by Fructuoso [500]. Using a GaAs laser, 6 J/cm^2, in a double-blind study, a significant improvement of the salivary production of the parotid gland was achieved. Treatment was given three times a week for three weeks, followed by one week of rest and repeated sessions, with a total number of 25 sessions.

Nagasawa [106] treated patients with Sjögren's syndrome with a GaAlAs laser (20 mW) intraorally, five minutes per treatment. Approximately

15 to 20 treatment sessions were administered. After this treatment period, the patients' parotid gland function returned for an extended period.

Kats [279] treated 88 patients with sialoadenitis with HeNe laser. The treatment led to a quicker decline in inflammation and pain, higher salivation, longer discomfort-free periods, and an improvement of the gland structure.

Arao [1110] reports that the salivation in two patients with xerostomia could be stimulated with LPT.

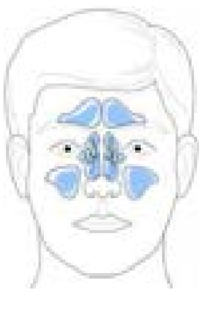
A clinical case study reports on dry mouth symptoms in a patient with Sjögren's syndrome (SS) who was treated with LPT by Simões [2119]. A 60-year-old woman diagnosed with SS was referred to the laboratory for lasers in dentistry to treat her severe xerostomia. A diode laser (780 nm, 3.8 J/cm^2, 15 mW) was used to irradiate the parotid, submandibular, and sublingual glands, three times per week, for a period of 8 months. The salivary flow rate and xerostomia symptoms were measured before, during, and after LPT. Dry mouth symptoms improved during LPT. After LPT, the parotid salivary gland pain and swelling were no longer present. Treatment with LPT was an effective method to improve the quality of life of this patient with SS.

The aim of a study by Simões [2120] was to verify how LPT could influence xerostomia symptoms and hyposalivation of patients undergiong radiation therapy. Patients were divided into two groups: 12 individuals receiving three laser irradiations per week (G1) and 10 patients receiving one laser irradiation per week (G2). A diode laser (660 nm, 6 J/cm(2), 0.24 J, 40 mW) was used until completely healing of the lesions or the end of the RT. At the first and last laser sessions, whole resting and stimulated saliva were collected, and questionnaires were administered. According to Wilcoxon and Student statistical test, xerostomia for G1 was lower than for G2, and salivary flow rate was no different before and after RT, except forstimulated collection of G2, which was lower. These results suggest that LPT can be beneficial as an auxiliary therapy for hypofunction of salivary glands.

The aim of a study by Lonar [2330] was to investigate the effect of LPT on the secretory function of salivary glands in 34 patients with xerostomia. In this study, GaAs laser, 904 nm was applied bilaterally on each salivary gland area: extraorally on the parotid and submandibular gland areas and intraorally on the sublingual gland area. The operational probe distance from the irradiated area was 0.5 cm resulting in an irradiance of 246 mW/cm^2. The exposure time was 120 sec per daily treatment during 10 consecutive days. The average energy density per exposure was 29.5 J/cm^2 . The control group consisted of 16 patients who were treated with 15 mL of a 2% citric acid solution applied as a mouth rinse for 30 sec. The average difference in the amount of salivation (dQ-sal, mL/min) before and after laser therapy increased linearly from dQ-sal = 0.05 mL/min on the first day, up to dQ-sal = 0.13 mL/min on the last (10th) day of therapy. In the control group, the average dQ-sal initially demonstrated a gradual increase, with a reversal of the trend toward the end of the therapy period and eventually yielding no *correlation between the duration of therapy and dQ-sal. The results of this study indicate that the effects of LPT on salivary glands are not only stimulating, but also regenerative to a degree since the glandular response to the same amount of applied laser energy increased linearly over time.*

The purpose of a study by Vidovic Juras [2394] was to evaluate the effects of LPT on salivation of patients suffering from xerostomia. The study included 17 patients with mouth dryness (MD). Their major salivary glands were treated with LPT on 10 occasions. The whole unstimulated and stimulated saliva quantities were measured just before the 1st, after the 10th and thirty days following the last (10th) treatment. In the samples of unstimulated saliva con-centrations of sIgA were estimated by using ELISA method and its quantity in the time unit was calculated. The VAS score was used to assess burning and/or pain intensity at these three time points. Statistical tests revealed significant salivation improvement quantitatively and qualitatively, i.e. increase in the quantity of saliva and sIgA. VAS score was also significantly improved and no side effects were observed. According to the results of this study, application of LPT to xerostomic patients' major salivary glands stimulates them to produce more saliva with better antimicrobial characteristics and improves the difficulties that are associated with MD. This simple non-invasive method could be used in everyday clinical practice for the treatment of MD.

The paper by Alfaya [2409] reports the case of a 62-year-old female patient with a diagnosis of Sjogren's syndrome confirmed by the criteria of the European Study Group on Sjogren's syndrome. The patient used artificial saliva and complained of xerostomia and orofacial pain (8 on the pain scale) with no oral manifestations (eg, dental caries, secondary candidiasis, or periodontal disease). Non-stimulated sialometry revealed salivary flow of 0.9 ml/15 min. LPT was administered bilaterally in the region of the parotid and submandibular glands. Forty sessions were performed using 4 J/cm^2, with a 48-hour interval between sessions. At the end of the treatment, there was a significant improvement in pain symptoms (0 on the pain scale) and the results of the sialometry (2.1 ml/15 min). The patient is currently followed up every 30 days, with stabilisation in salivary volume and no complaints of facial pain.



4.1.47 Sinuitis

Patients suffering from maxillary sinuitis or allergic rhinitis can have difficulty breathing through the nose during dental treatment. A total of 4-6 J is given intraorally over the bottom of the sinus at three to four points on the buccal and palatal side in contact mode. The sinus opening inside the nose is irradiated in a non-contact mode, 2-3 J. The projections of the ethmoidal and frontal sinuses are also irradiated, if involved.

Intra-cavitary irradiation is reported by Plushnikov [513]. The cavity is irradiated with HeNe through a lightguide inserted into the cavity by a puncture needle.

Acute sinuitis responds more quickly to treatment than chronic. During extraoral treatment, the eyes should be protected by asking the patient to close them. Protective glasses may be obstructive.

Figure 4.28 Sinuitis maxillaris before and after GaAlAs LPT.
Courtesy: M. Hacarova and J. Hubacek
http://www.sld.cu/galerias/pdf/sitios/rehabilitacion-fis/laser_y_sinusitis.pdf

Literature:

Roshal [104] treated two groups of 227 and 120 children with allergic rhinitis. HeNe laser light was administered directly on the mucosa, via fibre optics, with excellent results. The positive results of this study were confirmed by tomography and direct inspection. Although this study does not report on sinuitis, it shows the importance of reaching the inflamed mucosa with the irradiation.

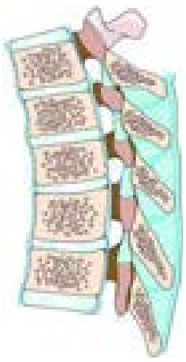
Kaiser [507] used HeNe laser in a double-blind study of acute maxillary sinuitis. Thirty patients participated in each group; 7 J/cm^2 was given on the skin and 4 J/cm^2 intraorally over the bottom of the sinus. The oedema of the mucosa was reduced.

Kruchinina [541] examined the effect of HeNe LPT in young patients with sinuitis through conjunctival biomicroscopy. LPT produced a positive effect on microcirculation. The primary effects were on vessel permeability (decrease of oedema) and red blood cell aggregation. The best results were obtained in acute cases.

The aim of a study by Naghdi [2221] was to evaluate the effect of LPT in patients with chronic rhinosinusitis (CRS). Fifteen adult patients with CRS participated in this pilot pretest-posttest clinical study. Patients were treated with a 830 nm laser, 30 mW, 1 J. Laser irradiation was delivered on six points over each maxillary or frontal sinus with 33 sec irradiation for each point and a total treatment duration of 198 sec for each sinus. Patients were *given LPT three times per week for ten treatment sessions. Patients were asked to score their symptoms in accordance with a four-point scale (0-3), and a total symptom score (TSS) for each patient was calculated. Percentage improvement of TSS was considered as the primary outcome measure. TSS was calculated at baseline (T0), at 2 weeks (T1) and at 4 weeks (T2). The TSS was improved significantly at T1 (39%) and at T2 (46.34%). A large effect size for LPT was found. The therapeutic effect was sustained for a mean of 5 months.*

The objective of a study by Yildirim [2336] was to investigate the effect of intranasal phototherapy on nasal microbial flora in patients with allergic rhinitis. This prospective, self-comparised, single blind study was performed on patients with a history of at least two years of moderate-to-severe perennial allergic rhinitis that was not controlled by anti-allergic drugs. Thirty-one perennial allergic rhinitis patients were enrolled in this study. Before starting the test population on their intranasal phototherapy, the same trained person took a nasal culture from each subject by applying a sterile cotton swab along each side of the nostril and middle meatus. Each intranasal cavity was irradiated three times a week for two weeks with increasing doses of irradiated. At the end of the intranasal phototherapy, nasal cultures were again obtained from the each nostril. The study found that after intranasal phototherapy, the scores for total nasal symptoms decreased significantly but bacterial proliferation was not significantly different before and after phototherapy.

Further literature: [103, 340, 466, 534, 541, 542, 543, 555, 886, 1036, 1155]



4.1.48 Spinal cord injuries

Spinal cord injuries can, in seconds, change the life of a person from being fit to becoming crippled with the prospect of spending the rest of his/her life in a wheel chair. The actual injury normally has very small potential for healing. It is therefore a bit surprising that the potential of LPT has met with so little interest. The LPT should preferably be one of the first therapies used, in order to improve the healing capacity of the nerves.

Literature:

Animal studies

The purpose of an experiment by Shi [839] was to elucidate the influence of the HeNe laser on the regeneration of peripheral nerves. Forty-four rabbits were used in the experiment. The animals were divided into 4, 8, 12, 16 week groups according to the observation period. Six animals were used in each irradiated group, and five rabbits were used in the control group during each observation period. Regeneration of the axons and myelinic sheaths, the latent rate of the common peroneal nerve, the condition of the *anterior tibial muscle and the toe expansion test were all observed systematically in both groups. The experimental results were: A few thin regenerated axons were seen at 4 weeks in the irradiated group, while in the control group it could be not be observed until the 8th week. A low amplitude latent rate of the common peroneal nerve was determined at the peroneal side of the anterior tibial muscle in a few animals at 4 weeks in the irradiated group, but it was not observed in the control group until weeks 12 -16. The regeneration of the myeline sheath was evident in the irradiated group. At 16 weeks postoperatively, the toe expansion test was normal in the irradiated group, while in the control group it was the same as seen at 12 weeks after operation in the irradiated group.*

Rochkind [561] and his group subjected 17 dogs to laminectomy and transection of the spinal cord at TH12-L1. An autograft of the left sciatic nerve was then implanted into the injured area. Neurorrhaphy was performed on the right sciatic nerve. Altogether 7 dogs did not receive any additional treatment and served as a control. The other 10 were treated transcutaneously with 16 mW of HeNe laser light for 20 days (high doses) over the operated area. The 7 dogs in the control group became paralysed as expected. The 10 dogs that underwent the same operation but were immediately treated with a laser were able to stand after 7-9 weeks, and could walk a few steps after 9-12 weeks. The histological picture obtained from the dogs 21 days post operation showed no rejection and no prominent scar tissue at the site of contact between the spinal cord tissue and the transplanted nerve. Moreover, new axons and blood vessels originating in the spinal tissue extended into the graft. These were seen only in the laser treated group and not in the control group, in which scar tissue had developed at the site of transection.

The study by Shamir [1182] evaluated the therapeutic effect of LPT on peripheral nerve regeneration after complete transection and direct anastomosis of the rat sciatic nerve. Thirteen out of twenty-four rats received post-operative LPT, 780 nm, applied transcutaneously, 30 min daily for 21 consecutive days, to corresponding segments of the spinal cord and to the injured sciatic nerve. Positive somatosensory evoked responses were found in 69.2% of the irradiated rats, as compared to 18.2% of the non-irradiated rats. Immunohistochemical staining in the laser-treated group showed an increased total number of axons and a better functioning regeneration process, due to an increased number of large-diameter axons compared to the non-irradiated control group.

Further literature: see “Nerve regeneration”.

4.1.49 Snake bites

New indications for LPT are being discovered continuously. LPT as an adjunct treatment modality to reduce tissue breakdown after snake bites is just one of them.

Literature:

In a study by Dourado [1327], the venom of the bothrops moojeni snake was injected into the gastrocnemius of mice to mimic the effect of snakebites. Traditional therapies for this snakebite have proven rather ineffective. Three groups were tested: A=saline, B=venom, and C=venom+ laser. Two sessions of HeNe laser at 4 J/cm^2 for 1 min 32 s were administered and the animals were sacrificed at 24 h, and on days 3 and 7, respectively. The analysis showed myonecrosis with inflammation and an extensive area of degenerated fibres. In the laser group there was, by day 3, an incipient number of regenerating fibres. Laser accelerated the fagocytosis of fibre remnants and recovery of the tissue, decreasing the oedema and increasing regeneration.

The article by Barbosa [1814] reports the effect of LPT on the oedema formation and leukocyte influx caused by Bothrops jararacussu snake venom as an alternative treatment for snakebites. The inflammatory reaction was induced by an injection of 0.6mg/kg of B. jararacussu venom in the gastrocnemius muscle. Cell influx and oedema were evaluated at 3 or 24h after venom injection. Mice were irradiated at the site of injury by a 685nm laser with a dose of 4.2J/cm^2. A therapy that combines LPT and antivenom was also studied. B. jararacussu venom caused a significant oedema formation 3 and 24h after its injection, and a prominent leukocyte infiltrate composed predominantly of neutrophils at 24h after venom inoculation. LPT significantly reduced oedema formation by 53% and 64% at 3 and 24h, respectively, and resulted in a reduction of neutrophils accumulation. The combined therapy showed to be more efficient than each therapy acting separately. In conclusion, LPT significantly reduced the oedema and leukocyte influx into the envenomed muscle, suggesting that LPT should be considered as a potentially therapeutic approach for the treatment of the local effects of Bothrops species.

In another study by Barbosa [2061] myonecrosis was induced in mice by injection of 0.6 mg/kg of B. jararacussu venom in the right gastrocnemius muscle and was evaluated at 3 or 24 h after venom injection. The site of venom administration was irradiated for 29 s with 685 nm at a dose of 4.2 J/cm^2. Intravenous anti venom (AV) therapy (0.5 mL dose) was administered at different times: 30 min before venom injection or 0, 1, or 3 h afterward. Both AV therapy and LPT treatments were duplicated in mice groups killed at 3 or 24 h. B. jararacussu venom caused a significant myonecrotic effect 3 and 24 h after venom injection. LPT significantly reduced myonecrosis by 83.5% at 24 h but not at 3 h, and AV therapy alone was ineffective for reducing myonecrosis at 3 and 24 h. Only LPT significantly reduced myonecrosis of the envenomed muscle, suggesting that LPT is a potentially therapeutic approach for treating the local effects of B. jararacussu venom.

In a study by Doin-Silva [1998], the tibialis anterior muscle of rats was injected with snake venom, diluted in 0.9% saline solution or saline solution alone. Sixty minutes after venom injection, HeNe treatment was administered at three incident energy densities: dose 1, a single exposure of 3.5 J/cm²; dose 2, three exposures of 3.5 J/cm², dose 3, a single exposure of 10.5 J/cm². Muscle function was assessed through twitch tension recordings, whereas muscle damage was evaluated through histopathologic analysis, morphometry of the area of tissue affected and creatine kinase (CK) serum levels, and compared to un-irradiated muscles. Laser application at the dose of 3.5 J/cm² reduced the area of injury by 64%, decreased the neuromuscular blockade (NMB) by 62% and reduced CK levels by 58% , when compared to un-irradiated controls. Dose 2 showed a lesser benefit than dose 1, and dose 3 was ineffective in preventing the venom's effects. Measurements of the absorbance of un-irradiated and irradiated venom solution showed no difference in absorption spectra. In addition, no difference in the intensity of partial NMB in nerve-muscle preparation was shown by un-irradiated and irradiated venom. The results indicate that the laser light did not alter venom toxicity.

Figure 4.29 A bite on a finger from a Montpellier snake (Wikipedia)

Nadur-Andrade [2466] studied the effectiveness of LPT and LED irradiation alone or in combination with AV in reducing local edema formation and hemorrhage induced by Bothrops moojeni venom (BmV) in mice. Oedema formation was induced by injection of 1 mcg per paw of BmV into the right paw and was evaluated before and at several intervals after BmV intraplantar injection. Hemorrhagic activity was evaluated after intradermal injection of 20 mcg of BmV by measuring the diameter of the hemorrhagic area on the inner side of the skin. The site of BmV injection was irradiated by LPT or LED 30 min after BmV inoculation. AV was also administered intravenously 30 min after BmV injection. Irradiation with LPT at a wavelength of 685 nm and a dose of 2.2 J/cm² and with a red LED and an infrared LED at wavelengths of 635 nm and 945 nm, respectively, and a dose of 4 J/cm² reduced oedema formation and haemorrhage induced by BmV. The combined AV and LPT or LED treatment showed the same reduction as LPT or LED irradiation separately.

Further literature: [1484, 2378]

4.1.50 Sports injuries

The use of lasers in sports medicine is widespread. Top-level sportsmen and women often suffer from injuries, and it is vital the injuries heal quickly, so that the individual can resume training. Sports injuries have the “advantage” that the subject often knows when the injury occurred and where it is situated. The subjects also often have experience of how long it takes for a particular injury to heal. It is therefore easy to "calibrate" the effect of the laser. A rule of thumb is that a sports injury heals almost twice as fast if the healing process is stimulated by LPT. A common problem is that the subjective discomfort in the injured area soon disappears and the individual wants to return to training immediately. It is essential that the injured area be allowed to rest and that training be resumed gradually. Treatment should not be interrupted just because pain is gone. This is only the first sign of recovery.

LPT on chronic pain conditions can increase the pain level initially. This reaction is absent when treating acute injuries. Acute injuries can actually receive higher doses than chronic cases without side effects. Common conditions such as delayed onset muscle soreness and periostitis react very favourably to LPT. Therapy should be started as soon as possible after training or competition. In some instances, therapy before training/competition is useful. There is a strong incentive for the professional athlete to use LPT. Acc. to Swedish horse racing rules, LPT is not allowed during a period of 96 hours before a race.

Oedema is a common element in sports injuries. If there are a number of injured places, the patient should be treated according to the"proximal priority principle". This means that the proximal injury is treated first, the distal last. If the distal injury is treated first, lymph accumulation increases because the proximal injury prevents drainage. The result in such a case could be increased pain.

GaAs lasers with multiprobes give the shortest treatment times and have the widest range of indications. A GaAlAs laser is good for superficial and more limited injuries. However, the recent advent of high-powered GaAlAs lasers (500 mW or more) has widened the range of their indications. The handy format of medium-powered GaAlAs lasers makes them very useful for ambulatory work. (See chapter 4.1.53 “Tendinopathies” on page 407.)

The ability of LPT to stimulate stem cells and progenitor cells means that muscle satellite cells may respond well to LPT and help muscle repair. Furthermore the ability of LPT to reduce inflammation and lessen oxidative stress is also beneficial in cases of muscle fatigue and injury. A review by Ferraresi [2264] covers the literature relating to LPT and muscles in both preclinical animal experiments and human clinical studies. Athletes, people with injured muscles, and patients with Duchenne muscular dystrophy may all benefit according to this review.

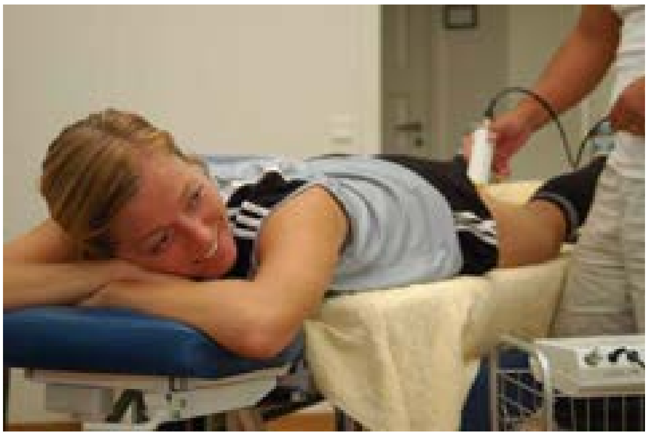


Figure 4.30 Soccer player getting treated with laser
Courtesy: Liljeholmens idrottsklinik

Literature:

Animal studies

Weiss [276] and Bibikova [277] observed improved muscle regeneration as a result of the use of HeNe and GaAs lasers in experiments on rats and batrachians (a kind of frog), respectively.

Fung [1302] transsected the medial collateral ligaments in 24 rats. Of these, 16 animals were treated with a single dose of a 660 nm laser, and 8 served as control. The ligaments were mechanically tested at three or six weeks post operation. It is suggested that ultimate tensile strength and stiffnes can be improved by LPT.

A study by Bayat [1638] sought to investigate whether or not LPT with a helium-neon laser increased biomechanical parameters of transected medial collateral ligament (MCL) in rats. Thirty rats received surgical transection to their right MCL, and five were assigned as the control group. After surgery, the rats were divided into three groups: group 1 (n=10) received laser with 0.01 J/cm^2 energy density per day, group 2 (n=10) received laser with 1.2 J/cm^2 energy density per day, and group 3 (sham exposed group; n=10) received daily placebo laser, while the control group received neither surgery nor laser. Biomechanical tests were performed on day 12 and 21 days after surgery. The data was analysed by one-way analysis of variance. The ultimate tensile strength (UTS) of group 2 on day 12 was significantly higher than that of groups 1 and 3. Furthermore, the UTS and energy absorption of the control (uninjured) group were significantly higher than those of the other groups.

The study by Santos [2508] aimed to evaluate the effects of LPT immediately before tetanic contractions in skeletal muscle fatigue development *and possible tissue damage. Male rats were divided into two control groups and nine active LPT groups receiving one of three different laser doses (1, 3, and 10 J) with three different wavelengths (660, 830, and 905 nm) before six tetanic contractions induced by electrical stimulation. Skeletal muscle fatigue development was defined by the percentage (%) of the initial force of each contraction and time until 50 % decay of initial force, while total work was calculated for all six contractions combined. Blood and muscle samples were taken immediately after the sixth contraction. Several LPT doses showed some positive effects on peak force and time to decay for one or more contractions, but in terms of total work, only 3 J/660 nm and 1 J/905 nm wavelengths prevented significantly the development of skeletal muscle fatigue. All doses with wavelengths of 905 nm but only the dose of 1 J with 660 nm wavelength decreased creatine kinase (CK) activity. Qualitative assessment of morphology revealed lesser tissue damage in most LPT-treated groups, with doses of 1-3 J/660 nm and 1, 3, and 10 J/905 nm providing the best results. Optimal doses of LPT significantly delayed the development skeletal muscle performance and protected skeletal muscle tissue against damage. These findings also demonstrate that optimal doses are partly wavelength specific and, consequently, must be differentiated to obtain optimal effects on development of skeletal muscle fatigue and tissue preservation. These findings also suggest that the combined use of wavelengths at the same time can represent a therapeutic advantage in clinical settings.*

Clinical studies

Glinkowski [503] compared two groups of patients with sprained ankles. One group was treated conservatively with plaster casts for two weeks; the other received GaAs 3.6 J/cm² for one week. The results observed with plaster casts after two weeks were achieved within one week with LPT.

In three Danish studies by Axelsen [547], Darre [548] and Nissen [535], there were no effects seen on sprained ankles, achilles tendinitis, or medial tibial stress syndrome, using 830 nm, 30-40 mW. The laser type and dose may not be suitable for these indications. The dose in [547] is very low. Winther [549] was also unsuccessful until switching to GaAs for tendinitis.

De Bie failed to obtain positive results in ankle sprain treatments. GaAs of either 0.5 J/cm² or 5 J/cm², or placebo, were used. However, only a very small area (1 cm²) was treated.

Simunovic [957] confirms the positive effect of LPT in sports injuries in a double-blind multi centre study using a combination of GaAlAs and HeNe laser.

Ohshiro [961] selected six Japanese sumo wrestlers and treated their symptoms. LPT resulted in an alleviation of their symptoms and an increased win rate.

Stergioulas [1492] randomly selected 47 soccer players with second degree ankle sprains. They were divided into the following groups: The first group (n=16) was treated with the conventional initial treatment (RICE: rest, *ice, compression, elevation), the second group (n=16) was treated with the RICE method plus placebo laser, and the third group (n=15) was treated with the RICE method plus a 820 nm GaA1As diode laser with a radiant power output of 40 mW at 16 Hz. Before the treatment and 24, 48, and 72 h later, the volume of the oedema was measured. The group treated with the RICE plus a 820 nm laser presented a statistically significant reduction in the volume of the oedema after 24 h.*

Zhao [2192] wanted to determine the effect of red light on sleep quality and endurance performance of Chinese female basketball players. Twenty athletes of the Chinese People's Liberation Army team took part in the study. Participants were divided into red-light treatment (n=10) and placebo (n=10) groups. Intervention(s): The red-light treatment participants received 30 minutes of irradiation from a red-light therapy instrument every night for 14 days. The placebo group did not receive light illumination. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed, serum melatonin was assessed, and 12-minute run was performed at preintervention (baseline) and postintervention (14 days). The 14-day whole-body irradiation with red-light treatment improved the sleep, serum melatonin level, and endurance performance of the elite female basketball players. The authors found a correlation between changes in global Pittsburgh Sleep Quality Index and serum melatonin levels. This study confirmed the effectiveness of body irradiation with red light in improving the quality of sleep of elite female basketball players and offered a nonpharmacologic and noninvasive therapy to prevent sleep disorders after training.

Figure 4.31 Laser teatment on hamstring
Courtesy: Liljeholmens idrottsklinik

The objective of a literature analysis by Borsa [2224] was o critically evaluate original research addressing the ability of phototherapeutic devices, such as lasers and light-emitting diodes (LEDs), to enhance skeletal *muscle contractile function, reduce exercise-induced muscle fatigue, and facilitate postexercise recovery. Eligible studies had to be original research published in English as full papers, involve human participants, and receive a minimum score of 7 out of 10 on the Physiotherapy Evidence Database (PEDro) scale. Data of interest included elapsed time to fatigue, total number of repetitions to fatigue, total work performed, maximal voluntary isometric contraction (strength), electromyographic activity, and post exercise biomarker levels. The authors recorded the PEDro scores, beam characteristics, and treatment variables and calculated the therapeutic outcomes and effect sizes for the data sets. In total, 12 randomised controlled trials met the inclusion criteria. However, data from 2 studies were excluded, leaving 32 data sets from 10 studies. Twenty-four of the 32 data sets contained differences between active phototherapy and sham (placebo-control) treatment conditions for the various outcome measures. Exposing skeletal muscle to single-diode and multidiode laser or multidiode LED therapy was shown to positively affect physical performance by delaying the onset of fatigue, reducing the fatigue response, improving post exercise recovery, and protecting cells from exercise-induced damage. In conclusion, phototherapy administered before resistance exercise consistently has been found to provide ergogenic and prophylactic benefits to skeletal muscle.*

de Almeida [2328] performed a randomised double-blind placebo-controlled crossover trial was performed in ten healthy male volunteers. They were treated with active red LPT, active infrared LPT (660 or 830 nm, 50 mW, 17.85 W/cm², 100 s irradiation per point, 5 J, 1.785 J/cm² at each point irradiated, total 20 J irradiated per muscle) or an identical placebo LPT at four points of the biceps brachii muscle for 3 min before exercise (voluntary isometric elbow flexion for 60 s). The mean peak force was significantly greater following red and infrared LPT than following placebo LPT, and the mean average force was also significantly greater following red (13.09%) and infrared LPT (13.24%) than following placebo LPT. There were no significant differences in mean average force or mean peak force between red and infrared LPT. The authors conclude that both red than infrared LPT are effective in delaying the development skeletal muscle fatigue and in enhancement of skeletal muscle performance.

A study by Toma [2292] aimed to investigate the effects of LPT on skeletal muscle fatigue in elderly women. Twenty-four subjects divided in two groups entered a crossover randomised triple-blinded placebo-controlled trial. Active LPT (808 nm, 100 mW, energy 7 J) or an identical placebo LPT was delivered on the rectus femoris muscle immediately before a fatigue protocol. Subjects performed a fatigue protocol which consisted of voluntary isotonic contractions of knee flexion-extension performed with a load corresponding to 75 % of 1-MR (Maximum Repetition) during 60 s. Surface electromyography (SEMG) signals were recorded from rectus femoris muscle of dominant lower limb to evaluate peripheral fatigability using median frequency analysis of SEMG signal. The number of repetitions of flexion-exten-

sion during fatigue protocol was also compared between groups. The values of median frequency were used to calculate the slope coefficient. The results showed no difference in the slope comparing placebo LPT and active LPT groups. However, a significant difference was observed in the number of repetitions between groups, after active LPT, subjects demonstrated significantly higher number of repetitions.

The aim of a study by Morimoto [2434] was to evaluate the efficacy of LPT for sports injuries. Forty one patients underwent LPT in a hospital. These patients included 22 men and 19 women with an average age of 38.9 years old. Patients were irradiated by diode laser at points of pain and/or acupuncture points. Patients underwent LPT a maximum treatment of 10 times (mean 4.1 times). The author evaluated the efficacy of LPT using a Pain relief score (PRS). A score of 2 to 5 after treatment was regarded as very good, 6 to 8 as good, and 9 to 10 as poor. A PRS score of less than 5 was regarded as effective. The rate of effectiveness (PRS of 5 or less) after LPT was 65.9% (27/41 patients).

The aim of the study by Dos Santos Maciel [2491] was to investigate the effect of LPT on the tibialis anterior muscle of regular physical activity practitioners by electromyographic, biomechanical, and biochemical (lactate) analysis. Double-blind controlled clinical trials were conducted with 12 healthy females, regular physical activity practitioners, between 18 and 30 years. The LPT application (780 nm, 30 mW, 0.81 J/point, beam area of 0.2 cm² 27 s, and 29 points) in the tibialis anterior muscle occurred after the delimitation of the points on every 4 cm² was held. It was observed that (a) a significant torque increase post-LPT compared to the values after placebo therapy at the beginning of resistance exercise, (b) both muscle torque (isokinetic) and median frequency (EMG) showed a faster decay of the signals collected after placebo and laser treatment when compared to control values, (c) no significant change in torque in the strength test of five repetitions, (d) a significant muscle activity decrease after laser therapy compared to control values, and (e) an increase in lactate levels post-LPT after 30 min of exercise. It is concluded that the LPT increased the muscle torque at the beginning of the exercise and maintained the levels of lactate after resistance exercise. Therefore, the LPT with the parameters used in this study can be utilised in rehabilitation to improve muscle performance in elite athletes.

The purpose of the study by Dos Reis [2495] was to investigate the effect of LPT before and after exercise on quadriceps muscle performance, and to evaluate the changes in serum lactate and creatine kinase (CK) levels. A sample of 27 healthy volunteers (male soccer players) were divided into three groups: placebo, pre-fatigue laser, and post-fatigue laser. The experiment was performed in two sessions, with a 1 week interval between them. Subjects performed two sessions of stretching followed by blood collection (measurement of lactate and CK) at baseline and after fatigue of the quadriceps by leg extension. LPT was applied to the femoral quadriceps muscle using an infrared laser device (830 nm), 0.0028 cm² beam area, six 60 mW *diodes, energy of 0.6 J per diode (total energy to each limb 25.2 J (50.4 J total), energy density 214.28 J/cm², 21.42 W/cm² power density, 70 sec per leg. The investigators measured the time to fatigue and number and maximum load (RM) of repetitions tolerated. Number of repetitions and time until fatigue were primary outcomes, secondary outcomes included serum lactate levels (measured before and 5, 10, and 15 min after exercise), and CK levels (measured before and 5 min after exercise). The number of repetitions, RM and duration of fatigue were similar among the groups. Post-fatigue laser treatment significantly decreased the serum lactate concentration relative to placebo treatment and also within the group over time (after 5 min vs. after 10 and 15 min). The CK level was lower in the post-fatigue laser group. Laser application either before or after fatigue reduced the post-fatigue concentrations of serum lactate and CK. The results were more pronounced in the post-fatigue laser group.*

Further literature: [74, 122, 123, 281, 298, 299, 431, 709, 734, 735, 739, 1242]

4.1.51 Stem cells

Stem cells are characterised by the ability to renew themselves through mitotic cell division and differentiating into a diverse range of specialised cell types. Using stem cells in medicine has a very promising potential and a lot of research is directed into this field. It can be taken for granted that stem cells will react to laser irradiation, just as all other cells. By finding the optimal parameters, LPT could become a very valuable tool in boosting stem cell viability and proliferation.

Literature:

The long term effects of LPT can involve mechanisms connected with activation of migration of stem cells towards damaged areas. Migration of stem cells was tested by Gasparyan [1627] under the influence of laser light alone, as well as in cases of combined influences of light and stromal cell-derived factor-1 alpha (SDF-1 alpha). This cytokine plays an important role in stem cell homing. Group 1 cells were the control, group 2 cells received red laser light irradiation, group 3 cells had IR laser light irradiation, group 4 cells were treated with SDF-1 alpha, group 5 cells were irradiated with red laser light in addition to SDF-1 alpha, and group 6 cells with IR laser light and SDF-1 alpha. The migrated cell count was 1496,5±409 (100%) in the control group. Red and IR laser light increased migration activity of stem cells up to 1892±283 (126%) and 2255,5±510 (151%) respectively. Influence of SDF-1 alpha was more significant than the effects of light irradiation alone: 3365,5±489 (225%). Combined effects of light irradiation and SDF-1 were significantly stronger: 5813±1199 (388%) for SDF-1 alpha and red laser light, and 6391,5±540 (427%) for SDF-1 alpha and IR laser light.

The aim of an in vitro study by Eduardo [1895] was to evaluate the potential effect of laser irradiation (660 nm) on human dental pulp stem cell (hDPSC) proliferation. Cells cultured under nutritional deficit (10% FBS) were either irradiated or left untreated (control) using two different power settings (20 mW/6 seconds to 40 mW/3 seconds). Cell growth was indirectly assessed by measuring the cell mitochondrial activity through the MTT reduction-based cytotoxicity assay. The group irradiated with the 20 mW setting presented significantly higher MTT activity at 72 hours than the other two groups (negative control -10% FBS- and lased 40 mW with 3-second exposure time). After 24 hours of the first irradiation, cultures grown under nutritional deficit (10% FBS) and irradiated presented significantly higher viable cells than the non-irradiated cultures grown under the same nutritional conditions. Under the conditions of this study it was possible to conclude that the cell strain hDPSC responds positively to laser phototherapy by improving the cell growth when cultured under nutritional deficit conditions. Thus, the association of laser phototherapy and hDPSC cells could be of importance for future tissue engineering and regenerative medicine.

The study by Mvula [1808] investigated the effect of LPT on primary cultures of adult human adipose derived stem cells,using a 635 nm laser, at 5 J/cm^2 with a power output of 50.2 mW and a power density of 5.5 mW/cm^2. Cellular morphology did not appear to change after irradiation. Using the trypan blue exclusion test, the cellular viability of irradiated cells increased by 1% at 24 h and 1.6% at 48 h but was not statistically significant. However, the increase of cellular viability as measured by ATP luminescence was statistically significant at 48 h. Proliferation of irradiated cells, measured by optical density, resulted in statistically significant increases in values compared to non-irradiated cells at both time points. Western blot analysis and immunocytochemical labeling indicated an increase in the expression of stem cell marker ß1-integrin after irradiation. These results indicate that cm^2 of laser irradiation can positively affect human adipose stem cells by increasing cellular viability, proliferation, and expression of ß1-integrin.

The aim of the study by Tuby [1809] was to investigate the effect of LPT on the proliferation of mesenchymal stem cells (MSCs) and cardiac stem cells (CSCs). Isolation of MSCs and CSCs was performed. The cells were cultured and laser irradiation was applied at energy densities of 1 and 3 J/cm^2. The number of MSCs and CSCs up to two and four weeks respectively, post-LPT, demonstrated a significant increase in the laser-treated cultures as compared to the control. These results may have an important impact on regenerative medicine.

Souza [1718] divided 60 amputated worms into three study groups: a control group, and two other groups submitted to daily 1 and 3 min long laser treatment sections at approximately 910 W/m2 power density. A 685 nm laser with 35 mW optical power was used. Samples were sent for histological analysis on the 4th, the 7th and the 15th day after amputation. A remarkable *increase in stem cells counts for the 4th day of regeneration was observed when the regenerating worms were stimulated by the laser radiation.*

Abramovitch-Gottlib [1810] irradiated mesenchymal stem cells (MSCs) seeded on three dimensional (3D) coralline (Porites lutea) biomatrices with laser irradiation. The consequent phenotype modulation and development of MSCs towards ossified tissue were studied in this combined 3D biomatrix/LPT system and in a control group, which was similarly grown, but not treated by LPT. The irradiated and non-irradiated MSC were tested on days 1-7, 10, 14, 21 and 28 of culturing via analysis of cellular distribution on matrices (trypan blue), calcium incorporation to newly formed tissue (alizarin red), bone nodule formation (von Kossa), fat aggregates formation (oil red O), alkaline phosphatase (ALP) activity, scanning electron microscopy (SEM) and electron dispersive spectrometry (EDS). The results obtained from the irradiated samples showed enhanced tissue formation, appearance of phosphorous peaks and calcium and phosphate incorporation to newly formed tissue. Moreover, in irradiated samples, ALP activity was significantly enhanced in early stages and notably reduced in late stages of culturing. These findings of cell and tissue parameters up to 28 days of culturing revealed higher ossification levels in irradiated samples compared with the control group. The authors suggest that both the surface properties of the 3D crystalline biomatrices and the LPT have biostimulatory effects on the conversion of MSCs into bone-forming cells and on the induction of ex-vivo ossification.

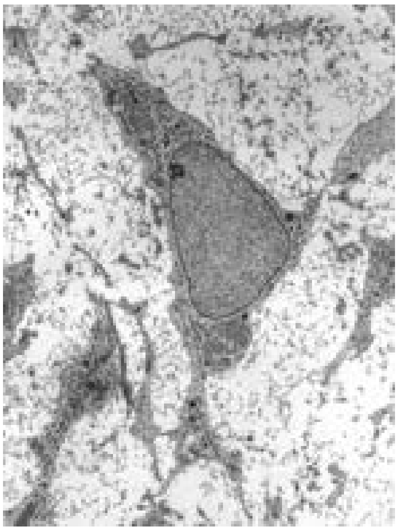


Figure 4.32 Adult stem cell. (Wikipedia)

Bone marrow derived mesenchymal stem cells (BMSCs) have shown to be an appealing source for cell therapy and tissue engineering. Previous studies have confirmed that the application of LPT could affect the cellular process. However, little is known about the effects of LPT on BMSCs. The aim of a study by Zhang [2009] was designed to investigate the influence of LPT at different energy densities on BMSCs proliferation, secretion and myogenic differentiation. BMSCs were harvested from fresh rat bone marrow and exposed to a 635 nm diode laser (60 mW; 0, 0.5, 1.0, 2.0, or 5.0 J/cm²). The lactate dehydrogenase (LDH) release was used to assess the cytotoxicity of LPT at different energy densities. Cell proliferation was evaluated by using 3-(4, 5-dimethylithiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assays. Production of vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) were mea-

sured by enzyme-linked immunosorbent assay (ELISA). Myogenic differentiation, induced by 5-azacytidine (5-aza), was assessed by using immunocytochemical staining for the expression of sarcomeric alpha-actin and desmin. Cytotoxicity assay showed no significant difference between the non-irradiated group and the irradiated groups. LPT significantly stimulated BMSCs proliferation and 0.5 J/cm^2 *was found to be an optimal energy density. VEGF and NGF were identified and LPT at 5.0 J/cm*^{2} *significantly stimulated the secretion. After 5-aza induction, myogenic differentiation was observed in all groups, LPT at 5.0 J/cm*^{2} *dramatically facilitated the differentiation. LPT may provide a novel approach for the preconditioning of BMSCs in vitro prior to transplantation.*

The aim of a study by Huo [2056] was designed to investigate the influence of LPT at different energy densities on bone marrow derived mesenchymal stem cells (BMSCs) proliferation, secretion and myogenic differentiation. BMSCs were harvested from rat fresh bone marrow and exposed to a 635 nm diode laser (60 mW; 0, 0.5, 1.0, 2.0, or 5.0 J/cm^2*). The lactate dehydrogenase (LDH) release was used to assess the cytotoxicity of LPT at different energy densities. Cell proliferation was evaluated by using 3-(4, 5-dimethylithiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assay. Production of vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) were measured by enzyme-linked immunosorbent assay (ELISA). Myogenic differentiation, induced by 5-azacytidine (5-aza), was assessed by using immunocytochemical staining for the expression of sarcomeric alpha-actin and desmin. Cytotoxicity assay showed no significant difference between the non-irradiated group and irradiated groups. LPT significantly stimulated BMSCs proliferation and 0.5 J/cm*^{2} *was found to be an optimal energy density. VEGF and NGF were identified and LPT at 5.0 J/cm*^{2} *significantly stimulated the secretion. After 5-aza induction, myogenic differentiation was observed in all groups and LPT at 5.0 J/cm*^{2} *dramatically facilitated the differentiation. In conclusion, LPT stimulates proliferation, increases growth factors secretion and facilitates myogenic differentiation of BMSCs.*

The purpose of a study by Wu [2293] was to investigate the anti-inflammatory effect of LPT on human adipose-derived stem cells (hADSCs) in an inflammatory environment. The experiment showed that the hADSCs expressed Toll-like Receptors (TLR) 1, TLR2, TLR3, TLR4, and TLR6 and that lipopolysaccharide (LPS) significantly induced the production of pro-inflammatory cytokines (Cyclooxygenase-2 (Cox-2), Interleukin-1beta (IL-1beta), Interleukin-6 (IL-6), and Interleukin-8 (IL-8)). LPLI markedly inhibited LPS-induced, pro-inflammatory cytokine expression at an optimal dose of 8 J/cm^2*. The inhibitory effect triggered by LPLI might occur through an increase in the intracellular level of cyclic AMP (cAMP), which acts to down-regulate nuclear factor kappa B (NF-kappaB) transcriptional activity. These data collectively provide insight for further investigations of the* *potential application of anti-inflammatory treatment followed by stem cell therapy.*

The study by Shen [2446] investigated the effects of large-area irradiation from a low-level laser on the proliferation and differentiation of i-ADSCs in neuronal cells. The probe of the laser irradiation device was fixed vertically on a clean, open experimental bench. The distance between the probe and the cell culture dish was 30 cm. Laser irradiation was applied in a 25°C environment by using 660 nm at an output power of 50 mW and frequency of 50 Hz. MTT assays indicated no significant difference between the amount of cells with (LS+) and without (LS-) laser treatment. However, immunofluorescent staining and western blot analysis results indicated a significant increase in the neural stem-cell marker, nestin, following exposure to laser irradiation. Furthermore, stem cell implantation was applied to treat rats suffering from stroke. At 28 days posttreatment, the motor functions of the rats treated using i-ADSCs (LS+) did not differ greatly from those in the sham group and HE-stained brain tissue samples exhibited near-complete recovery with nearly no brain tissue damage. However, the motor functions of the rats treated using i-ADSCs (LS-) remained somewhat dysfunctional and tissue displayed necrotic scarring and voids. The western blot analysis also revealed significant expression of oligo-2 in the rats treated using i-ADSCs (LS+) as well as in the sham group. The results demonstrated that laser irradiation exerts a positive effect on the differentiation of i-ADSCs and can be employed to treat rats suffering from ischemic stroke to regain motor functions.

Arany [2517] showed that LPT can be used as a minimally invasive tool to activate an endogenous latent growth factor complex, transforming growth factor-beta1 (TGF-beta1), that subsequently differentiates host stem cells to promote tissue regeneration. LPL treatment induced reactive oxygen species (ROS) in a dose-dependent manner, which, in turn, activated latent TGF-beta1 (LTGF-beta1) via a specific methionine residue (at position 253 on LAP). Laser-activated TGF-beta1 was capable of differentiating human dental stem cells in vitro. Further, an in vivo pulp capping model in rat teeth demonstrated significant increase in dentin regeneration after LPL treatment. These in vivo effects were abrogated in TGF-beta receptor II (TGF-betaRII) conditional knockout (DSPP(Cre)TGF-betaRII(fl/fl)) mice or when wild-type mice were given a TGF-betaRI inhibitor. These findings indicate a pivotal role for TGF-beta in mediating LPL-induced dental tissue regeneration

4.1.52 Stroke, irradiation of the brain

Is it safe to irradiate the brain? Part of the answer is given in the study by Ilic [1590]:

"The aim of the present study was to investigate the possible short- and long-term adverse neurological effects of LPT given at different power densities, frequencies, and modalities on the intact rat brain. One hundred and eighteen rats were used in the study. Diode laser (808 nm) was used to deliver power densities of 7.5, 75, and 750 mW/cm^2 transcranially to the brain cortex of mature rats, in either continuous wave (CW) or pulse (Pu) modes. Multiple doses of 7.5 mW/cm^2 were also applied. Standard neurological examination of the rats was performed during the follow-up periods after laser irradiation. Histology was performed at light and electron microscopy levels. Both the scores from standard neurological tests and the histopathological examination indicated that there was no long-term difference between laser-treated and control groups up to 70 days post-treatment. The only rats showing an adverse neurological effect were those in the 750 mW/cm^2 (about 100-fold optimal dose), CW mode group. In Pu mode, there was much less heating, and no tissue damage was noted. Long-term safety tests lasting 30 and 70 days at optimal 10× and 100× doses, as well as at multiple doses at the same power densities, indicate that the tested laser energy doses are safe under this treatment regime. Neurological deficits and histopathological damage to 750 mW/cm^2 CW laser irradiation are attributed to thermal damage and not due to tissue-photon interactions."

Thus, irradiation of the brain at reasonable intensities appears to be safe and interesting reports on the effects of LPT in this area have appeared. Animal models have demonstrated safety and efficacy of LPT for stroke, warranting randomised controlled trials in humans. NEST-1 (phase 2) [1807] and NEST-2 (phase 3) [2447] confirmed the safety of transcranial laser therapy, although efficacy was not found in NEST-2. Pooled analysis of NEST-1 and NEST-2 revealed a significantly improved success rate in patients treated with laser therapy. Further phase 3 testing was initiated with the aim of treating 1000 stroke patients. However, this study was interrupted due to inconclusive effects in its early phase. With the animal studies in mind and the promising outcome of NEST-1, this should not be interpreted as a proof of the inefficacy of LPT for this condition. Rather, the parameters used may have been suboptimal and LPT being of varying efficacy depending on the condition of the patient. However, a great initiative ended in failure this time.

Literature:

Animal studies

Jagdeo [2194] measured the transmission of near infrared light energy, using red light for purposes of comparison, through intact cadaver *soft tissue, skull bones, and brain using a commercially available LED device at 830 nm and 633 nm. The results demonstrate that near infrared measurably penetrates soft tissue, bone and brain parenchyma in the formalin preserved cadaveric model, in comparison to negligible red light transmission in the same conditions. These findings indicate that near infrared light can penetrate formalin fixed soft tissue, bone and brain and implicate that benefits observed in clinical studies are potentially related to direct action of near infrared light on neural tissue.*

In a study by Lapchak [1427], the rabbit small clot embolic stroke model (RSCEM) was used to assess whether laser treatment (7.5 or 25 mW/cm^2) altered clinical rating scores (behaviour) when given to rabbits starting 1 to 24 hours post embolisation. Behavioural analysis was conducted from 24 hours to 21 days after embolisation, allowing for the determination of the effective stroke dose (P50) or clot amount (mg) that produces neurological deficits in 50% of the rabbits. Using the RSCEM, a treatment is considered beneficial if it significantly increases the P50 compared with the control group. In the present study, the P50 value for controls were 0.97+/-0.19 mg to 1.10+/-0.17 mg; this was increased by 100% to 195% if laser treatment was initiated up to 6 hours, but not 24 hours, post embolisation (P50=1.23+/-0.15 mg). Laser treatment also produced a durable effect that was measurable 21 days after embolisation. Laser treatment (25 mW/cm^2) did not affect the physiological variables that were measured. This study shows that laser treatment improved behavioural performance if initiated within 6 hours of an embolic stroke and that the effect of laser treatment is durable.

Nitric oxide (NO) has been shown to be neurotoxic while transforming growth factor-ß 1 (TGF-ß-1) and it is neuroprotective in the stroke model. The study by Leung [1707] investigated the effects of LPT on nitric oxide synthase (NOS) and TGF-ß-1 activities after cerebral ischemia and reperfusion injury. Cerebral ischemia was induced for one hour in male adult rats by a unilateral occlusion of the middle cerebral artery. Laser irradiation was then applied to the cerebrum at different time intervals (1, 5 or 10 minutes). The wavelength of the laser was 660 nm, 8.8 mW, 2.64 J/cm^2, 10 kHz. The activity of NOS and the expression of TGF-ß-1 were evaluated in groups with different time intervals of laser irradiation. After ischemia, the NOS activity increased gradually from day three, became significantly higher from day four to six, but returned to the normal level after day seven. The activity and expression of the three isoforms of NOS were significantly suppressed to different extents after laser irradiation. In addition, laser irradiation was shown to trigger the expression of TGF-ß-1.

Oron [1756] performed two sets of experiments. Stroke was induced in rats by (1) permanent occlusion of the middle cerebral artery through a craniotomy, or (2) insertion of a filament. After induction of stroke, a battery of neurological and functional tests (neurological score, adhesive removal) were performed. At 4 and 24 hours post stroke, a GaAs diode laser was used transcranially to illuminate the hemisphere contra lateral of the stroke at a *power density of 7.5 mW/cm^2. In both models of stroke, laser significantly reduced neurological deficits when applied 24 hours post stroke. Application of the laser at 4 hours post stroke did not affect the neurological outcome of the stroke-induced rats as compared with controls. There was no statistically significant difference in the stroke lesion area between control and laser-irradiated rats. The number of newly formed neuronal cells, assessed by double immunoreactivity to bromodeoxyuridine and tubulin isotype III as well as migrating cells (doublecortin immunoactivity), was significantly elevated in the subventricular zone of the hemisphere ipsilateral to the induction of stroke when treated by laser. These data suggest that a non-invasive intervention of laser issued 24 hours after acute stroke may provide a significant functional benefit with an underlying mechanism possibly being the induction of neurogenesis.*

Random irradiation of the brain is a general caveat because the balance between stimulating and inhibiting effects is not well-known. The above studies suggest an important indication for LPT on brain tissue, but since the brain is a very complex organ, nothing can be taken for granted. The researchers below have been looking at the effects of irradiation of brain tissue:

The aim of a study by Ahmed [2021] was to investigate the effects of three different intensities of infrared diode laser radiation on amino acid neurotransmitters in the cortex and hippocampus of rat brains. Lasers are known to induce different neurological effects such as pain relief, anesthesia, and neurosuppressive effects; however, the precise mechanisms of these effects are not clearly elucidated. Amino acid neurotransmitters (glutamate, aspartate, glutamine, gamma-aminobutyric acid [GABA], glycine, and taurine) play vital roles in the central nervous system (CNS). The shaved scalp of each rat was exposed to different intensities of infrared laser energy (500, 190, and 90 mW) and then the rats were sacrificed after 1 h, 7 d, and 14 d of daily laser irradiation. The control groups were exposed to the same conditions but without exposure to laser. The concentrations of amino acid neurotransmitters were measured by high-performance liquid chromatography (HPLC). The rats subjected to 500 mW of laser irradiation had a significant decrease in glutamate, aspartate, and taurine in the cortex, and a significant decrease in hippocampal GABA. In the cortices of rats exposed to 190 mW of laser irradiation, increases in aspartate accompanied by a decrease in glutamine were observed. In the hippocampus, other changes were seen. The rats irradiated with 90 mW showed a decrease in cortical glutamate, aspartate, and glutamine, and an increase in glycine, while in the hippocampus an increase in glutamate, aspartate, and GABA were recorded. It is concluded that daily laser irradiation at 90 mW produced the most pronounced inhibitory effect in the cortex after 7 d. This finding may explain the reported neurosuppressive effect of infrared laser energy on axonal conduction of hippocampal and cortical tissues of rat brains.

In a study by Shen-Zheng [2022], low power lasers were guided by optic fibres into the rat caudate nucleus or frontal cortex during conditioned avoidance response (CAR) training. The changes in striatal monoamine and amino acid concentrations were subsequently determined. Of six training groups tested, only the experimental group with helium-neon laser radiation to the caudate nucleus exhibited the formation of CAR and an increase of unconditioned leg contractions. The striatal concentrations of dopamine (DA) and norepinephrine (NE) were increased simultaneously in the group.

Igarashi [2023] studied the effect of LPT on the development of synapses in the radiatum layer and the lacunosum-molecular layer of field CA3 of the neonatal rat hippocampus. Neonatal rats were irradiated with a laser (830 nm, 60 mW) at two points located above the hippocampi for 15 s, respectively, twice per day from birth (day 1) to day 5. The mean body weights of the laser-irradiated animals were found to be lower than those of the control animals, the deficit on day 20 being 22.6%. Moreover, the density of synaptic junctions stained by ethanolic phosphotungstic acid per unit area of the radiatum layer and the lacunosum-molecular layer of the neonatal rat hippocampus was significantly reduced on day 20. It was suggested that the low-power diode laser irradiation affected the development of synapses in the neonatal rat brain.

Xuan [2289] developed a mouse model of severe TBI induced by controlled cortical impact and explored the effect of different treatment schedules. Adult male BALB/c mice were divided into 3 broad groups (a) sham-TBI sham-treatment, (b) real-TBI sham-treatment, and (c) real-TBI active-treatment. Mice received active-treatment (transcranial LPT by continuous wave 810 nm laser, 25 mW/cm^2, 18 J/cm^2, spot diameter 1 cm) while sham-treatment was immobilisation only, delivered either as a single treatment at 4 hours post TBI, as 3 daily treatments commencing at 4 hours post TBI or as 14 daily treatments. Mice were sacrificed at 0, 4, 7, 14 and 28 days post-TBI for histology or histomorphometry, and injected with bromodeoxyuridine (BrdU) at days 21-27 to allow identification of proliferating cells. Mice with severe TBI treated with 1-laser Tx (and to a greater extent 3-laser Tx) had significant improvements in neurological severity score (NSS), and wire-grip and motion test (WGMT). However 14-laser Tx provided no benefit over TBI-sham control. Mice receiving 1- and 3-laser Tx had smaller lesion size at 28-days (although the size increased over 4 weeks in all TBI-groups) and less Fluoro-Jade staining for degenerating neurons (at 14 days) than in TBI control and 14-laser Tx groups. There were more BrdU-positive cells in the lesion in 1- and 3-laser groups suggesting LPT may increase neurogenesis. Transcranial NIR laser may provide benefit in cases of acute TBI provided the optimum treatment regimen is employed.

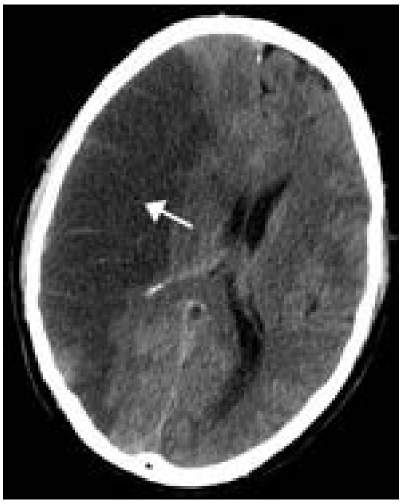


Figure 4.33 CT scan slice of the brain, ischemic stroke. (Wikipedia)

Clinical studies

The aim of a study by Karabegovic [2057] was to determine the effects of LPT and to correlate with electrotherapy (TENS, stabile galvanisation) in subjects after stroke.The researchers analysed 70 subjects after stroke with pain in shoulder and oedema of a paralysed hand. The examinees were divided in two groups of 35, and they were treated during 2006 and 2007. Experimental group (EG) had a treatment with LPT, while the control group (CG) was treated with electrotherapy. Both groups had kinesis therapy and ice massage. All patients were examined on the admission and discharge by using the VAS, DASH, Barthel index and FIM. The pain intensity in shoulder was significantly reduced in EG, swelling is lowered in EG. Barthel index in both groups was significantly higher. DASH was significantly improved after LPT in EG. EG had a higher level of independence. LPT used on EG shows significantly better results in reducing pain, swelling, disability and improvement of independence.

The first controlled clinical study demonstrating the beneficial effects of transcranial laser stimulation on cognitive and emotional functions in humans is presented by Barrett [2279], writing as follows: LPT with red to near-infrared light is a novel intervention shown to regulate neuronal function in cell cultures, animal models, and clinical conditions. Light that intersects with the absorption spectrum of cytochrome oxidase was applied to the forehead of healthy volunteers. We tested whether low-level laser stimulation produces beneficial effects on frontal cortex measures of attention, memory and mood. Reaction time in a sustained-attention psychomotor vigilance task (PVT) was significantly improved in the treated (n=20) vs. placebo control (n=20) groups, especially in high novelty-seeking subjects. Performance in a delayed match-to-sample (DMS) memory task showed also a significant improvement in treated vs. control groups as measured by memory retrieval latency and number of correct trials. The Positive and Negative Affect Schedule (PANAS-X), which tracks self-reported positive and negative affective (emotional) states over time, was administered immediately before treatment and 2weeks after treatment. The PANAS showed that while participants generally reported more positive affective states than negative, overall affect improved significantly in the treated group due to more sustained positive *emotional states as compared to the placebo control group. These data imply that transcranial laser stimulation could be used as a non-invasive and efficacious approach to increase brain functions such as those related to cognitive and emotional dimensions. Transcranial infrared laser stimulation has also been proven to be safe and successful at improving neurological outcome in humans in controlled clinical trials of stroke. This innovative approach could lead to the development of non-invasive, performance-enhancing interventions in healthy humans and in those in need of neuropsychological rehabilitation.*

The subject of a case study by Boonswang [2191] is a 29-year-old woman who suffered a brainstem stroke. She remained severely dizzy, had a non-functional left hand secondary to weakness, severe spasticity in the right hand, right lateral sixth nerve palsy and was unable to ambulate on presentation. The stroke occurred 2 years before presentation. The subject had been treated for 21 months at two different stroke rehabilitation centres before presentation. The stroke protocol includes photobiomodulation administered with the XR3T-1 device and 'muscle/bone/joint/soft tissue' recovery techniques. The patient was seen once a week for 8 weeks and treatment sessions lasted approximately 60 mins. The results were dramatic: after 8 weeks of implementation of the photobiomodulation protocol, the patient demonstrated positive change in every area of her deficits as determined by improvements in physical examination findings. The gains achieved at 8 weeks have been maintained to this day and she continues to be treated once every 4 weeks.

LPT was tested by Lampl [1807] for the ability to improve 90-day outcomes in ischemic stroke patients treated within 24 hours from stroke onset. This was a prospective, intention-to-treat, multicenter, international, double-blind trial involving 120 ischemic stroke treated patients, randomised 2:1 ratio, with 79 patients in the active treatment group and 41 in the sham (placebo) control group. Only patients with baseline stroke severity measured by NIHSS scores of 7 to 22 were included. Patients who received tissue plasminogen activator were excluded. Time of treatment ranged from 2 to 24 hours. More patients (70%) in the active treatment group had successful outcomes than did controls (51%). Similarly, more patients (59%) had successful outcomes than did controls (44%) as measured on day 90. Also, more patients in the active treatment group had successful outcomes than controls as measured by the change in mean NIHSS score from baseline to 90 days and the full mRS ("shift in Rankin"). Mortality rates and serious adverse events did not differ significantly .This study indicates that infrared LPT has shown to be initially safe and effective in the treatment of ischemic stroke in humans when initiated within 24 hours of stroke onset.

Two randomised trials suggested that transcranial laser therapy (TLT) may benefit patients with acute ischemic stroke although efficacy has not been confirmed [2002, 2057]. Supportive proof of concept could be demonstrated if TLT reduces the volume of cortical infarction. The NeuroThera

Efficacy and Safety Trial-2 [2228] was a randomised trial of TLT versus sham in patients with acute ischemic stroke treated within 24 hours of onset. Infarct volumes were measured quantitatively and semiquantitatively on all protocol-required computed tomography (or MRI, if clinically indicated) scans performed on day 5 (+/-2). Two approaches assessed treatment effects on cortex: (1) indirectly, by analysing total infarct volume among patients with clinical presentations suggesting cortical involvement; and (2) directly, by assessing the cortical Alberta Stroke Program Early CT Score (cASPECTS) components (M1-M6, anterior, posterior) on a 0- to 8-point modified scale. A total of 640 subjects had scans (576 computed tomography, 64 MRI) on day 5. No effect was seen in any of the following prespecified subgroups selected to indicate cortical involvement: baseline National Institutes of Health Stroke Scale score >10, Oxfordshire Total Anterior Circulation Syndrome, subjects with aphasia or extinction at baseline, or subjects with radiographic involvement of cortex. TLT was not associated with a reduction in overall or cortical infarct volume as measured on computed tomography in the subacute phase.

Kumazaki [2480] investigated the effects of a continuous laser at 660 nm on intrinsic membrane properties and excitability of presumed pyramidal neurons in the thalamocortical input layer (layer 3/4) and in layer 5 of mouse primary auditory cortex using the whole-cell patch-clamp recording technique. In layer 3/4 neurons, 660 nm laser irradiation (LLI-660) at 20 mW for 5 min gradually increased resting membrane potentials, which reached a plateau after irradiation. Concomitantly, LLI-660 decreased onset latency of first action potentials (spikes) without changing spike threshold or peak amplitude, but increased inter-spike interval of initial bursting spike doublets and their peak amplitude ratio. None of these changes was observed in layer 5 neurons. Instead, LLI-660 at 20 mW rapidly reduced spike width ~5 % within 1 min of irradiation onset. The magnitude of this reduction did not change during 5 or 10 min irradiation, and returned quickly to at least baseline levels after turning the laser off. Decreasing laser power to 10 mW reduced spike width to a lesser extent, suggesting laser power dependence of this phenomenon.

Further literature: [1589, 1590, 1804, 1257, 1935, 2446]

4.1.53 Tendinopathies

Bjordal [732] has analysed the literature regarding the treatment of shoulder tendinitis/bursitis and concludes: “The methodological quality of the LPT-trials of shoulder tendinitis/bursitis is similar to or higher than in trials with medical interventions for shoulder tendinitis/bursitis. Total sample size of high quality LPT-trials is similar to or higher than total sample size of high quality NSAID-trials or steroid injection-trials on the same diagnosis. The four LPT-trials should serve as a valid platform for drawing conclusions on clinical effects of LPT.” Bjordal further concludes: “There is consistent evidence of clinical effects of LPT in all four shoulder trials, as the results are in favour of active LPT with confidence intervals not including zero. The trials with fewest treatment sessions per week had the lowest success rate. Best clinical effects were seen in patients with short duration of symptoms (less than one month).”

Daily sessions for 5-6 days are needed to reduce inflammation, 8-10 days to increase collagen production. Steroids should be avoided when LPT is used [1462, 1463].

Dosage per point is adapted to the distance between skin and tendon (depth), and the number of points is adapted to the area of the inflammation. According to measurements performed by Bjordal, the various tendon locations have different characteristics that affect the determination of the dose. The figures below represent:

Indication	Tendon depth to target tendon	Tendon thickness	Area to treat
Plantar fasciitis	10.0 - 12.0 mm	3.0 - 4.0 mm	0.1 - 0.8 cm^2
Achilles tendinitis	1.5 - 3.0 mm	4.5 - 6.0 mm	0.5 - 2.0 cm^2
Patellar tendinitis	2.5 - 4.0 mm	5.5 - 8.0 mm	1.0 - 4.0 cm^2
Epicondylitis	1.5 - 2.5 mm	2.0 - 4.0 mm	0.09 - 0.3 cm^2
Rotatorcuff	5.0 - 10.0 mm	5.5 - 8.0 mm	0.5 - 1.5 cm^2

Table 4.2 Tendinitis/Bursitis different characteristics

Literature:

Animal studies

In a tendon healing experiment, Xu [781] used 50 white Leghorn hens. A total of 10 were randomly assigned as a normal control group; the other 40 were used in the study. After anaesthetising, one half of the profundus tendons of the second and third toe on both sides of the feet were cut. Postoperatively, the hens moved freely in the cages. One foot was randomly chosen to *belong to the treatment group, the other foot served as an un-irradiated control group. The injured tendons in the treatment group were irradiated for twenty minutes daily with a HeNe laser at a constant power density of 12.74 mW/cm^2, the first exposure taking place 24 hours after the operation. The longest course of treatment was 3 weeks. The control group was not irradiated. On day 3 day and at weeks 1, 2, 3 and 5 after surgery, 8 hens were sacrificed and their tendons were examined. The experimental results: (1) active, passive flexion and tendon gliding functional recovery were significantly better in the treatment group ($p < 0.01$); (2) width and thickness of the tendon at the cut site were significantly smaller in the treatment group ($p < 0.01$); (3) degrees of tendon adhesions were significantly lighter in the treatment group ($p < 0.05$). The experimental results demonstrate that HeNe laser radiation had significant effects on anti-inflammation, detumescence, progressive hematoma absorbing, inhibiting tendon extrinsic healing, reducing tendon adhesions, improving tendon intrinsic healing, i.e., stimulating epitenon and endotenon cell proliferation and migration into the gap, stimulating collagen synthesis in the tendon gap, and enhancing the late remodelling of fibrous peritendonous adhesion.*

Enwemeka [124] cut and sutured the Achilles tendons of twenty rabbits. Six of these rabbits were treated locally with HeNe, seven with GaAs laser. The other seven served as a control. After 14 days, the tensile strength of the tendons was checked. The mean value in the HeNe group was 251, in the GaAs group 233, and in the control group 154.

Early mechanical loading and LPT have been shown to promote tendon healing. Reddy [725] combined these two parameters, using HeNe laser on rabbit achilles tendons. The findings indicate that the combination of LPT and early mechanical loading of tendons increase collagen production, with marginal biomechanical effects on repaired tendons.

Reddy [546] tenectomised and repaired the Achilles tendons in rabbits. The limbs were immobilised and treated with 1 J/cm^2 of HeNe light for 14 days. Control animals received sham laser treatment. The collagen content in the treated tendons was significantly higher than in the control group. Extraction of collagen from the regenerating tissues revealed that the laser-treated tendons yielded significantly higher concentrations of neutral salt soluble and insoluble collagen than control tendons.

Parizotto [653] tenectomised the Achilles tendons in 32 rats and resutured the skin. After 24 hours, HeNe laser was applied daily for 10 days. Doses of 0.5, 5 and 50 J/cm^2 were used. HeNe laser enhanced the intra- and intermolecular hydrogen bonding in the collagen molecules. The treated tendons were more organised than controls.

The study by Elwakil [1747] was conducted to evaluate the role of HeNe laser on the healing process of surgically repaired Achilles tendons. Thirty unilateral Achilles tendons of 30 rabbits were transected and immediately repaired. Operated Achilles tendons were randomly divided into two equal groups. Tendons in group A were subjected to HeNe laser, while ten-

dons in group B served as a control group. Laser irradiation was carried out; continuous wave at 1 J/cm². It was done on a daily basis, transcutaneously, by using computerised scanning software starting from the 1st to the 5th postoperative day, then continued after removal of the casts until the 14th postoperative day. Two weeks later, the repaired Achilles tendons were histopathologically and biomechanically evaluated. The histopathological findings suggest a favourable qualitative pattern of the newly synthesised collagen of the regenerating tendons after the laser stimulation. The biomechanical results support the same favourable findings from the functional point of view as denoted by the better biomechanical properties of the regenerating tendons after HeNe laser with a statistical significance in most of the biomechanical parameters. HeNe laser irradiation produced a great improvement after surgical repair of ruptured and injured tendons for a better functional outcome.

The aim of the study by Casalechi [2481] was to investigate the effect of 830 nm LPT in tendon inflammation, tendinitis induced by mechanical trauma in rat Achilles tendon. For this 65 rats were divided into different groups: C = control (n=5) and experimental (n=10/group), with two different times of sacrifice such as treated with L = laser, D = treated with diclofenac, and T = untreated injured. The tendon inflammation was induced by controlled contusion in the medial region of the Achilles tendon of the animals. The treated groups received some kind of intervention every 24 h, all groups were sacrificed on the 7th or 14th day after the trauma. The tendons were dissected, extracted, and sent for analysis. Histological analysis of the L group showed a decrease in the number of inflammatory cells in relation to other groups in both periods studied. The comparative results between the number of inflammatory cells in the control and treated groups at 7 and 14 days showed statistically significant differences. Qualitative analysis findings obtained by the picrosirius red technique under polarised light showed that in 7 days, the T group presented collagen types I and III in the same proportion; group D presented a predominance of type III fibres, while in group L, type I collagen predominated. The 14-day group D showed collagen types I and III in the same proportion, while in group L, there was a predominance of type I fibres. Biomechanical analysis showed that 7-day groups L and C showed similar stiffness and increased breaking strength. The 14-day groups L and C showed greater rupturing strength as well as increased stiffness angle. Group D showed a decrease of maximum traction strength and degree of rigidity. It was concluded that treatment with LPT in the parameters used and the times studied reduces migration of inflammatory cells and improves the quality of repair while reducing the functional limitations.

Salate [1624] divided 96 rats into three groups subject to treatment during three, five and seven days post-lesion. In each group, 32 animals were used. The groups were further divided into four subgroups with 8 animals in each, receiving InGaAlP laser, 660 nm, treatment at (1) a mean output of 10 mW, or (2) 40 mW during 10 sec, (3) a sham subgroup, and (4) a non-treat-

ment subgroup. Each animal was subjected to a lesion of the Achilles tendon by dropping a 186 g weight from a 20 cm height over the tendon. Treatment was initiated six hours post-injury for all the groups. Blood vessels were coloured with India ink injection and examined in a video microscope. Laser exposure promoted an increase in blood vessel count when compared to controls. The 40 mW group showed early neovascularisation, with the greatest number of microvessels after three laser applications. The 10 mW subgroup showed angiogenesis activity around the same time as the sham laser group did, but the net number of vessels was significantly higher in the former than in the controls. After seven irradiations, the subgroup receiving 40 mW experienced a drop in microvessel numbers, but it was still higher than in the control groups.

A study by Fillipin [1708] investigated the effects of LPT on oxidative stress and fibrosis in an experimental model of Achilles tendon injury induced by a single impact trauma. Rats were randomly divided into four groups (n=8): control, trauma, trauma+laser for 14 days, and trauma+laser for 21 days. Achilles tendon traumatism was produced by dropping a load with an impact kinetic energy of 0.544 J. A GaAs laser of 45 mW average power was used, 5 J/cm^2 dosage, for a duration of 35 seconds, continuously. Studies were carried out on day 21. Histology showed a loss of normal architecture, with inflammatory reaction, angiogenesis, vasodilatation, and extracellular matrix formation after trauma. This was accompanied by a significant increase in collagen concentration when compared to the control group. Oxidative stress was also significantly increased in the trauma group. Administration of laser for 14 or 21 days markedly alleviated histological abnormalities, reduced collagen concentration and prevented oxidative stress. Superoxide dismutase activity was significantly increased by laser treatment over control values.

The objective of a study by Carrinho [1801] was to evaluate the effects of 685 nm and 830 nm laser irradiations at different fluences on the healing process of Achilles tendon of mice after tenotomy. Forty-eight male mice were divided into six experimental groups: Group A, tenomised animals, treated with 685 nm laser, at the dosage of 3 J/cm^2; group B, tenomised animals, treated with 685 nm laser, at the dosage of 10 J/cm^2; group C, tenomised animals, treated with 830 nm laser, at the dosage of 3 J/cm^2; group D, tenomised animals, treated with 830 nm laser, at the dosage of 10 J/cm^2; group E, injured control (placebo treatment); and group F, non-injured standard control. Animals were killed on day 13 post-tenotomy, and their tendons were surgically removed for a quantitative analysis using polarisation microscopy, with the purpose of measuring collagen fibres organisation through the birefringence (optical retardation, OR). All treated groups showed higher values of OR when compared to the injured control group. The best organisation and aggregation of the collagen bundles were shown by the animals of group A, followed by the animals of group C and B, and finally, the animals of group D. All wavelengths and fluences used in this *study were efficient at accelerating the healing process of Achilles tendon post-tenotomy, particularly the 685 nm laser irradiation, at 3 J/cm^2. It suggests the existence of wavelength tissue specificity and dose dependency.*

Ng [1879] investigated the effects of different intensities of therapeutic laser and running exercise, and their combined effects on the repair of Achilles tendons in rats. 36 Sprague-Dawley rats that received surgical hemi-transection of their right Achilles tendon were tested. Three laser dosages (4 J/cm^2, 1 J/cm^2 and 0 J/cm^2) and three running periods (30 min, 15 min, and 0 min) resulting in nine different dosages and time groups were studied with four rats in each group. The treatments were given on alternate days starting on day 5 post-injury. On day 22, the tendons were tested for load-relaxation, stiffness, and ultimate strength. There was a significant effect of laser on normalised load-relaxation; the rats receiving 4 J/cm^2 had less load-relaxation than those receiving no laser treatment. Results of stiffness testing revealed a significant effect, and rats that ran for 30 min had more stiffness than those that did not run. For ultimate strength, due to a significant interaction, the two factors were analysed separately, and the results showed that for rats receiving no LPT, those that had run for 15 min and 30 min had more strength than those that did not run. In conclusion, both LPT and running were found to hasten Achilles tendon repair. In general, the rats that received higher dosages of laser energy (4 J/cm^2) and ran for longer periods (30 min) performed better than those that received lower dosages of laser energy and ran for shorter periods.

In another study, Ng [2018] found that a combination of certain herbs and LPT had a better effect than either of them separately.

The objective of a study by Barbosa [2297] was to investigate the effects of LPT treatment alone (660 nm and 830 nm) or associated with platelet-rich plasma (PRP). The investigators used 54 male rats divided into six groups, with nine animals each: group 1, partial tenotomy; group 2 (GII), PRP; group 3 (GIII): 660 nm; group 4 (GIV), 830 nm; group 5 (GV), PRP + 660 nm; and group 6 (GVI), PRP + 830 nm. The protocol used was 0.35 W/cm^2, energy 0.2 J, energy density 7.0 J/cm^2, time 20 s per irradiated point, and number of points 3. Animals in groups GII, GV, and GVI received treatment with PRP, consisting of a single dose of 0.2 mL directly into the surgical site, on top of the tenotomy. Animals were killed on the 13th day post-tenotomy and their tendons were surgically removed for a quantitative analysis using polarisation microscopy. The percentages of collagen fibres of types I and III were expressed as mean +/- SD. Higher values of collagen fibres type I were obtained for groups GV and GVI when compared with all other groups whereas groups GIII and GIV showed no significant difference between them. For collagen type III, a significant difference was observed between GII and all other groups but no significant difference was found between GIII and GIV and between GV and GVI. Results showed that the deposition of collagen type I was higher when treatment with PRP and LPT was combined, suggesting a faster regeneration of the tendon.

A study by Delbari [1873] sought to investigate whether or not LPT with a helium-neon laser would increase fibril diameter of transected medial collateral ligament (MCL) in rats. Thirty rats received surgical transections to their right MCL, and five were assigned as the control group. After surgery, the rats were divided into three groups: group 1 (n= 0) received LPT with a HeNe laser and 0.01 J/cm^2 fluence per day, group 2 (n=10) received LPT with 1.2 J/cm^2 fluence per day, and group 3 (sham-exposed group; n=10) received daily placebo laser with the laser equipment turned off, while the control group received neither surgery nor LPT. Transmission electron microscope (TEM) examination was performed on days 12 and 21 after surgery and dimension and density of ligament fibrils were measured. On day 12, the fibril dimension of group 2 and their density were higher than those of groups 1 and 3.

In a study by Marcos [2042], rats weighing about 250 g were used. After anaesthesia, local collagenase injection was performed. The animals were sacrificed by CO_2 inhalation at different times. After the removal of skin and connective tissue, Achilles tendons were removed and processed for further analysis. Real Time PCR was employed to evaluate COX-1 and COX-2 expression in tendons. PGE_2 production was measured by commercial ELISA kits. A low level of COX-1 RNA expression was attained after collagenase injection. On the other hand, a high and significant level of COX-2 expression in tendon tissue, occurring two hours after collagenase injection, was observed. Although COX-2 expression was much more pronounced than COX-1 in tendon tissue, we could observe that Prostaglandin E_2 production was about the same (no significant difference) as a product of COX1 and COX-2. LPT was unable to produce any modification on PGE_2 production derived from COX-1 enzyme. However, it was quite effective in reducing PGE_2 production derived from COX-2 isoform. The authors could observe that 1 Joule and 3 Joules of energy significantly reduced PGE_2 production in the tendon tissue, while 6 Joules presented no difference when compared to the collagenase group. The infrared laser radiation operating with a wavelength of 810 nm was effective in reducing important inflammatory markers in rat tendons, thus becoming a promising tool for treating tendon disorders.

Yet another study by Marcos [2401] investigated if a safer treatment such as LPT could reduce tendinitis inflammation, and whether a possible pathway could be through inhibition of either of the two-cyclooxygenase (COX) isoforms in inflammation. Wistar rats (six animals per group) were injected with saline (control) or collagenase in their Achilles tendons. Then treated with three different doses of IR LPT (810 nm; 100 mW; 10 s, 30 s and 60 s; 3.57 W/cm^2 ; 1 J, 3 J, 6 J) at the sites of the injections, or intramuscular diclofenac, a nonselective COX inhibitor/NSAID. It was found that LPT dose of 3 J significantly reduced inflammation through less COX-2-derived gene expression and PGE_2 production, and less oedema formation compared to non-irradiated controls. Diclofenac controls exhibited significantly lower PGE_2 cytokine levels at 6 h than collagenase control, but COX isoform 1-

derived gene expression and cytokine PGE_2 levels were not affected by treatments. As LPT seems to act on inflammation through a selective inhibition of the COX-2 isoform in collagenase-induced tendinitis, LPT may have potential to become a new and safer non-drug alternative to coxibs.

The aim of another study by Marcos [2402] was to evaluate the short-term effects of LPT or sodium diclofenac treatments on biochemical markers and biomechanical properties of inflamed Achilles tendons. Wistar rats Achilles tendons (n=6/group) were injected with saline (control) or collagenase at peritendinous area of Achilles tendons. After 1 h animals were treated with two different doses of LPT (810 nm, 1 and 3 J) at the sites of the injections, or with intramuscular sodium diclofenac. Regarding biochemical analyses, LPT significantly decreased COX-2, TNF-alpha, MMP-3, MMP-9, and MMP-13 gene expression, as well as PGE_2 production when compared to collagenase group. Interestingly, diclofenac treatment only decreased PGE_2 levels. Biomechanical properties were preserved in the laser-treated groups when compared to collagenase and diclofenac groups.

It is interesting to note that the lowest energy produced the best results, all in accordance with Castano [1840].

The Achilles tendon has a high incidence of rupture, and the healing process leads to a disorganised extracellular matrix (ECM) with a high rate of injury recurrence. To evaluate the effects of different conditions of LPT application on partially tenotomised tendons, Guerra [2199] selected adult male rats and divided them into the following groups: G1, intact; G2, injured; G3, injured + LPT therapy (LPT; 4 J/cm^2 continuous); G4, injured + LPT (4 J/cm^2, 20 Hz); G5, injured; G6, injured + LPT (4 J/cm^2 continuous); and G7, injured + LPT (4 J/cm^2, 20 Hz until the 7th day and 2 kHz from 8 to 14 days). G2, G3, and G4 were euthanised 8 days after injury, and G5, G6, and G7 were euthanised on the 15th day. The quantification of hydroxyproline (HOPro) and non-collagenous protein (NCP), zymography for MMP-2 and MMP-9, and Western blotting (WB) for collagen types I and III were performed. HOPro levels showed a significant decrease in all groups (except G7) when compared with G1. The NCP level increased in all transected groups. WB for collagen type I showed an increase in G4 and G7. For collagen type III, G4 presented a higher value than G2. Zymography for MMP-2 indicated high values in G4 and G7. MMP-9 increased in both treatment groups euthanised at 8 days, especially in G4. Our results indicate that the pulsed LPT improved the remodelling of the ECM during the healing process in tendons through activation of MMP-2 and stimulation of collagen synthesis.

Clinical studies

Strupinska [821] treated 50 patients with Achilles injuries and 50 patients with external epicondyalgia. The patients were irradiated with GaAs laser separately or together with HeNe laser. The result of the therapy was *based on patient interviews and examinations, as well as on the Laitinen pain questionnaire. The results proved an analgesic effect.*

Hutchinson [2229] conducted a randomised controlled trial to determine whether active intense pulsed light (IPL) is an effective treatment for patients with chronic mid-body Achilles tendinopathy. A total of 47 patients were randomly assigned to three weekly therapeutic or placebo IPL treatments. The primary outcome measure was the Victorian Institute of Sport Assessment - Achilles (VISA-A) score. Secondary outcomes were a Visual Analogue Scale for pain (VAS) and the Lower Extremity Functional Scale (LEFS). Outcomes were recorded at baseline, six weeks and 12 weeks following treatment. Ultrasound assessment of the thickness of the tendon and neovascularisation were also recorded before and after treatment. There was no significant difference between the groups for any of the outcome scores or ultrasound measurements by 12 weeks, showing no measurable benefit from treatment with IPL in patients with Achilles tendinopathy.

Seven patients with bilateral Achilles tendinitis (14 tendons) who had aggravated symptoms by pain-inducing activities, were included in a study by Bjordal [1461]. A total of 1.8 Joules for each of three points along the Achilles tendon with a 904nm infrared laser or a placebo laser were administered to either Achilles tendons in a random order to which patients and therapist were blinded. Inflammation was examined by invasive microdialysis for measuring the concentration of the inflammatory marker PGE_2 in the peritendinous tissue, ultrasound with Doppler measurement of peri- and intratendinous blood flow, and pressure pain algometry. PGE_2 levels were significantly reduced at 60, 75, and 90 minutes after active laser compared both to pretreatment levels and to placebo. Changes in pressure pain threshold (PPT) were significantly different between groups. PPT increased by a mean value of 0.19 kg/cm^2 after treatment in the active laser group, while pressure pain threshold was reduced by -0.20 kg/cm^2 after placebo.

In a feasibility study by Tumilty [1987], 20 patients were randomised into an active laser group or a placebo group; all patients, therapists, and investigators were blinded to allocation. All patients were given a 12-week eccentric exercise programme and irradiated three times per week for 4 wk with either an active or placebo laser at standardised points over the affected tendons. Irradiation parameters in the active treatment group were: 810 nm, 100 mW, applied to six points on the tendon for 30 s, with a total dose of 3 J per point and 18 J per session. Outcome measures used were the VISA-A questionnaire, pain, and isokinetic strength. Patients were measured before treatment and at 4 and 12 wk. Within groups, there were significant improvements at 4 and 12 wk for all outcome measures, except eccentric strength for the placebo group at 4 wk.

In the study by Stergioulas (180 seconds per point), a total of 52 recreational athletes with chronic Achilles tendinopathy symptoms were randomised to groups receiving either Eccentric Exercises (EE) + LPT or EE + placebo LPT over 8 weeks in a blinded manner. LPT (820 nm, 30 mW) was *administered in 12 sessions by irradiating six points along the Achilles tendon with a power density of 60 mW/cm^2 and a total dose of 5.4 J per session. The results of the intention-to-treat analysis for the primary outcome, pain intensity during physical activity on the 100-mm Visual Analogue Scale, were significantly lower in the LPT group than in the placebo LPT group, with 53.6 mm versus 71.5 mm at 4 weeks, 37.3 mm versus 62.8 mm at 8 weeks, and 33.0 mm versus 53.0 mm at 12 weeks after randomisation. Secondary outcomes of morning stiffness, active dorsiflexion, palpation tenderness, and crepitation showed the same pattern in favour of the LPT group. LPT, with the parameters used in this study, accelerates clinical recovery from chronic Achilles tendinopathy when added to an EE regimen. For the LPT group, the results at 4 weeks were similar to the placebo LPT group's results after 12 weeks. An important feature of this study is the low power density and long irradiation time used to target the inflammation rather than the pain.*

In another study by Stergioulas [1878], 63 patients with a frozen shoulder condition were randomly assigned to one of two groups. In the active laser group (n=31), patients were treated with a 810 nm laser with a continuous output of 60 mW, applied to 8 points on the shoulder for 30 sec each, for a total dose of 1.8 J per point and 14.4 J per session. In the placebo group (n=32), patients received placebo laser treatment. During 8 wk of treatment, the patients in each group received 12 sessions of laser or placebo, 2 sessions per week (for weeks 1-4), and 1 session per week (for weeks 5-8). Relative to the placebo group, the active laser group had: (1) a significant decrease in overall, night, and activity pain scores at the end of 4 wk and 8 wk of treatment, and at the end of 8 wk additional follow-up (16 wk post-randomisation); (2) a significant decrease in shoulder pain and disability index (SPADI) scores and Croft shoulder disability questionnaire scores at those same intervals; (3) a significant decrease in disability of arm, shoulder, and hand questionnaire (DASH) scores at the end of 8 wk of treatment, and at 16 wk posttreatment; and (4) a significant decrease in health-assessment questionnaire (HAQ) scores at the end of 4 wk and 8 wk of treatment. There was some improvement in range of motion, but this did not reach statistical significance.

al-Shenqiti [1319] performed a double-blind, randomised study in 60 patients suffering from rotator cuff symptoms. Trigger points associated with this condition were treated with a 820 nm laser of 100 mW, modulated at 5000 Hz, dose 32 J/cm^2. On the whole 12 treatment sessions were given over four weeks. The outcome measures were pain, range of movement, functional activities and pressure pain threshold. Outcome measures were carried out pre- and post treatment, then three months later at follow-up. All outcome measures were considerably improved as compared to the control group.

In a clinical study by Bingöl [1623], 40 shoulder pain patients were randomly assigned to either Group I (n=20, laser treatment) or Group II (n=20, control). In Group I, patients were given laser treatment and an exercise protocol for 10 sessions over a two-week period. Laser was applied over *tuberculum majus and minus, bicipital groove, and anterior and posterior faces of the capsule, regardless of the existence of sensitivity, for 1 min at each location at each session with a pulse repetition rate of 2000 Hz using a GaAs diode laser, 2.98 J/cm² per point. In Group II, placebo laser and the same exercise protocol was given for the same time period. Patients were evaluated according to the parameters of pain, palpation sensitivity, algometric sensitivity, and shoulder joint range of motion before and after treatment. Analysis of measurement results within each group showed a significant post treatment improvement for some active and passive movements in both groups, and also for algometric sensitivity in Group I. Post treatment palpation sensitivity values showed improvement in 17 patients (85%) for Group I and in 6 patients (30%) for Group II. A comparison between the two groups showed superior results in Group I for the parameters of passive extension and palpation sensitivity, but no significant difference for the other parameters.* ***This study has been criticised by Bjordal [1740] for lack of parameter control. The given dose of 2.98 J/cm² is probably anything between 0.3 and 0.7 J/cm². WALT recommendation for muskoloskeletal pain is a minimum of 2 J/cm² per point for 904 nm.***

In a systemic review on the literature on treatment of frozen shoulder, Favejee [2201] found strong evidence for the effectiveness of steroid injections and LPT in short-term and moderate evidence for steroid injections in mid-term follow-up. Moderate evidence was found in favour of mobilisation techniques in the short and long term, for the effectiveness of arthrographic distension alone and as an addition to active physiotherapy in the short term, for the effectiveness of oral steroids compared with no treatment or placebo in the short term, and for the effectiveness of SSNB compared with acupuncture, placebo or steroid injections. For other commonly used interventions no or only limited evidence of effectiveness was found. Most of the included studies reported short-term results, whereas symptoms of frozen shoulder may last up to 4 years.

The aim of the study by Yavuz [2445] was to compare the effectiveness of LPT and ultrasound therapy in the treatment of subacromial impingement syndrome. Thirty-one patients with subacromial impingement syndrome were randomly assigned to LPT group (n=16) and ultrasound therapy group (n=15). Study participants received 10 treatment sessions of LPT or ultrasound therapy over a period of two-consecutive weeks (five days per week). Outcome measures (visual analogue pain scale, Shoulder Pain and Disability Index -SPADI-, patient's satisfactory level and sleep interference score) were assessed before treatment and at the 1st and 3rd months after treatment. All patients were analysed by the intent-to-treat principle. Mean reduction in VAS pain, SPADI disability and sleep interference scores from baseline to after 1 month, and 3 months of treatment was statistically significant in both groups. However, there was no significant difference in the mean change in VAS pain, SPADI disability and sleep interference scores between the two groups. The results suggest that efficacy of both treatments were comparable *to each other in regarding reducing pain severity and functional disability in patients with subacromial impingement syndrome.*

The aim of the study by Abrisham [2484] was to evaluate the additive effects of LPT with exercise in comparison with exercise therapy alone in treatment of the subacromial syndrome. The authors conducted a randomised clinical study of 80 patients who presented to the clinic with subacromial syndrome (rotator cuff and biceps tendinitis). Patients were randomly allocated into two groups. In group I (n=40), patients were given laser treatment (pulsed infrared laser) and exercise therapy for ten sessions during a period of 2 weeks. In group II (n=40), placebo laser and the same exercise therapy were given for the same period. Patients were evaluated for the pain with Visual Analogue Scale (VAS) and shoulder range of motion (ROM) in an active and passive movement of flexion, abduction and external rotation before and after treatment. In both groups, significant post-treatment improvements were achieved in all parameters. In comparison between the two groups, a significant improvement was noted in all movements in group I. Also, there was a substantial difference between the groups in VAS scores, which showed significant pain reduction in group I. This study indicates that LPT combined with exercise is more effective than exercise therapy alone in relieving pain and in improving the shoulder ROM in patients with subacromial syndrome.

The aim of the study by Yavuz [2492] was to compare the effectiveness of low-level laser therapy and ultrasound therapy in the treatment of subacromial impingement syndrome. Thirty one patients with subacromial impingement syndrome were randomly assigned to an LPT group (n=16) and ultrasound therapy group (n=15). Study participants received 10 treatment sessions of LPT or ultrasound therapy over a period of two-consecutive weeks (five days per week). Mean reduction in VAS pain, SPADI disability and sleep interference scores from baseline to after 1 month, and 3 months of treatment was statistically significant in both groups. However, there was no significant difference in the mean change in VAS pain, SPADI disability and sleep interference scores between the two groups. The mean level of patient satisfaction in group 1 at the first and third months after treatment was 72.45 ± 23.45 mm and 71.50 ± 16.54 mm, respectively. The mean level of patient satisfaction in group 2 at the first and third months after treatment was 70.38 ± 21.52 mm and 72.09 ± 13.42 mm, respectively. There was no significant difference in the mean level of patient satisfaction between the two groups. The results suggest that efficacy of both treatments were comparable to each other in regarding reducing pain severity and functional disability in patients with subacromial impingement syndrome. Based on our findings, we conclude that LPT may be considered as an effective alternative to ultrasound based therapy in patients with subacromial impingement syndrome, especially where ultrasound based therapy is contraindicated.

According to a study by Kelle [2519], the effectiveness of LPT was similar to that of local corticosteroid injection in patients with subacromial impingement syndrome.

Frozen shoulder is a common condition, yet its treatment remains challenging. In a literature review on frozen shoulder therapies by Jain [2485], the current best evidence for the use of physical therapy interventions (PTI) was evaluated. 39 articles describing the PTI were analysed using Sackett's levels of evidence and were examined for scientific rigor. The PTI were given grades of recommendation that ranged from A to C. Therapeutic exercises and mobilisation are strongly recommended for reducing pain, improving range of motion (ROM) and function in patients with stages 2 and 3 of frozen shoulder. LPT is strongly suggested for pain relief and moderately suggested for improving function but not recommended for improving ROM. Corticosteroid injections can be used for stage 1 frozen shoulder. Acupuncture with therapeutic exercises is moderately recommended for pain relief, improving ROM and function. Electrotherapy can help in providing short-term pain relief. Continuous passive motion is recommended for short-term pain relief but not for improving ROM or function. Deep heat can be used for pain relief and improving ROM. Ultrasound for pain relief, improving ROM or function is not recommended.

The aim of the analysis of Tumilty [2110] was to assess the clinical effectiveness of LPT in the treatment of tendinopathy. Secondary objectives were to determine the relevance of irradiation parameters to outcomes, and the validity of current dosage recommendations for the treatment of tendinopathy. Controlled clinical trials evaluating LPT as a primary intervention for any tendinopathy were included in the review. Methodological quality was classified as: high (>/=6 out of 10 on the PEDro scale) or low (<6) to grade the strength of evidence. Accuracy and clinical appropriateness of treatment parameters were assessed using established recommendations and guidelines. Twenty-five controlled clinical trials met the inclusion criteria. There were conflicting findings from multiple trials: 12 showed positive effects and 13 were inconclusive or showed no effect. Dosages used in the 12 positive studies would support the existence of an effective dosage window that closely resembled current recommended guidelines. In two instances where pooling of data was possible, LPT showed a positive effect size; in studies of lateral epicondylitis that scored >/=6 on the PEDro scale, participants' grip strength was 9.59 kg higher than that of the control group; for participants with Achilles tendinopathy, the effect was 13.6 mm less pain on a 100 mm Visual Analogue Scale. Conclusion: LPT can potentially be effective in treating tendinopathy when recommended dosages are used. The 12 positive studies provide strong evidence that positive outcomes are associated with the use of current dosage recommendations for the treatment of tendinopathy.

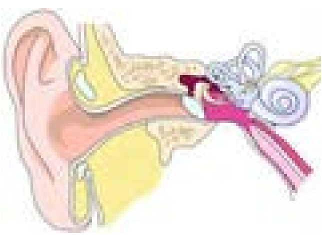
The aim of the study by Montes-Molina [2457] was to test the safety of interferential laser therapy generated by two independent low level *lasers and compare its effectiveness with conventional single probe laser therapy in the reduction of shoulder musculoskeletal pain and associated disability. 200 patients with shoulder musculoskeletal pain were randomly assigned in two groups, 100 people each. Group I, experimental (n=100) received "interferential" laser, placing two probes opposite each other over the shoulder joint. Group II, control (n=100) received conventional laser therapy, using a single probe along with a second inactive dummy probe. Lasers used were 810 nm, 100 mW, in continuous emission. Laser was applied in contact mode through ten sessions, on 5 shoulder points (7 Joules/ point) per session. There were no differences between both groups in the reduction of pain, either assessed by VAS scale or SPADI index, using the Mann-Whitney U-test. Comparison between the scores recorded before and after the treatment, within each group, showed significant differences for VAS during movement and SPADI index for both groups. In this study, the application of two lasers in order to generate interference inside the irradiated tissue showed to be a safe therapy. Both interferential and conventional laser therapy reduced shoulder pain and disability. Nevertheless, differences between them were not detected.*

American Physical Therapy Association (APTA) Clinical Guidelines [2327] recommends LPT for Achilles tendinopathies. The report says "Clinicians should consider the use of LPT to decrease pain and stiffness in patients with Achilles tendinopathy.

(Also see chapter 4.1.20 “Epicondylitis” on page 265.)

Further literature: [195, 242, 736, 737, 1061, 2307]

4.1.54 Tinnitus, vertigo, Ménière´s disease



A new and promising indication for LPT is tinnitus. This supposed inner ear condition seems to be a growing problem in our noisy, modern society, and the number of persons suffering from tinnitus seems to be increasing. Traditional treatments for tinnitus include psychological support or various masking procedures. Acupuncture and ginko extracts have been tried with limited success. LPT alone offers a new and promising treatment modality. Irradiation is given partly through the meatus, partly behind the ear; provided the problem really is located in the inner ear. Since the bone behind the ear is very compact, high power densities and prolonged treatment times are necessary to reach a sufficient dose in the inner ear when irradiating through the bone. The dose at target depends on wavelength, power density, the distance between the laser eye and tissue, and the contact or pressure technique used. When irradiating through the meatus, the distance from the ear drum and the direction of the beam are important. The main objective is to obtain a reasonable dose at target, but since the variation in the mentioned parameters is so great, the discussion about the optimal therapy becomes rather confusing. Applying high energies (Joules) does not automatically mean that the dose at target (J/cm²) is high. The laser should not give any unpleasant sensations of heat or pressure in the ear. If doing so, the power density should be reduced. This can easily be done by just distancing the probe a centimetre or so from the ear, unless the beam is collimated.

A closer look at the literature will reveal many studies using low to very low doses. Further, some studies do not give enough information even to make an estimation of the dose possibly used.

Literature:

Pionering studies:

Witt [1084] is one of the pioneers in this field, but to the knowledge of the authors, his results have not been published in any peer-review journals. Witt combines infusion of Gingko biloba (Egb 761, 17.5 mg dry extract per 5 ml ampoule) and laser. This may be a favourable combination, but an evaluation of the contribution of the laser is not possible. More than 500 patients have been treated since 1989 and Witt claims that more than 60% of the patients have attained a considerable or total relief. The laser used is a combination of a HeNe laser with a 12 mW output and a GaAs laser with five laser diodes, each with an average power output of 15 mW. ***Treatment technique is not stated but is supposed to be via the mastoid.***

Swoboda [1085] did not find any significant effect of gingko/laser. However, the ginkgo infusion used was at a homeopathic level (D3 = 1:1000 dilution), according to Witt.

Partheniadis-Stumpf [1086] also failed to find any effect from the combined ginkgo (6 ml Tebonin) infusion and laser. However, the laser was applied at a distance of one cm above the mastoid. The non-contact mode reduces penetration considerably and the mastoid is not ideal for reaching the inner ear.

Plath [306] treated 40 tinnitus patients with 50 mg ginkgo biloba; 20 patients received sham laser irradiation, 20 real laser. A HeNe laser with 12 mW output and a GaAs laser with five laser diodes, each with an average power output of 15 mW, were used; the irradiation procedure being approximately the same as for Partheniadis-Stumpf. In this study, however, 50% of the patients reported a reduction of the tinnitus by more than 10 dB, as compared with 5% in the control group, in both self-assessment and audiometric findings.

A similar study has been performed by von Wedel [1087]. One hundred fifty-five patients were treated with ginkgo infusion (5 ml Syxyl D3) and laser. The outcome was negative. ***No information about the type of laser, treatment technique or dosage is given, making an evaluation impossible. However, in a book by Stennert, published by Louis Calero, Cologne, Germany, we have found the following: Laser parameters were HeNe 12 mW, GaAs five diodes, each of 30 W peak power. Average output at 1200 Hz 5.4 mW, 8.1 mW at 1800 Hz. Total dose at 1200 Hz 2.59 J, 3.88 J at 1800 Hz,***

power density for HeNe 17.4 mW/cm². Treatment via the mastoid at a distance of 2 cm from the skin. Total irradiation time per session eight minutes, 3 sessions per week, total number of sessions 12. Total dose of GaAs 77.64 J (at skin). HeNe has no possibility of reaching the cochlea via the mastoid and can be overlooked, except for a possible systemic effect.

Shiomi [686] has investigated the effect of infrared laser applied directly into the meatus acousticus, 21 J, once a week for 10 weeks. The result of this non-controlled study is as follows: 26% of the patients reported improved duration, 58% reduced loudness, and 55% reported a general reduction in annoyance.

The same author [687] has also examined the effect of light on the cochlea using guinea pigs. Direct laser irradiation was administered to the cochlea through the round window. The amplitude of CAP was reduced to 53-83% immediately after the onset of irradiation. The amplitude then returned to the original level. The results of this investigation suggest that LPT might lessen tinnitus by suppressing the abnormal excitation of the eighth nerve of the organ of Corti.

More or less the same parameters were used in a controlled study by Mirtz [1088], but in this case there was no significant effect.

Nakashima [1266] treated 68 ears in 68 patients with tinnitus. A 60 mW laser was applied for six minutes (21.6 J), once a week for four weeks in a double-blind study. There was no significant difference between the two groups, which is not surprising considering the few sessions and the low energy applied. ***No differential diagnosis between somatosensory and other causes of tinnitus was performed.***

Wilden [474, 1089] has pioneered a different method with a considerably increased dose. A set consisting of one visible laser and three powerful GaAlAs lasers is used, covering a large area over and around the ear in the non-contact mode. Doses between 3000 and 5000 J are given each session. Laser is applied as a monotherapy. More than 800 patients have been treated with this concept and positive effects are reported even for vertigo. Recent injuries in "the disco generation" are more easily treated than long-term chronic conditions. In a separate study [1090], Wilden reports improved hearing capacity in these patients, as evaluated by audiometry.

Tauber [1091] has performed an ex-vivo laser penetration study. Based on these findings, it was possible to calculate the energy needed to obtain a dose of 4 J/cm² in the cochlea itself. Irradiation via the mastoid showed values 103 to 105 times smaller (depending on wavelength) than irradiation through the tympanic membrane.

The above feasibility study presented a laser application system enabling dose-controlled transmeatal cochlear laser-irradiation (TCL). It was followed by preliminary clinical results in patients with chronic cochlear tinnitus [1092]. The laser TCL-system, consisting of four diode lasers (635 nm - 830 nm) and a new specific head-set applicator, was developed on the basis of dosimetric data from the former light-dosimetric study. In a prelimi-

nary clinical study, the TCL-system was applied to 35 patients with chronic tinnitus and sensorineural hearing loss. The chronic symptoms persisted after standard therapeutic procedures for at least six months, while retrocochlear or middle-ear pathologies have been ruled out. The patients were randomised and received five single diode laser treatments (635nm, 7.8 mW CW, n=17 and 830 nm, 20 mW CW, n=18) of 4 J/cm² at the site of the supposed maximal cochlear injury. For evaluation of laser-induced effects, complete otolaryngologic examinations with audiometry, tinnitus masking and matching, and a tinnitus-self-assessment were performed before, during and after the laser irradiation. The first clinical use of the TCL-system has been well tolerated without side-effects and produced no observable damage to the external, middle or inner ear. After a follow-up period of six months tinnitus loudness was attenuated in 13 of 35 irradiated patients, while 2 of 35 patients reported their tinnitus as totally absent. Hearing threshold levels and middle ear function remained unchanged.

Prochazka [1093] has evaluated the effect of combined Egb 761 Ginkgo infusion and laser in a blind study. A total of 37 patients were divided into three groups. One group was given Egb 761 only, one Egb761 and placebo laser, and one Egb761 and real laser, 830 nm. The results in the three groups were as follows: no effect 29/26/19, less than 50% relief 44/48/29, more than 50% relief 18/26/36, no more tinnitus 9/0/26. Irradiation was performed over the mastoid and over the meatus acousticus, twice a week, 8-10 sessions.

In an extended study over three years, Prochazka [1263] evaluated the effect of laser in a group of 200 patients. These patients were taking gingko biloba preparations (73%) or Betahistadine (39%) and also had physical therapy, mainly directed at the neck vertebrae. LPT was performed with a 300 mW GaAlAs laser, 75 J/cm² into the ear and 135 J/cm² behind the ear. The outcome was: no more tinnitus 26%, more than 50% relief 43%, less than 50% relief 15%, no effect 16%. In addition, a group of 31 patients were selected for a double blind study where the same therapy as above was performed, but one group received placebo laser. At six months the outcome was as follows, with laser/no laser: no more tinnitus 25.8%/0.0%, more than 50% relief 35.5%/25.8%, less than 50% relief 19.4%/48.4%, no effect 19.4%/ 25.8%.

Hahn [1310] examined 120 patients with an average tinnitus duration of 10 years. The patients underwent pure-tone audiometry, speech audiometry and objective audiometry tests. The intensity and frequency of tinnitus were also determined. EGb 761 was administered three weeks before the start of LPT. The patients underwent 10 sessions of LPT, each lasting 10 minutes. An improvement in tinnitus was audiometrically confirmed in 50.8% of the patients; 10 dB in 18, 20 dB in 22, 30 dB in 10, 40 dB in 6 and 50 dB in 5 patients.

Rogowski [1094] divided a group of 32 tinnitus patients into one group receiving LPT and one receiving a placebo procedure. The 890 nm *laser irradiation, 3000 Hz, was performed via the meatus with a maximum dose of 2,3 J/cm², and via the mastoid with a maximum dose of 0,028 J/cm². Ten daily sessions were given. The effect was evaluated through VAS. Transiently evoked otoacoustic emissions (TEOAE) were measured before, during and after therapy. No significant difference between laser and placebo was found in annoyance or loudness of the tinnitus and in changes of TEOAE amplitude. These results indicate that there is no relationship between the effect of low-power laser and changes in cochlear micromechanics* ***at these very low doses.***

LPT of the cochlea has been shown to modify the collagen organisation within the cochlea and also in the basilar membrane. Wenzel [1434] excised four guinea pig cochleae. These were stained with trypan blue. Two were irradiated with a 600 nm pulsed dye laser and two were used as controls. Collagen organisation was visualised using a polarisation microscopy. Laser irradiation reduced the birefringence within the basilar membrane as well as within other stained collagen-containing structures. Larger reductions in birefringence were measured when more laser pulses were given. The effects were similar across all turns of each cochlea. Laser irradiation causes immediate alterations in collagen organisation within the cochlea that can be visualised with polarisation microscopy. These alterations may affect cochlear tuning. As would be expected, increased basilar membrane stiffness shifted the resonant frequency towards higher frequencies. Doubling basilar membrane stiffness raised the resonant frequency by a factor of 1.5 (from 1 to 1.5 kHz at the apex and from 20 to 30 kHz at the base). Doses were 5-30 J/cm². The author writes that it is conceivable that this technique may have therapeutic benefits for patients with high-frequency sensorineural hearing loss.

In a further study, Wenzel [1797] writes: The cochlea is the mammalian organ of hearing. Its predominant vibratory element, the basilar membrane, is tonotopically tuned, based on the spatial variation of its mass and stiffness. The constituent collagen fibres of the basilar membrane affect its stiffness. Laser irradiation can induce collagen remodelling and deposition in various tissues. We tested whether similar effects could be induced within the basilar membrane. Trypan blue was perfused into the scala tympani of anesthetised mice to stain the basilar membrane. We then irradiated the cochleas with a 694 nm pulsed ruby laser at 15 or 180 J/cm². The mice were sacrificed 14 to 16 days later and collagen organisation was studied. Polarisation microscopy revealed that laser irradiation increased the birefringence within the basilar membrane in a dose-dependent manner. Electron microscopy demonstrated an increase in the density of collagen fibres and the deposition of new fibrils between collagen fibres after laser irradiation. As an assessment of hearing, auditory brainstem response (ABR) thresholds were found to increase moderately after 15 J/cm² and substantially after 180 J/cm². Our results demonstrate that collagen remodelling and new collagen *deposition occurs within the basilar membrane after laser irradiation in a similar fashion to that found in other tissues.*

The hearing performance with conventional hearing aids and cochlear implants is dramatically reduced in noisy environments and for sounds more complex than speech (e. g. music), partially due to the lack of localised sensorineural activation across different frequency regions with these devices. Laser light can be focused in a controlled manner and may provide more localised activation of the inner ear, the cochlea. Wenzel [2098] sought to assess whether visible light with parameters that could induce an optoacoustic effect (532 nm, 10-ns pulses) would activate the cochlea. Auditory brainstem responses (ABRs) were recorded preoperatively in anesthetised guinea pigs to confirm normal hearing. After opening the bulla, a 50-mum core-diameter optical fibre was positioned in the round window niche and directed toward the basilar membrane. Optically induced ABRs (OABRs), similar in shape to those of acoustic stimulation, were elicited with single pulses. The OABR peaks increased with energy level (0.6 to 23 mJ/pulse) and remained consistent even after 30 minutes of continuous stimulation at 13 mJ, indicating minimal or no stimulation-induced damage within the cochlea. These findings demonstrate that visible light can effectively and reliably activate the cochlea without any apparent damage.

A few other indications in otorhinolaryngology have been treated with lasers, even with intravenous irradiation [688, 689, 690, 1095, 1096].

Animal studies

Acute in vivo experiments using gerbils were conducted by Izzo [1749] to record optically evoked compound action potentials (CAPs) from the cochlea. Optical radiation evokes CAPs in normal hearing animals and in deafened animals, in which cochleae lack outer and inner hair cells. The optical source was a Ho:YAG laser, with a wavelength of 2120 nm, pulse duration of 250 microseconds, operating at 2 Hz. The laser output was coupled to a low-OH 100-mm-diameter optical fibre. The optical fibre was inserted at the basal turn of the cochlea, approximated to the round window membrane and visually oriented toward the modiolus as allowed by the surgical access. The fibre is fixed in place and was not in direct contact with cochlear structures. Stimulation threshold was measured as 0.018+/-0.003 J/cm^2. Laser radiation could be increased by 30-40 dB until drastic changes were seen in cochlear function. Cochlear response amplitudes to optical radiation were stable over extended stimulation times. The experiments showed that it is possible to stimulate the auditory nerve with optical radiation. No neural damage could be detected even after hours of continual stimulation. It may be argued that optical radiation stimulates outer or inner hair cells. However, the results from experiments with deafened animals support the view that auditory neurons are stimulated directly. If hair cells were involved in optical stimulation of auditory neurons, the optical CAP amplitude should have decreased drastically concurrent with the increase in *acoustic thresholds. Moreover, it was possible to optically evoke CAPs after hair cells were destroyed by neomycin injection in the chronic deafened animals.*

Rhee [2207] investigated the effect of LPT on rescuing hair cells of the cochlea after acute acoustic trauma and hearing loss. Nine rats were exposed to noise. Starting the following day, the left ears (NL ears) of the rats were irradiated at an energy output of 100 to 165 mW/cm² for 60 min for 12 days in a row. The right ears (N ears) were considered as the control group. Frequency-specific hearing levels were measured before the noise exposure and also after the 1st, 3rd to 5th, 8th to 10th and 12th irradiations. After the 12th treatment, hair cells were observed using a scanning electron microscope. Compared to initial hearing levels at all frequencies, thresholds increased markedly after noise exposure. After the 12th irradiation, hearing threshold was significantly lower for the NL ears compared to the N ears. When observed using an electron microscope, the number of hair cells in the middle turn of the NL ears was significantly larger than that of the N ears. These findings suggest that LPT promotes recovery of hearing thresholds after acute acoustic trauma.

Based on the idea that cochlea hair cells and neural cells are from same developmental origin, the effect of LPT on hearing loss in animal models was evaluated by Rhee [2336]. Hearing loss animal models were established, and the animals were irradiated by 830 nm once a day for 10 days. Power density of the laser treatment was 900 mW/cm², and the fluence was 162 to 194 J. The tympanic membrane was evaluated after LPT. Thresholds of auditory brainstem responses were evaluated before treatment, after gentamicin, and after 10 days of LPT. Quantitative scanning electron microscopic (SEM) observations were done by counting remaining hair cells. Tympanic membranes were intact at the end of the experiment. No adverse tissue reaction was found. On SEM images, LPT significantly increased the number of hair cells in middle and basal turns. Hearing was significantly improved by laser irradiation. After LPT treatment, both the hearing threshold and hair-cell count significantly improved.

The objectives of a study by Rhee [1919] were: 1: To investigate preventive effects of LPT on gentamicin-induced vestibular ototoxicity. 2: To evaluate the effectiveness of LPT in the treatment of tinnitus. Twenty guinea pigs were divided into control and laser groups. Vestibular ototoxicity was induced by intratympanic injection of gentamicin into the left ear. LPT was irradiated into the left ear canal of the animals in the laser group. Vestibular function of the animals was evaluated with vertical and off-vertical axis rotation testing. 2: Forty patients with tinnitus were treated with ginkgo biloba orally and randomly divided into control and laser groups. In a clinical study, twenty patients of the laser group received 80.4 J/cm² of a 830 nm laser, three times per week for four weeks, via transmeatal irradiation. Tinnitus was evaluated by Visual Analogue Scale (VAS) and tinnitus handicap inventory (THI). Results: 1. Preventive effect of LPT to gentamicin induced *vestibular ototoxicity was demonstrated by preventing reduction of gain in a slow harmonic acceleration test and modulation in the off-vertical axis rotation test. 2. Eleven out of twenty laser group patients have shown significant improvement in VAS and THI compared to those in the control group. Conclusions are: 1. LPT therapy may have a preventive effect on vestibular ototoxicity. 2. LPT therapy in combination with ginkgo biloba seems to be worth trying on patients with tinnitus.*

The aim of a study by Park [2266] was to find out the effect of LPT on salicylate-induced tinnitus in the rat model. 14 rats were divided into 2 groups (study group, control group). Rats of both groups were treated with 400mg/kg/day of sodium salicylate for 8 consecutive days. Tinnitus was monitored using GPIAS (Gap Prepulse Inhibition of Acoustic Startle) 2h after first salicylate treatment, and every 24h during 9 days of treatment. Rats in laser group were irradiated to each ear with wavelength of 830 nm laser (165 mW/cm^2) for 30 min daily for 8 days. During salicylate treatment, rats of study group irradiated with LPT showed significantly higher GPIAS values throughout the experiment.

Clinical studies

The objective of the study by Zazzio [1622] was to investigate if LPT in combination with pulsed electromagnetic field therapy/repetitive transcranial magnetic stimulation (rTMS) and the control of Reactive Oxygen Specimen (ROS) would lead to positive treatment results for hyperacusis patients. Eight of the ten treated tinnitus patients also suffering from chronic hyperacusis claimed they had improvements on hyperacusis levels. Based upon that a prospective, unblinded, uncontrolled, clinical trial was planned and conducted. ROS and hyperacusis pain thresholds were measured. The patients were treated twice a week with a combination of therapeutic laser, rTMS and adjustment of ROS. A magnetic field of a maximum of 100 µT was oriented behind the outer ear, in the area of the mastoid bone. ROS were measured and controlled by administrating different antioxidants. Every treatment session 177-504 J of laser light of two different wavelengths was administrated towards the inner ear via meatus acusticus. The improvements were significantly better in the verum group than in a placebo group where 40% of the patients were expected to get a positive treatment effect. The patients in the long-term follow-up group received significantly greater improvements than the patients in the short-term follow-up group.

A pilot study was performed by Gable [1224] on three individuals who were suffering from Chronic Otitis Externa, "Swimmer´s ear" or "Tropical Ear", which had been unresponsive to conservative medical management for a minimum period of three months. Each patient was classed as chronic and referred by a medical practitioner for LPT. Each patient was irradiated over a two to six week period with a progressively increasing energy of 15 to 30 Joules via the single source of the ear canal using a 100 mW probe. Allowing for beam divergence within the confined canal, reflection and inverse square *spread from the emission source to the tympanic membrane; these factors would roughly balance, equating to an approximate energy density dose of 15-30 J/cm². The individual patient's existing medical regime was continued unchanged. Each patient showed full condition resolution for a minimum period of one month post discharge. Two of the patients were swimmers, one competitive at state level. In both cases it enabled the individuals to return to swimming within one to three weeks of treatment commencing, and to remain in the water during the completion of the treatment period through to full resolution and post discharge follow-up at one month. On a six-month follow-up of one patient, a 9-year-old boy with grommets and a life history of ongoing ear infections, had remained infection free for the first time for a period longer than six weeks. A secondary effect was a reduction of motion sickness, indicating that the LPT had also affected the cochlear and vestibular apparatus.*

Twenty patients with unilateral Ménière's Disease (MD) were included in a study by Teggi [1861]; all presented with uncontrolled vertigo. The patients were randomly divided into two groups: In group 1, the patients received LPT 20 min a day with a 5 mW red laser for six months, while group 2 received 16 mg ß-histine twice a day for six months. According to American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines, the main outcome for vertigo control was considered to be the number of spells per month in a six-month period before treatment compared with the same parameters during six months of therapy. The duration of spells expressed in minutes was also considered. Moreover, a hearing test was performed before and after therapy and results were reported as the pure tone average of 500-, 1000-, 2000-, and 3000 Hz frequencies. All results were valued at baseline, and after three and six months of therapy. Compared to baseline, the number and duration of spells were significantly reduced in both groups; statistical significance was detected for the three-month control in both groups.ß-histine seems to work faster in spell reduction. Audiometric examination did not show a statistically significant difference between the two groups. In the experience of the researchers, LPT seems to prevent vertigo spells in MD, although results indicate that it works slower than ß-histine. Dose-dependent therapeutic effects could explain the last result. The authors speculate that increased blood flow in the inner ear is the main mechanism leading to the therapeutic results.

The objective in a study by Gungor [1885] was to evaluate the effectiveness of 5 mW laser irradiation in the treatment of chronic tinnitus in a prospective, randomised, double-blind study. This investigation included 66 ears in 45 patients with chronic unilateral or bilateral tinnitus. A 5 mW laser with a wavelength of 650 nm, or placebo laser, was applied transmeatally for 15 minutes, once daily for a week. A questionnaire was administered which asked patients to score their symptoms on a five-point scale, before and two weeks after laser irradiation. A decrease of one scale point, regarding the loudness, duration and degree of annoyance of tinnitus, was accepted to rep-

resent an improvement. The loudness, duration and degree of annoyance of tinnitus were improved, respectively, in up to 48.8, 57.7 and 55.5% of the patients in the active laser group. No significant improvement was observed in the placebo laser group.

In the clinical study by Cuda [1923], 47 patients suffering from tinnitus, mean age 56 years, were divided into two groups. One group received 5 mW red laser and the other group placebo laser, 20 minutes per day for four months. After the active period, 16 patients in the laser group had a 60% improvement on the Tinnitus Handicap Inventory VAS scale, which was significantly different from the patients in the placebo group.

Mollasadeghi [2441] performed a double-blind randomised clinical trial on subjects suffering from tinnitus accompanied by noise-induced hearing loss. The study intervention was 20 sessions of LPT every other day, 20 minutes each session. The laser had a wavelength of 650 nm, 5 mW, and total energy per session 6 J over the mastoid. Tinnitus was assessed by three methods (VAS, tinnitus handicap inventory, and tinnitus loudness) at baseline, immediately and 3 months after the intervention. All subjects were male workers with age range of 30-51 years. The mean tinnitus duration was 1.85 ± 0.78 years. All three measurement methods have shown improved values after LPT compared with the placebo both immediately and 3 months after treatment. LPT revealed a U-shaped efficacy throughout the course of follow-up. Nonresponse rate of the intervention was 57% and 70% in the two assessment time points, respectively. This study found LPT to be effective in alleviating tinnitus in patients with noise-induced hearing loss, although this effect had faded after 3 months of follow-up.

The aim of a study by Ngao [2257] was to examine the effectiveness of transmeatal low level laser stimulation (TLLS) in treating tinnitus. This was a prospective, double-blinded, randomiserandomised, placebo-controlled trial. Patients with persistent subjective tinnitus as their main symptom were recruited into the study from the outpatient clinics. The recruited patients were randomised into the experimental group or TLLS+ group (patients in this group were prescribed to use TLLS at 5 mW, 650 nm for 20 min daily and oral ß-histine 24 mg twice per day for a total of 10 weeks) and the control group or TLLS- group (patients in this group were prescribed with a placebo device to use and oral ß-histine 24 mg twice per day for 10 weeks). All patients were required to answer two sets of questionnaires: the Tinnitus handicap inventory (THI) and Visual Analogue Scales (VAS) symptoms rating scales, before starting the treatment and at the end of the 10-week treatment period. The total score of the THI questionnaire was further graded into five grades, grade 1 being mild and grade 5 being catastrophic. Forty-three patients successfully and diligently completed their treatment. Transmeatal LPT stimulation did not demonstrate significant efficacy as a therapeutic measure in treating tinnitus

Fridberger [1884] writes: "Light produces force when interacting with matter. Such radiation pressure may be used to accelerate small objects *along the beam path of a laser. Here, we demonstrate that a moderately powerful laser can deliver enough force to locally stimulate the hearing organ, in the absence of conventional sound. Damped mechanical oscillations are observed following brief laser pulses, implying that the organ of Corti is locally resonant. This new method will be helpful for probing the mechanical properties of the hearing organ, which have crucial importance for the ear's ability to detect sound."*

A total of 30 adult subjects were enrolled in the study by Goldman [2359]. An Erchonia EHL laser was used to provide the laser stimulation. The device was a portable unit that consisted of a hand-held probe and a main body. The probe contained two laser diodes. One diode produced light in the green part of the visible light spectrum (532 nm), and the other diode produced light in the red part of the visible light spectrum (635 nm). Both diodes produced energy levels of 7.5 mW. The laser beams from both diodes were dispersed through lenses to create parallel line-generated beams, rather than spots. The 532 nm light was constant, and the 635 nm light was pulsed, with frequencies of 15 and 33Hz. The pulsing alternated between frequencies every 30 seconds. A second device served as the placebo. No statistically significant effect of LPT on auditory function was found, as assessed by pure-tone audiometry, speech understanding, and TEOAEs. Additionally, no individual subjects showed any clinically significant change.

In the above study by Goodman, the cochlea is reported to be one of the targets of the irradiation, although seven areas of the head were irradiated. The negative outcome of the study is therefore obvious, in that few, if any, photons reached this area or any area of the brain or cochlea. The combined energy of the two lasers was 15 mW and the energy density was considerably decreased by using a line generated beam. With an irradiation time of 225 seconds, the total energy was 3.4 J. Given the large area of irradiation, this energy is insufficient even at the surface and at a homeopathic level beneath the bony areas. Light in the red spectrum has primarily been used to treat superficial conditions, due to its lower penetration through tissues. Infrared light has therefore been preferred to reach deeper areas, such as the cochlea. Kolárová et al. [1130] used CCD camera technique to establish the penetration of 50 mW, 632.8 nm and 21 mW, 675 nm. In the thickest skin sample (19 mm with epidermis + dermis + subcutaneous fat from regio abdominalis) approximately 0.3% of the HeNe and 2.1% of the diode laser light penetrated. So the power of the 7.5 mW red laser light would have reached a level of 0.2 mW after passing through the skin, and still not being inside the bone. The penetration of the 532 nm wavelength is three times lower. The above is, regrettably an example of a very qualified team of scientists using parameters that are bound to fail.

Summing up, the clinical literature is contradictory and difficult to evaluate, since some studies using similar methods come to different conclusions and the overall parameters used vary a lot. Lack of differential diagnoses (see below for somatosensory tinnitus) lower the credability of most of *the above studies. At best, it can be said that LPT using some clinical parameters show promising results and are worthy of further exploration, especially when considering the bleak outcome of other therapies. But if seems reasonable to believe that at least some photons should reach the cochlea for an effect to be elicited. The best support for this therapy is found in the animal studies, clearly indicating that there is a regenerative potential in the hearing organ, when subjected to laser light.*

Further literature: [874, 1174, 1227, 1228, 1599, 1883, 2443]

Somatosensory tinnitus

All the above studies assume that tinnitus and vertigo are always inner ear problems. However, these conditions frequently have a muscular origin (“somatosensory tinnitus”). There also seems to be a correlation between sudden sensorineural hearing loss and muscular (TMD - Temporo-Mandibular Disorders) conditions, as reported by Axelsson [1633].

The percentage of patients with a muscular origin for their tinnitus/vertigo is not known but seems to be large. A differential diagnosis is therefore important before any therapy is applied; whether laser or traditional therapies. If this is not done, studies of the effect of transmeatal LPT become a gamble. The outcome would rather be related to the type of tinnitus dominating in the verum group than the actual effect of the therapy. An interdisciplinary co-operation between the ENT physician, a physiotherapist and a dentist is ideal.

The meatus acusticus is very close to the temporomandibular joint (TMJ) and to the posterior insertions of the lateral pterygoid muscle. If can therefore be hypothesised that the laser irradiation affects the pain and inflammation in the TMJ and also relaxes the lateral pterygoid. The laser irradiation would then supress the somatosensory effect of the malocclusion during the period of laser irradiation. If this were the case, a follow up control would catch such changes. In none of the five double blind studies mentioned [1861, 1885, 1923, 2257, 2448], such a follow up has been performed. There is some discussion about muscular relaxation techniques in one study, but not at all in the other four. Two of the five studies have a positive outcome, one a fairly positive outcome and two a negative outcome.

The lack of a proper diagnosis in these studies complicates the evaluation of the potential of LPT in the treatment of tinnitus. From the scant literature it seems reasonable to believe that LPT is a viable and safe method, but the optimal parameters are far from resolved. On the other hand, the literature support for a somatosensory background is stronger.

Meniere’s disease is a condition first described by the French physician Ménière in 1861. It is a clinical entity consisting of vertigo, fluctuating hearing loss and tinnitus. Few medical conditions have been so thoroughly studied and described, yet lacking an effective therapy. Tinnitus, however, is not necessarily associated with Meniere; it is often an isolated condition. But the treatment of somatosensory Meniere and somatosensory tinnitus is very similar. We will therefore, in the following text, simplify the terms and speak only about "tinnitus".

Muscular tension is a key element in somatosensory tinnitus. The role of the laser is to create an immediate reduction of muscle pain through consecutive relaxation. Thus, this intervention will make all the following therapy faster and more successful. Somatosensory tinnitus has been difficult to treat and is often passed by without a diagnosis. The combination of LPT in the traditional therapy of temporomandibular disorders (TMD) and cervical spine disorders (CSD) has been reported to be a more successful way of helping these patients, compared to traditional therapies. However, it is not to be expected that all symptoms will subdue rapidly. The skill of the dentist, the co-operation of the patient and the concomitant physiotherapy are all important factors. Many patients will not be completely relieved of symptoms, but the majority will experience a great reduction of their problems.

According to Bjorne [1263] and Estola-Partanen [1267], the treatment of somatosensory tinnitus reduces the severity of tinnitus more than the incidence. The three-year follow-up study by Bjorne [1263] showed simultaneous decreases in the intensities of vertigo, non-whirling dizziness, tinnitus, feeling of fullness in the ear, pain in the face and jaws, pain in the neck and shoulders, and headache that were both longitudinal and highly significant. Significant reductions in the frequency of vertigo, non-whirling dizziness and headache were also reported by the patients as well as a complete disappearance of pain located in the vertex area. A significant relief of TMD symptoms and a decrease in nervousness were also achieved. It must be underlined that the success in the study [1263] reflects the outcome of the therapy before the author started to use LPT as an additional method. The addition of LPT has then further improved the progress in this category of patients. Frequently, these patients can notice a change in the character of their tinnitus when the lateral pterygoid muscle is irradiated.

The aim of a study by Tullberg [1890] was to investigate the presence of symptoms and signs of temporomandibular disorders (TMD) in patients with tinnitus, and to evaluate the effect of TMD treatment on tinnitus in a long-term perspective in comparison with a control group of patients on a waiting list. One hundred twenty patients with tinnitus were subjected to a clinical examination of the masticatory system and whether they had co-existing TMD to TMD treatment. Ninety-six patients had TMD, most frequently localised myalgia. Seventy-three of these completed the treatment and responded to a questionnaire two years later. Fifty patients with tinnitus who were on the waiting list served as a control group. Eighty percent of the patients had signs of TMD, most commonly myofascial pain. Forty-three percent of the patients reported that their tinnitus was improved at the two-year follow-up, 39% that it was unchanged, and 17% that it was impaired compared to before the treatment. Twelve percent of the subjects in the control group reported that their tinnitus was improved compared to two years previously, 32% that it was unchanged, and 56% that it was impaired. The difference between groups was significant. In conclusion, these results showed that TMD symptoms and signs are frequent in patients with tinnitus and that TMD treatment has a good effect on tinnitus in a long-term perspective, especially in patients with fluctuating tinnitus.

The suboccipital muscles should also be palpated, since these muscles and the masticatory muscles are closely functionally connected. In fact, the mandible and the upper cervical joint (C0/C1) constitute an integrated motor system. This area is often tender to palpation. The patient should be made aware of his/her posture and taught to perform stretching exercises. Attention should be given to the posture of the patient, and tenderness and protrusion of C7 (“vulture neck”) should be observed and corrected. Tenderness in the suboccipital and/or C7 is often related to vertigo.

Tinnitus patients have a higher incidence of TMD problems [1488, 1722, 1723, 1724], so the participation of a dentist in the therapy is important.

The therapy outlined below brings new hope to a large group of "intractable" patients. It outlines the traditional therapy created by Bjorne, with the successful addition of LPT. Patients suffering from somatosensory tinnitus often live in a therapeutic “void”. Many medical doctors are not aware of this connection and most dentists alike. And the patient is not likely to inform the dentist, believing that the condition has nothing to do with dentistry. A first step on the road is to include questions about tinnitus into the standard anamnestic questionnaire.

Somatosensory tinnitus examination and therapy

Anamnesis

1 Does the patient experience a feeling of fatigue in the jaws, difficulties in mouth opening, sensations of tension in the jaws/neck, hypersensitive or tender teeth, clenching of tongue/jaws, tendency for general stress, or waking up at night due to tinnitus?

2 Can the patient manipulate his/her tinnitus through movements of the jaw and neck? Usual movements evoking this phenomenon are: opening the mouth wide, protrusion and side movements of the mandible, flexion/extension and side rotation of the upper cervical joints.

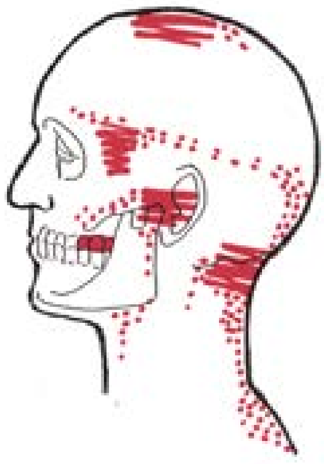


Figure 4.34 The predominant tender areas.
Courtesy: Assar Bjorne

3 Can the patient manipulate his/her tinnitus by putting pressure/stimulation in the areas of the sensory innervation of the trigeminal nerve? Usual areas evoking this phenomenon are putting pressure on tragus, over the cheek, jaw or temple and the stylomandibular ligament, but also gazing with the eyes.

4 Are there other symptoms related to tension: pain in the jaws, face, neck, and headache?

Status

5 Observation of hypertrophic masticatory muscles and possible abnormal posture of the head/neck (“Vulture neck”, C7). The physiotherapist will frequently find tender areas in the upper trapezius.

6 Palpation of the masticatory muscles (the lateral pterygoid muscle in particular), the TMJ, and the suboccipital muscles.

7 Range of movement of the mandible and neck.

8 Active shining bruxing facets as signs of active bruxism.

Therapy

9 Training in how to normalise abnormal head/neck posture (“vulture neck”), and training in how to relax masticatory, neck and shoulder muscles.

10 Training of autostretching of the suboccipital muscles (the rectus capitis posterior minor and major muscles and the obliquus capitis superior muscles), the upper and middle trapezius muscles and the levator scapulae muscles. LPT of tender areas in these muscles is also recommended.

11 Examination of occlusal function and presence of active interferences, followed by adjustment through selective grinding. The examination should preferably be performed with the patient in an upright position. Interferences in the central occlusion and in the retruded position are eliminated. Patient feedback is useful. Once the patient has experienced the positive feeling of having the occlusion improved, he/she will become quite aware of even minute interferences. It is typical to find a tender lateral pterygoid on one side and the "high" tooth on the contralateral side.

12 Information about the necessity of adjusting the patient's life style (stress).

13 Laser treatment of tender areas in the jaw and neck muscles, 5-15 J per point depending on the size and location of the muscle. Two to three sessions per week acc. to the evolution of improvement, with GaAlAs or GaAs laser.

14 Bite splint in selected cases.

15 Stop all intakes of analgesics in patients with bruxing habits. The use of analgesics can in many cases cause the patient to press the teeth even harder.

Common dental occlusal backgrounds:

16 The patient is clenching/bruxing on active shining facets of the front teeth, forcing the TMJ:s backwards in the fossa. This initiates a nociceptive reflex from the lateral pterygoid, trying to move the TMJ:s forwards.

17 Cross bite (sliding areas preventing central occlusion and balanced TMJ position).

18 Patients having had extractions of premolars for orthodontic reasons.

19 Crowns or bridges are a little bit too high. This may have been already on the initial crown or as a later effect, due to the fact that the abrasion rate of the material of the crown is less than that of the natural teeth.

4.1.55 Tonsillitis

"Laser peeling" of the tonsils has successfully been used at the hospital of Halmstad, Sweden, using a carbon dioxide laser. Children are able to eat without problems within 30 minutes after therapy. Considering the low depth of penetration (0.1-0.3 mm), this must partially be an example of therapeutic laser effects.

Literature:

In a pilot study, Petrek [524] used a HeNe laser to treat eight patients suffering from chronic tonsillitis. Three treatment sessions were given over a period of nine days. Shortly after the cessation of treatment, a significant increase of secretory immunoglobulin A in saliva was observed, followed by an increase of IgA serum levels after four weeks of follow-ups. These findings correlated well with the clinical improvement in seven out of the eight patients.

Hubacek [1036] irradiated each palatal tonsil with a HeNe laser, 0.6 J/cm² for one week and found an increase of T lymphocytes and plasmatic cells in the tonsils after therapy.

Further literature: [700, 701, 707]

4.1.56 Trigeminal neuralgia

There are no entirely effective treatment methods for this painful condition. Laser treatment comes with no guarantee of success, but bearing in mind that the method is painless and without side effects, it should be a more attractive initial choice than deep blockades and strong analgesics. Patients receiving LPT can often reduce their Carbamazapine dose. All three laser types can be used.

Both extraoral and intraoral trigger points and pain points are irradiated. A total of 2-3 J per standard point (standard points are the various foramina, such as the infraorbital, supraorbital, mental, mandibular, palatinum major, and incisivum) is an appropriate initial dosage. Pain points can be given 3-4 J. The course of the main nerve is then irradiated extra- or intraorally. When irradiating through bone, as with the n. mandibularis inferior, the dose must be increased by a factor of three to compensate for loss of penetration. A pain reaction is not unusual and should be interpreted as a positive sign. Patients should be warned about its likelihood beforehand. Treat twice a week initially and then allow a longer period between treatments. Treatment should not be interrupted if and when the pain disappears, but should continue at longer and longer intervals.

Literature:

Eckerdal [452, 595] used 830 nm laser light at 30 mW in a double-blind study of the effect of LPT on trigeminal neuralgia. A positive effect was evident. It is necessary to find the pertinent trigger points/zones and to include the II branch of the trigeminal nerve in the treatment. Treatment was given once a week for five weeks, 2 J per trigger point. At the end of the trial, 10 of the 14 patients in the verum group were free from pain and 2 improved. At the one-year follow-up, 6 patients were still free from pain and 10 were back to the initial condition. In the placebo group, 1 patient was free from *pain and 2 improved at six months. At the one-year follow-up, 1 was still free from pain and the other 13 were back to the initial state of pain. Consumption of analgesics was significantly reduced in the verum group at the end of the treatment period but was constant in the placebo group. If the patient had already received alcohol blocks, the treatment was less successful.*

The objective of a study by Takamoto [1481] was to evaluate the efficacy of LPT in cases of trigeminal pain. Thirty patients were evaluated, male and female, who were using 400 mg to 1200 mg/day of carbamazepin to control the pain. The patients were treated with a diode laser of 830 nm wavelength, 40 mW, continuouss emission, spot area 3 mm^2, with a total of 20 joules per weekly session. The LPT demonstrated moderate efficacy over the pain, allowing a reduction in the quantity of carbamezepin in most of the cases. The laser and drug treatments together enabled control of the pain using a smaller quantity of medicines.

The study by Aghamohammadi [2412] aimed to assess whether adding LPT to trigeminal ganglion block has a substantial effect in increasing pain relief in trigeminal neuralgia. This case-control study recruited 42 patients with trigeminal neuralgia over a 15 month period. The patients were randomised to 2 equal groups. Group A received Gasserian ganglion block along with LPT, and group B, the control group, received only the ganglion block. The severity of pain was determined by the Visual Analogue Scale at baseline, before each block, and at 1, 3, 5, and 7 days and 1, 3, and 6 months after the intervention. The dose of carbamazepine taken by the patients was also documented during the study period. The severity of pain was significantly lower in group A, from day 7 until the end of the study period (month 6). The number of carbamazepine tablets taken was also significantly lower in group A compared with group B from the initial months until the end of the study period (month 6). The period of a pain-free state was significantly higher in group A than in group B.

The purpose of the study by Seada [2490] was to determine which of the transcranial electromagnetic stimulation or LPT is more effective in the treatment of trigeminal neuralgia of multiple sclerosis patients. Thirty multiple sclerosis patients of both sexes participated in this study. The age of the subjects ranged from 40 to 60 years and their mean age was (56.4-6.6). Participants were randomly selected. Patients were randomly divided into two equal groups of 15. The Laser group received 830 nm, 10 Hz and 15 min duration, while the Electromagnetic group received repetitive transcranial electromagnetic stimulation at a frequency of 10 Hz, intensity of 50 mA and duration of 20 minutes. Patients were assessed pre and post treatment for degree of pain using a numerical rating scale, maximal oral mouth opening using a digital calibrated caliper, masseter muscle tension using a tensiometer and a compound action potentials of masseter and temporalis muscles. There were significant improvements after treatment in both groups, with a significant difference between the Electromagnetic and Laser groups, in favour of the Electromagnetic group. Repetitive transcranial electromagnetic *stimulation at 10 Hz, 50 mA, and 20 minutes duration is more effective than LPT therapy at reducing trigeminal pain, increasing maximum oral mouth opening, masseter and temporalis muscle tension in multiple sclerosis patients.*

Further literature: [191, 211, 218, 444, 452, 509, 517, 595, 635, 755, 757, 758, 762, 1057, 1070, 1111]

4.1.57 Thrombophlebitis

Literature:

In a study by Dudenko [567], a HeNe laser was used to treat thrombophlebitis. The laser produced a marked analgesic, desensitising, hypocoagulative and immunostimulating effect.

4.1.58 Tuberculosis

In a Cohrane Meta analysis of the available literature on the subject, Vlassov [1283] concludes that there is no support for any effect of LPT on tuberculosis. The studies analysed contain a wide variety of lasers, doses, therapeutical approaches and co-interventions. Further to that, the exact parameters are seldom accounted for.

Literature:

Bhagwanani [715] has used nitrogen laser (337 nm) for the treatment of tuberculosis in patients resistant to traditional antibiotics. A needle is inserted into the lung and used as the carrier of the light. Ten minutes of irradiation is often enough for a clinical improvement in 90% of the patients. Altogether 60% of the patients showed an improvement on their X-rays.

Agaev [716] compared the effect of HeNe laser treatment in two groups of patients with chronic destructive pulmonary tuberculosis or post-operative broncopulmonary complications. A group of 50 patients had HeNe laser treatment and a non-irradiated group of 30 patients served as control. The post surgery complication rate was 32% in the laser group and 63% in the control group.

Zhuk [1141] divided a number of patients with chronic tuberculosis into two groups. One group (group I, 174 patients) received chemotherapy and another (group II, 240 patients) chemotherapy and laser irradiation, 890 nm. Transcutaneous irradiation over the lung projection and skin irradiation of great blood vessels were used. Dose at skin varied between 0.002-0.05 J/cm^2, depending on the pulse repetition rate used. Within three months, sputum smear conversation/cavity closure was observed in 60/36% of the patients in treatment group II, and in 36/16% in group I. After six months, the percentages were 85/65 % in group II and 49/29% in group I.

Dube [1563] investigated the effect of nitrogen laser irradiation (337 nm) on viability of clinical isolates of Mycobacterium tuberculosis. Bacteria were exposed to a nitrogen laser (average power 2.0 mW) in vitro at a power *density of 70 ± 0.7 W/m² for 0-30 min, and the cell viability was determined by a luciferase reporter phage assay. Immediately after laser exposure, all the clinical isolates investigated showed a dose-dependent decrease in cell viability. However, when the laser-exposed isolates were incubated in broth medium for three days, most of these showed a significant recovery from laser-induced damage. An addition of 5.0 g/ml acriflavine (a DNA repair inhibitor) to the incubation medium had no significant effect on recovery. This suggests that DNA damage may not be involved in the cell inactivation. Electron paramagnetic resonance studies using 5-doxyl strearic acid as a probe suggest alterations in lipid regions of the cell wall.*

Further literature: [710, 965, 966, 1177, 1540, 1642]

4.1.59 Urology

LPT appears to be a promising therapy for male infertility and for inflammation in the genital organs.

Literature:

In vitro studies

In a study by Lubart [592], it was found that 780 nm laser light inhibits Ca^{2+} uptake by sperm mitochondria and enhances Ca^{2+} binding to sperm plasma membranes. The effect of light on Ca^{2+} uptake by plasma membrane vesicles in the absence of ATP was much greater than in the presence of ATP.

Lubart [1196] found that HeNe laser irradiation of human spermatozoa resulted in a significant increase in its egg-penetration ability. The effect appeared only in men with low sperm penetration rates. Using the electron paramagnetic resonance technique it was established that OH radicals are produced in irradiated spermatozoa.

Sato [580] found that LPT increases the mobility and speed of sperm in vitro.

Ocaña-Quero [683] compared the effects of HeNe laser, calcium and heparin with regard to the induction of the acrosome reaction and mortality in bull sperm cells. It is concluded that the application of HeNe laser at doses from 2 to 16 J/cm² induced the acrosome reaction and decreased the bull sperm cell mortality percentage in vitro significantly better than the other capacitation agents, and as compared to the control group.

Sperm motility depends on energy consumption. Laser irradiation increases adenosin triphosphate (ATP) production and energy supply to the cell. The aim of a study by Corral-Baqués [1557] was to analyse whether the irradiation affects the parameters that characterise dog sperm motility. Fresh dog sperm samples were divided into four groups and irradiated with a 655 nm continuous wave diode laser with varying doses: 0 (control), 4, 6 and 10 J/cm². At 0, 15 and 45 min following irradiation, pictures were taken of all the groups in order to study motility with computer-aided sperm analysis. Functional tests were also performed. Average path velocity, linear coefficient and beat cross frequency were statistically and significantly different *when compared to the control. The functional tests also showed a significant difference. At these parameters, the 655 nm continuous wave diode laser improves the speed and linear coefficient of the sperm.*

By means of a Computer Aided Sperm Analysis (CASA) Corral-Baqués [2379] has studied the effects of a 655 nm continuous wave laser irradiation at different power outputs with a dose of 3.34 J on sperm motility. After an eosine-nigrosine stain to establish its quality, the second fraction of fresh beagle dog sperm was divided into 5 groups, 1 control and four to be irradiated respectively with an average output power of 6.84 mW, 15.43 mW, 33.05 mW and 49.66 mW. At times 0 and 45 minutes from irradiation pictures were taken and analysed with the Sperm class Analyzer SCA2002 programme. The motility parameters of 4987 spermatozoa studied were: curvilinear velocity (VCL), progressive celocity (VSL), straightness (STR), wobble (WOB), average path velocity (VAP), linearity (LIN), mean amplitude of lateral head displacement (ALHmed), beat cross frequency (BCF) and the total motility (MT). At time 15 minutes after irradiation a hypoosmotic swelling test (HOST) was done. Several motility parameters that affect the overall motile sperm subpopulations structure have been changed by different output powers of a 655 nm diode laser irradiation, and prevents the decrease of the sperm motility properties along time.

Biological tissues respond to low-level laser irradiation and so do dog spermatozoa. Among the main parameters to be considered when a biological tissue is irradiated is the output power. Corral-Baqués [2380] studied the effects on sperm motility of 655 nm continuous wave diode laser irradiation at different output powers with 3.34 J (5.97 J/cm^2) The second fraction of fresh dog sperm was divided into five groups: control, and four to be irradiated with an average output power of 6.8 mW, 15.4 mW, 33.1 mW and 49.7 mW, respectively. At 0 min and 45 min after irradiation, pictures were taken and a computer aided sperm analysis (CASA) performed to analyse different motility parameters. The results showed that different output powers affected dog semen motility parameters differently. The highest output power showed the most intense effects. Significant changes in the structure of the motile sperm subpopulation were linked to the different output powers used.

Kipshidze [1041] used HeNe laser on human corpus cavernosum smooth muscle cells in vitro. Laser induced an increase in the expression of NO and an elevation of cyclic guanosine monophosphate (cGMP). This substance is important in the process of smooth muscle relaxation in the corpus cavernosum and consequently for the erection. It is suggested that LPT could be used in a combination with pharmaceuticals, or as the sole therapy for patients with coronary artery disease or hypertension.

The purpose of the study by Yazdi [2471] was to evaluate how LPT affects the human sperm motility. Fresh human semen specimens of asthenospermic patients were divided into four equal portions and irradiated by 830 nm laser irradiation with varying doses as: 0 (control), 4, 6 and 10 J/cm^2. At the times of 0, 30, 45 and 60 min following irradiation, sperm motilities are *assessed by means of computer-aided sperm analysis in all samples. Two additional tests [HOS and sperm chromatin dispersion (SCD) tests] were also performed on the control and high irradiated groups as well. Sperm motility of the control groups significantly decreased after 30, 45 and 60 min of irradiation, while those of irradiated groups remained constant or slightly increased by passing of time. Significant increases have been observed in doses of 4 and 6 J/cm^2 at the times of 60 and 45 min, respectively. SCD test also revealed a non-significant difference. These results showed that irradiating human sperms with 830 nm laser can improve their progressive motility depending on both laser density and post-exposure time.*

Animal studies

Cohen [596] reports an enhanced fertilisation rate of mouse spermatozoa in vitro using 633 nm laser light. The results suggest that the effect of 633 nm HeNe laser irradiation is mediated through the generation of hydrogen peroxide by the spermatozoa, and that this effect plays a significant role in the augmentation of the sperm cell's capacity to fertilise in vitro.

The aim of the study by Taha [1548] was to determine the quantitative and qualitative changes of the seminiferous epithelium after 830 nm laser irradiation. The left testes of rats were daily exposed to laser light for 15 days; so that the cumulative doses used were 28.05 and 46.80 J/cm^2 in two experimental groups. Samples collected 24 hours after the last treatment were processed for light microscopy and transmission electron microscopy scrutiny. The number of germ cells, specially the pachytene spermatocytes and elongated spermatids, increased after 28.05 J/cm^2 laser irradiation. Ultrastructural features of germ and Sertoli cells in this group were similar to that of the control; while laser irradiation at 46.80 J/cm^2 had a destructive effect on the seminiferous epithelium such as dissociation of immature spermatids and evident ultrastructural changes in them. The findings confirmed the existence of a biostimulatory threshold of applied laser energy and the importance of determining it for clinical applications. Moreover, it was revealed that low doses of laser light have a biostimulatory effect on the spermatogenesis and may provide benefits to the patients with oligospermia and azoospermia.

Corrral-Baqués [1902] studied the effects on sperm motility of 655 nm continuous wave diode laser irradiation at different output powers with 3.34 J (5.97 J/cm^2). The second fraction of fresh dog sperm was divided into five groups: control, and four to be irradiated with an average output power of 6.8 mW, 15.4 mW, 33.1 mW and 49.7 mW, respectively. At 0 min and 45 min after irradiation, pictures were taken and a computer aided sperm analysis (CASA) was performed to analyse different motility parameters. The results showed that different output powers affected dog semen motility parameters differently. The highest output power showed the most intense effects. Significant changes in the structure of the motile sperm subpopulation were linked to the different output powers used.

Testosterone (T) plays a vital role in the sexual function and many other health-related phenomena. Ahn [2407] conducted a study to examine the effects of LPT on the testis in elevating serum T level in rats. The researchers performed the study using 30 male rats aged six weeks, weighing 200 g. In rats of two laser groups (670 nm or an 808 nm), were irradiated to the testes at an intensity of 360 J/cm² /day (200 mW × 30 min) for five days. This was followed by the measurement of the depth of tissue penetration, that of serum T level and histopathological examination. The results showed that the rate of tissue penetration was significantly higher in the 808 nm wavelength group as compared with the 670 nm wavelength group. Serum T level was not significantly higher in the experimental groups as compared with the control group; but serum T level was significantly elevated in the 670 nm wavelength group on day 4. Thus the LPT using 670 nm was effective in increasing serum T level without causing any visible histopathological side effects. In conclusion, the LPT might be an alternative treatment modality to the conventional types of testosterone replacement therapy.

360 J over a rat testis is a lot! The reported dose suggests that the unlikely spot size was 1 cm² .

The aim of the study by Bianchi-Alves [2439] was to evaluate the effect of different LPT protocols on testes histopathological characteristics of rams submitted to scrotal insulation for the induction of the testicular degeneration. For this, 6 rams were divided in 3 groups: (1) control, without LPT treatment (n=2); (2) LPT treatment with a cumulative dose of 28 J/cm² (n=2); and (3) LPT treatment with a cumulative dose of 56 J/cm² (n=2). Treatment was performed once a day and repeated every 48h during a 15-day interval in the treated groups (2 and 3). The output power used was the same for the treated groups (30 mW). Scrotal insulation was done in all rams at 72h before the beginning of the treatment period. The rams were castrated after 35 days of scrotal insulation. Both testes were divided in 3 parts: ventral, medium, and dorsal. Analyses were performed by light microscopy to measure the lumen of the seminiferous tubules and the seminiferous tubules total area. Ten different areas of each testicular segment were analysed and, in each area, 2 seminiferous tubules were chosen randomly. For this analysis, the percentage of the lumen area of the seminiferous tubule in relation to the total area of the seminiferous tubule (lumen/lumen+tubule) was determined. In parallel, degree of degeneration was classified by blind analysis, as light, moderate, or severe, in each testicular segment. A treatment effect was observed. Group 2 (14.55±2.08%) presented a lower percentage of lumen than did group 1 (36.78±3%) and 3 (30.98±2.24%). The degeneration degree of ram testes of group 1 was classified as moderate for 1 ram and severe for the other, whereas, in group 2, it was classified as light for both rams. For group 3, it was classified as moderate for both rams. Thus, it is possible to conclude that LPT treatment is efficient, and that the cumulative dose of 28 J/cm² is more efficient than the cumulative dose of 56 J/cm² .

Clinical studies

Hasan [141] used LPT on male infertility. The testicles of 25 childless men were irradiated with a combination of HeNe and GaAs light. Of these 25, 4 were azoospermic, 9 were highly oligospermic, and 7 were moderately oligospermic. No result was achieved in the azoospermic group, while in the oligospermic groups the sperm count increased by between 200% and 500%. Libido also increased in 15 of the oligospermic patients. Treatment was administered twice a week, a total of ten times. As sperm creation takes two to three months, the mechanism at work here is not known. LPT is, however, shown to be a supplementary method for subfertile men.

Kovalev [684] treated 55 men suffering from aspermatogenic sterility with HeNe laser. The results indicate a stimulating effect on the testicular function.

Uchida [146] treated 20 patients with chronic prostatitis or prostatodynia. GaAs laser was administered through the perineum or the rectum. In some cases, the acupuncture point Tsubo was used. In all 2 patients were freed from their symptoms completely, and 14 experienced good to average improvement. The soreness in the prostate disappeared in most of those who received irradiation through the rectum.

Mazo [338] has also reported on transrectal treatment of prostatic problems.

The effect of different approaches to LPT of acute non-specific epididymitis was studied by Gomberg [681]. In a previous study by Reznikov [682], trans-scrotal HeNe irradiation had proved beneficial. Gomberg compared trans-scrotal endolymphatic and laser acupuncture for the treatment of a group of 28 patients. The endolymphatic treatment was performed via a small quartz fibre inserted into the regional lymphatic node, 0.15 J in total. The transdermal dose used was at a maximum of 2.7 J. Laserpuncture (Hegu and Zusanli) was performed using a maximum of 30 J per point. The clinical outcome as well as the polymorphonucleocyte/lymphocyte index, main population and subpopulations of lymphocytes were evaluated. Endolymphatic irradiation was found to be more efficient than trans-scrotal LPT. The former required four procedures at intervals of 24 hours, whereas trans-scrotal irradiation required one to three days longer. Laser acupuncture was not effective.

Induratio penis plastica is a rare affection of the penis, even though occurrence is reported in 6 - 9% of the male population. The dual mechanism of the effect of laser treatment can be employed in implicating overproduction of fibrin (and its resorption), as well as in exerting a direct influence on inflammatory processes.

In a study by Prochazka [895], 40 patients were followed under a period of more than five years. Classic medicamentous techniques (colchicine, vitamin E) were combined with laser treatment of the following parameters: probes 200 and 300 mW, 50 J/cm² continuous mode + 50 J/cm² with the beam modulated to a 5 Hz pulse repetition rate in one therapy bout. The *therapy was applied 20 times in succession, twice a week as an introductory series of procedures, followed by a maintenance series of three to five procedures 2 - 3 times a year. In combination with ultrasound, the total effect was very satisfactory.*

Longo [608, 672] has treated some 100 cases of induration penis plastica with GaAs or defocused CO_2 laser. Circular and/or transversal plaque formation is a contra indication for LPT. In other milder forms, LPT can reduce pain, recurvatio, signs of inflammation and ecographic findings. The increase of elasticity during the erection is the first visible result of the treatment. Around 4 J per point has been used.

Johnson [770] reports the preliminary results of a non-randomised trial using a 30 mW GaAlAs laser to treat patients with symptomatic Peyronie's disease. All patients in the study had the disease, consisting of a well-defined fibrous plaque causing pain and/or curvature of the penile shaft when erected, which interfered with satisfactory sexual intercourse. 3 J per point was administered, beginning at the base of the penis and extending to the coronal sulcus over the dorsum of the penis at 0.5 cm intervals. An additional 3 J was delivered to each 0.5 cm of palpable plaque. The ability of the therapy to reduce the size of the fibrous plaque, the severity of the penile curvature, and the severity of pain associated with penile erection and the treatment's effect on the patient's quality of life were assessed for each patient at completion of therapy and six weeks later.

Strada [983] has treated nearly 300 patients with Peyronie's disease. GaAs laser treatment in combination with ultrasound was performed once a week for five weeks. All the patients showed pain reduction at the two-month control. A total of 60% reported a reduction of recurvatio penis. A group of patients underwent phlebocavernosometry, showing a disappearance of patches in 30% of the cases. Strada has also treated more than 200 patients with chronic abacterial prostatitis. A GaAs laser probe was used in an endorectal approach (every second day, 12 sessions) and a 30 mW GaAlAs laser was used in a urethral approach (every third day, 8 sessions). More than 65% of the patients had symptom relief even after six months. Spermatic fluid was analysed before and after therapy. There was an increase in the total germinal cell count, and an improvement in motility and morphology. Prostate ultrasound showed a mean reduction of prostate volume from 29.9 cc to 21.9 cc, probably due to resolution of oedema.

Strada also reports that urethral strictures have been treated with GaAs laser, 10 sessions. Only patients with stricture diameters larger than 3 mm were treated. Five patients improved their micturation and flowmetry.

Male genital tract chronic inflammations were treated by Gasparyan [912] using combinations of transdermal, transrectal (prostate gland) and intravenous HeNe laser irradiation. The energy of a 2 mW HeNe laser was applied via a light guide into a vein. The projections of the male genital organ and the inguinal areas were irradiated with a 890 nm, 5W peak power cluster probe. For the transrectal prostate gland irradiation with a super-

pulsed GaAs laser 890 nm, 15W peak power was used. In all 36 patients were given conventional medical therapy and another 36 were given LPT in combination with medical therapy. Clinical and laboratory findings were statistically better in the LPT group and relapse rate was lower. It is suggested that LPT increases the local circulation and thus also improves the effect of antibiotics.

Further literature: [142, 606, 684, 722, 920, 1202, 1647, 1658, 2410]

4.1.60 Warts

LPT is widely used to treat common warts. The effect is not well documented and the results are inconsistent. The success rate in children is higher than in adults.

Literature: *[649, 1316]*

4.1.61 Whiplash-associated disorders

In the experience of the authors, secondary muscular involvement can be successfully treated with LPT, whereas the primary problems will possibly require prolonged therapy. Reduced pain, improved sleep and reduced consumption of analgesics can be expected in most cases. Neck pain often has secondary consequences for masticatory dysfunction [2015], and LPT appears to be a promising and non-invasive method to approach these problems.

Literature:

The study by Chow [1702] was undertaken to test the efficacy of a 300 mW, 830 nm laser in a prospective double-blind, randomised, placebo-controlled trial in patients with chronic neck pain. Ninety patients were enrolled. Laser was applied using the contact method over tender areas in the neck musculature, twice a week for 7 weeks. The primary outcome measure was change in a 10 cm Visual Analogue Scale for pain. Other measures used included a Self-Reported Improvement in pain, measured by a VAS, Short-Form 36 Quality-of-Life Questionnaire, Northwick Park Neck Pain Questionnaire, Neck Pain and Disability Scale and the McGill Pain Questionnaire. Measurements were taken at baseline, at the end of 7 weeks of treatment and at 12 weeks from baseline. Patients in the treated group experienced a mean self-reported improvement of 48.5% compared with 3.99% in the placebo group.

The aim of an article by Jensen [2100] was to summarise the existing evidence concerning interventions for non-specific neck pain. Neck-and-shoulder pain is commonly experienced by both adolescents and adults. Although the prevalence appears to vary among different nations, the situation is essentially the same, at least in the industrialised nations. Explanations for the wide variation in incidence and prevalence include various methodological issues. Back and neck disorders represent one of the most common causes for both short- and long-term sick leave and disability pen-

sion. Evidenced risk factors for the onset and maintenance of non-specific neck and back pain include both individual and work-related psychosocial factors. Based on the existing evidence different forms of exercise can be strongly recommended for at-risk populations, as well as for the acute and chronic non-specific neck pain patient. Furthermore, for symptom relief this condition can be treated with transcutaneous electric nerve stimulation, LPT, pulse electromagnetic treatment or radiofrequency denervation.

A double-blind, randomised, placebo-controlled study was carried out by Konstantinovic [2331]. Sixty subjects received a course of 15 treatments over 3 weeks with active or an inactivated laser as a placebo procedure. LPT was applied to the skin projection at the anatomical site of the spinal segment involved with the following parameters: 904 nm, f 5,000 Hz, power density 12 mW/cm^2, dose 2 J/cm^2 , treatment time 120 seconds, total dose 12 J/cm^2. The primary outcome measure was pain intensity as measured by a Visual Analogue Scale. Secondary outcome measures were neck movement, neck disability index, and quality of life. Measurements were taken before treatment and at the end of the 3-week treatment period. Statistically significant differences between groups were found for intensity of arm pain (and for neck extension.

Conforti [2337] conducted a short term prospective randomised study to test the effectiveness of a multi wave High Power Laser Therapy (HPLT) versus conventional simple segmental physical rehabilitation (PT) included in Italian tariff nomenclature performance physiotherapy. The authors identified 135 homogeneous patients with whiplash grade 1 - 2 of the Quebec Task Force classification (QTFC). Group A (84 patients) was treated with High Power Laser Therapy (HPLT), Group B (51 patients) received conventional simple segmental physical rehabilitation (PT). During the treatment period, no other electro-medical therapy, analgesics or anti-inflammatory drugs were allowed. All patients were assessed at baseline (T0) and at the end of the treatment period (T1) using a VAS, (T2) the date of return to work was registered afterwards. There was a reduction in VAS pain scores at T1. Group A (VAS = 20) Group B (VAS = 34.8). Laser treatment allowed quick recovery and return to work (T2). Group A after 48 days against 66 days of Group B.

This promising study is short of details and is unclear in the reporting of several parameters, but obviously a 12 W laser with three wavelengths within 780-1100 nm was used, Parameters not included in the abstract. Power density is reported to be 7.5 W/cm^2, five points irradiated for 40 seconds each, 20-30 J, using a cooling system to keep temperature rise below 2.5C. The authors claim that the high power increases penetration, which of course is incorrect. The laser treatment was performed with simultaneous micro-rotating electrical fields, which makes the actual LPT effect difficult to evaluate. A class 3B laser of 500 mW would require 60 seconds to deliver 30 J.

Gross [2433] found diverse evidence using LPT for neck pain in a systematic review. In the conclusion, the authors state that LPT may be beneficial for chronic neck pain/function/QoL. Larger long-term dosage trials are needed.

4.1.62 Vitiligo

Vitiligo is a type of hypopigmentation and is a result of lack of melanin production. There are two main causes for this condition. Either the epidermal melanocytes exist but are dormant, or they are failing to produce melanin granules as a result of an enzyme deficiency. Hypopigmentation is more difficult to treat than hyperpigmentation. Laser treatment of vitiligo was described already in 1988 by Ohshiro [978]. After first using an argon laser, Ohshiro tried the new GaAlAs laser, using 6 J/cm^2, four sessions. For the cicatrose type of vitiligo, the argon laser was used first since there are no melanocytes left in the scar area.

Literature:

In a study by Yu [1321], the author sought to determine the theoretical basis and clinical evidence for the effectiveness of helium-neon lasers in treating vitiligo. Cultured keratinocytes and fibroblasts were irradiated with 0.5-1.5 J per cm^2. The effects of the laser on melanocyte growth and proliferation were investigated. The results of this in vitro study revealed a significant increase in basic fibroblast growth factor release from both keratinocytes and fibroblasts, and a significant increase in nerve growth factor release from keratinocytes. Medium from laser irradiated keratinocytes stimulated (3H)thymidine uptake and proliferation of cultured melanocytes. Furthermore, melanocyte migration was enhanced either directly by HeNe laser irradiation or indirectly by the medium derived from laser treated keratinocytes. Thirty patients with segmental-type vitiligo on the head and/or neck were enrolled in this study. Helium-neon laser light was administered locally at 3.0 J/cm^2 with point stimulation once or twice weekly. The percentage of repigmented area was used for clinical evaluation of effectiveness. After an average of 16 treatment sessions, initial repigmentation was noticed. Marked repigmentation (>50%) was observed in 60% of patients with successive treatments.

In a study by Lan [1771], the researchers investigated the physiologic effects of He-Ne laser irradiation on two MB cell lines: the immature NCCmelb4 and the more differentiated NCCmelan5. The intricate interactions between MBs with their innate extracelluar matrix, fibronectin, were also addressed. The results showed that He-Ne laser irradiation enhanced NCCmelb4 mobility via enhanced phosphorylated focal adhesion kinase expression and promoted melanogenesis in NCCmelan5. In addition, He-Ne laser decreased the affinity between NCCmelb4 and fibronectin, whereas the attachment of NCCmelan5 to fibronectin increased. The alpha5ß1 integrin expression on NCCmelb4 cells was enhanced by He-Ne laser. In conclusion, *it was demonstrated that He-Ne laser induced different physiologic changes on MBs at different maturation stages and recapitulated the early events during vitiligo repigmentation process brought upon by He-Ne laser in vitro.*

Ataie [1322] treated vitiligo patches by using a 630 nm laser (20 mW, 1 J/cm^2), twice a week for a maximum of 24 treatments. Patients were followed for nine months and the effect of treatment was evaluated. Six patients were evaluated for the purposes of this analysis. Their ages ranged from 11 to 46 years. Decreases in surface area of depigmented lesions were seen ranging from 25% to 75%. Pigmented stippling within depigmented lesions occurred in all patients. In two patients, a repigmentation of previously depigmented hair was seen. Only one patient experienced arrest of progression of disease after 24 sessions of treatment.

Since segmental-type vitiligo lesions (SV) are resistant to conventional forms of therapy, its management represents a challenge for dermatologists. HeNe laser, wavelength 632.8 nm, has been employed as a therapeutic instrument in many clinical situations, including vitiligo management and repair of nerve injury. The purpose of the study by Wu [2013] was to evaluate the effectiveness and safety of HeNe lasers in treating SV, and determine the effects on the repair of sympathetic nerve dysfunction. Forty patients with stable-stage SV on the head and/or neck were enrolled in this study. He-Ne laser irradiation was administered locally at 3.0 J/cm^2 with point stimulation once or twice weekly. Cutaneous microcirculatory assessments in six SV patients were performed using a laser Doppler flowmeter. The sympathetic adrenoceptor response of cutaneous microcirculation was determined by measuring cutaneous blood flow before, during and after iontophoresis with sympathomimetic drugs (phenylephrine, clonidine and propranolol). All measurements of microcirculation obtained at SV lesions were simultaneously compared with contralateral normal skin, both before and after HeNe laser treatment. After an average of 17 treatment sessions, initial repigmentation was noticed in the majority of patients. Marked repigmentation was observed in 60% of patients with successive treatments. Cutaneous blood flow was significantly higher at SV lesions compared with contralateral skin, but this was normalised after HeNe laser treatment. In addition, the abnormal decrease in cutaneous blood flow in response to clonidine was improved by HeNe laser therapy.

4.1.63 Womens' health

Literature:

Takac [143] treated women suffering from menstrual pain with a GaAs laser. He administered 20 J over each ovary and over the uterus respectively, distributing the radiation over an area of about 3 x 15 cm^2. He treated the women every day from the 12th day of the cycle up to menstruation. Of 12 patients, 10 were entirely or partially free of pain and experienced greater *regularity in their menstrual cycles. A closer examination of the two who did not react showed microcysts on the ovaries.*

For menstrual cramps, Ohshiro [978] recommends contact irradiation over the abdominal wall. It is also reported that delivery pain has been relieved through GaAlAs irradiation over the mouth of the cervix.

Kovács [341] has successfully used a HeNe laser clinically to treat ectopium of the portio uteri. Havlik [1039] also reports this.

Kosilov [651] treated 120 young female patients with neurogenic hyperreflexic bladder dysfunctions. HeNe irradiation on the projection of the bladder combined with irradiation of biologically active points were more effective than conventional treatment.

Antipa [780] studied the effects of GaAs and HeNe laser irradiation, single or in combination, compared to placebo or conventional therapy on the recovery of 118 female patients with a diagnosis of chronic pelvic inflammatory disorders. LPT proved to be significantly more efficient than placebo or conventional therapy. The most efficient of all kinds of irradiation was the combination of GaAs and HeNe (laserpuncture and scanning).

In a study on menstrual pain by Kim [2105], 85% of the women reported pain relief from LPT. At the six-month control, the pain was back to baseline, indicating that the effect is transient. The authors also have excellent experience of treating Post Menstrual Stress. Here is an untapped therapeutic arsenal waiting for further exploration.

Fibrotic masses in the breast secondary to fat necrosis or haematoma is a complication of breast reduction mammoplasty. The treatment commonly recommended for this condition is early surgical debridement of necrotic tissue from the entire area, which causes scarring. A case report by Nussbaum [909] describes the use of LPT for fibrotic lumps following reduction mammaplasty. The patient was a 46-year-old woman who had breast reduction surgery 80 days prior to referral for physical therapy. At the time of referral, the largest mass was 8.0 cm in diameter. The patient reported pain and said she was distressed about the breast disfigurement. Laser irradiation was initiated at an energy density of 20 J/cm² and with a pulse repetition rate of 5000 pulses per second. The laser settings were adjusted during the eight-month treatment period. The final dose was 50 J/cm². The mass was 33% of its original size after three sessions over the initial 11-day period. Pain relief was immediate. The rate of resolution decreased after the initial period. The patient had some tissue thickening at the time of discharge after six months of treatment.

One of the successful treatments for cyclical mastalgia is bromocriptine evening primrose combination. A double blind study by Saied [2465] was applied on 80 patients with cyclical mastalgia. They were randomly divided into two groups (A and B). In group A, patients were treated by bromocriptine/evening primrose. To group B, LPT with specified dosimetry was applied, using a device that delivers He-Ne laser combined with 4 infra-red diode laser. Evaluation of treatment was both subjective (using VAS) and *objective (studying the degree of drop in plasma cortisol level). The drop of plasma cortisol with treatment was studied using the student -t distribution. A good response was observed in the laser group in 82.5%, compared to 63.9% in the bromocriptine/evening primrose group. There was a significant difference before and after treatment in both groups. This difference was more for the drug treated group than for the laser treated group, but in the latter, it acted on a wider sector of patients.*

Passeniouk [963] reports that LPT used in combination with chlorhexidine was more effective for vaginitis than daily 10 g metronidazole plus one initial dose of 150 mg fluconozole. LPT as well as conventional drug therapy were carried out for 10 consecutive days. The laser group consisted of 30 patients and the drug group of 20 patients.

Earlier studies show that one in three Swedish women suffer from menstrual pain. Although, analgesics may to some extent reduce the pain, the side effects of such treatments are not ignorable and thus other safe approaches must be sought. Twenty volunteer women suffering from painful menstruation participated in a pilot study by Kim [2105]. Every individual were treated 15 minutes per week for 8 weeks each time with a total of 200 joules energy using a GaAs multiprobe laser. Approximately 80% of treated individuals experienced milder pain during menstruation. The consumption of analgesics was considerably reduced during menstruation. This results show that laser therapy is efficient in reducing menstrual pain and may potentially replace analgesics.

The literature suggests that LPT can improve female infertility. Taniguchi [2354] has treated 588 infertile women with 830 nm laser over the reproductive organs and over the neck. The treatment resulted in 97 pregnancies. The mechanisms are unclear but may be found in the paper by Bartmann [2356]. The author writes: Mitochondria are organelles responsible for oxidative phosphorylation, the main energy source for all eukaryotic cells. In oocytes and embryos, it seems that mitochondria provide sufficient energy for fecundation by supporting spindle formation during meiosis II, and for implantation. Since mitochondria are inherited from mother to child, it is important that oocyte mitochondria should be intact. Older women seem to have more mitochondrial DNA mutations, which can be responsible for poor implantation and aneuploidy, two conditions that occur more often in this group. In the present report we propose a new model to explain why older women have poor implantation rates.

LPT and its effects on the mitochondria seem to be a reasonable connection.

Further literature: [142, 633, 920, 1123, 1274, 2355]

4.1.64 Wound healing

Non-healing skin wound before and after two days of HeNe LPT

Figure 4.35 Skin wound
Courtesy: René-Jean Bensadoun

One of the most thoroughly studied areas in LPT is wound healing. In fact, this was one of the first indications reported, with studies by Mester [733]and by Carney [520] as early as 1967. The first studies were done using healthy rats. This effect has been confirmed in the extensive animal studies by i.a. al-Watban [471, 475, 632]. However, the effect in a healthy individual is limited and the prime indication for LPT is for individuals or tissues in a compromised state. But it is not a good idea to wait and see whether or not a wound will heal, and then treat it with laser if it fails to heal. On the contrary, an evaluation of the actual state of the individual/tissue should be made in the first place and LPT applied if deemed favourable. We have touched upon this subject in the descriptions of various indications earlier in the book.

The suggested technique for extraoral wounds is as follows (for GaAlAs): start by administering 3-4 J/cm^2 on points along the periphery of the wound, using the contact method. Then sweep slowly over the open wound at a distance of 1 cm, with a dosage of 0.5 J/cm^2. The open wound receives a lower dosage than the skin-covered periphery, as the laser light is not reflected, scattered or absorbed by skin in the unprotected wound, and hence hits the uncovered cells directly. Treat daily for three to four days, then every other day, and evaluate the healing process. If no improvement has occurred, raise the dosage by 50%. Severe wounds with pus and exudates require higher doses. Varicose ulcers and bedsores are appropriate indications for LPT in combination with conventional therapies. In addition to improved wound healing, a considerable reduction in pain can be expected. The outcome of bedsore (pressure) wounds is less positive, except for pain scores [1424]. This may partly be due to the fact that the pressure is more or less permanent in these patients.

Before irradiating the wound area itself, it is a good idea to irradiate a rather large area proximally to the wound. This will increase microcirculation in the wound. Therapists should be aware of the fact that chronic wounds in the initial healing phase may appear to be worsening. However, this is a situation where the chronic phase is converting into an acute phase, with a healing possibility.

The above dosages apply to GaAlAs - for GaAs, about one-third of the above dosage should be given. HeNe has proved to be the best source for wound healing [471, 475], but the low outputs and high costs of HeNe lasers have been complicating factors. The advent of more high-powered and less expensive diode lasers in the 630-660 nm range will possibly solve this problem. Diodes require higher doses than HeNe, although the wavelength may be the same. This may be because of the superior length of coherence of the HeNe laser [1634]. LPT is always a supplementary method: wounds must be cleaned and dressed as usual. Infected wounds are sometimes mentioned as a caveat for LPT. It is true that the germs in the wound will be stimulated as well; however, the stimulation of the immune system and growth factors will be even greater. A reasonable caution could then be to treat the periphery of the wound only and to avoid irradiation over the open wound.

In the study by Gupta [2258], the healing effects of LPT mediated by different wavelengths (635, 730, 810, and 980 nm) delivered at constant fluence (4 J/cm^2) and fluence rate (10 mW/cm^2) were evaluated in a mouse model of partial-thickness dermal abrasion. Wavelengths of 635 and 810 nm were found to be effective in promoting the healing of dermal abrasions. However, treatment using 730- and 980 nm wavelengths showed no sign of stimulated healing. Healing was maximally augmented in mice treated with an 810 nm wavelength, as evidenced by significant wound area reduction, enhanced collagen accumulation, and complete re-epithelialisation as compared to other wavelengths and non-illuminated controls. Significant acceleration of re-epithelialisation and cellular proliferation revealed by immunofluorescence staining for cytokeratin-14 and proliferating cell nuclear antigen was evident in the 810 nm wavelength compared with other groups. LPT mediated by 635 nm and 810 nm suggests that the biological response of the wound tissue depends on the wavelength employed. The effectiveness of 810 nm wavelength agrees with previous publications and, together with the partial effectiveness of 635 nm and the ineffectiveness of 730 and 980 nm wavelengths, can be explained by the absorption spectrum of cytochrome c oxidase, the candidate mitochondrial chromophore in LPT.

For all types of treatment where infection is present, it is further beneficial to stimulate the immune system by irradiating the involved lymph nodes [915] before treatment of the wound begins. A total of 1-2 J per point is a common dosage, then administering 0.5 J per point along the lymphatic vessels leading to the wound area.

If heat is used in combination with LPT, should the laser treatment come first? Heat will increase blood flow in the tissue, and by increased absorption of light in the blood, the penetration will be reduced. On the other hand, more blood will be irradiated which can lead to positive systemic effects. Penetration of the laser can be increased by using pressure technique over skin areas. If cooling (ice) is used, blood flow in the area will be reduced and the light will have higher penetration rate after the application of cooling. For open wounds, contact technique is seldom used. However, if it is used, the area can be covered by e.g. a cling film

It has been argued that successful studies of rats cannot necessarily be extrapolated to apply to human skin. This is a point well taken, but studies on porcine models, dairy cattle models and humans all point in the same direction. It has also been argued that wound healing studies using healthy animals is not a suitable approach. The healing ability in healthy individuals can only be promoted slightly, whereas the best effect of LPT is shown in individuals with a less-than-optimal immune situation. Thus, diabetic rats have been used with greater success [922]. This, in itself, underlines the usefulness of LPT to treat the all too common circulatory complications in diabetic individuals. More about this in the chapter about diabetes.

Yet another drawback with early rat model wound healing studies is that bilateral wounds were studied, and the systemic effects in small animals are considerable. Certainly clear differences have been demonstrated in intra-individual studies, but for an accurate evaluation a non-irradiated control group is necessary.

Figure 4.36 Three sessions of LPT
Courtesy: Chrisse Bäckström

Since wound healing in rats is mainly dependent on contraction, a different irradiation technique should be used in such studies. The entire wound should be covered by the laser beam, in contrast to the recommendations for humans, as described above. In the above study by Reddy [922], two circular wounds were created on either side of the spine. The left wound of each animal was treated with HeNe 1.0 J/cm² for five days a week until the wound was closed (three weeks). Measurements of the biomechanical properties of the laser treated wounds indicated that there was an increase in maximum load (16%), stress (16%), strain (27%), energy absorption (45%) and toughness (84%) compared to control wounds of diabetic rats. Biochemical assays revealed that the amount of collagen was significantly increased in laser treated wounds. Sequential extraction of collagen from healing wounds showed that laser treated wounds had significantly greater concentrations of neutral salt soluble (15%) and insoluble collagen (16%) than control wounds, suggesting accelerated collagen production in laser treated wounds. There was an appreciable decrease in pepsin soluble collagen (19%), indicating higher resistance to proteolytic digestion.

To avoid the many interacting parameters in wound healing studies, Houghton [1098] used experimental wounds in the separated limbs of fetal mice. GaAs doses of 0.23, 1.37, 2.75 and 3.66 J/cm^2 improved wound healing, while 4.8 J/cm^2 showed no improvement as compared to control. The best outcome was noted with the two lowest doses. The 4.8 J/cm^2 group actually showed the best wound size change at day three, but at day seven all the other groups showed better results. Collagen deposition in dermis and bone was enhanced in the 0.23, 2.75 and 3.66 J/cm^2 groups, but not in the 1.37 J/cm^2 group. The above well illustrates the problem of establishing a “good-for-everything” dose.

In a 2004 Meta analysis of the available literature of LPT for wound healing by Woodruff [871], the laser treatment modality was found to be highly significant (d=+2.22). Further sub-analyses revealed that the efficacy for animals was +1.97 and for humans +0.54. Twenty-four studies met the inclusion and exclusion criteria. In another Meta analysis on tissue repair [872], the outcome was +1.81. The number of studies was thirty-four.

LPT is an appreciated tool in cosmetic circles and one reason for that is the effects seen on the fibroblasts. When wounds are treated with LPT, the fibroblasts are distributed among organised, parallel collagen bundles [906, 1904], leading to a smoother skin surface.

While there are many studies, the overall methodological quality of the LPT literature for wound healing is low, according to a review by Lucas [1184] in 2000. The quality has since then improved considerably but the documentation is still insufficient on the clinical side.

An important caveat in wound healing studies is the presence of steroids. These are known to reduce the effect of LPT, as described elsewhere in this book. A recent example is [2001], described below.

Different wavelengths and different power densities will yield different results in LPT. Without a refined knowledge about optimal parameters, LPT will be a bit random. However, the "therapeutic window" is rather wide, and even without optimal parameters LPT usually improves wound healing. The delicate selection of optimal parameters is well illustrated in the study by Nascimento [1453]. Eighteen standardised wounds were surgically created on the dorsum of rats, which were subsequently divided into two experimental groups according to wavelengths used, 670 or 685 nm. Each group was divided into three subgroups of three animals according to the intensity of the applied irradiation (2, 15, or 25 mW). Twelve animals were used as untreated controls and were not irradiated. The irradiation was carried out for seven consecutive days. The animals were sacrificed eight days after surgery. For all laser groups, light microscopy showed a substitution repair process, chiefly associated with shorter wavelength and low power density. Remarkably, all of the six laser groups had slight variations in the healing process. The results indicate that LPT improved cutaneous wound repair and that the effect is a result of an inversely proportional relationship between wavelength and intensity, with treatment being more effective when combining higher intensity with short wavelength or lower intensity with higher wavelength.

Doubts exist as to whether the LPT action on microorganisms can justify research aimed at investigating its possible effects on bacteria-infected wounds. To assess the effect of LPT on the rate of bacterial contamination in infected wounds in the skin of rats, an experimental study using 56 male Wistar rats was carried out by Silva [2273]. The animals were randomly divided into eight groups of seven each. Those in the "infected" groups were infected by Staphylococcus aureus MRSA in the dorsal region. A 658 nm laser, 5 J/cm^2 was used to treat the animals in the "treated" groups in scan for 3 consecutive days. Samples were drawn before inoculating bacteria and following laser treatment. The statistical analysis of median values showed that the groups submitted to laser treatment had low bacterial proliferation. The laser with a dose of 5J/cm^2 in both intact skin and in wounds of rats infected with Staphylococcus aureus MRSA, was shown to reduce bacterial proliferation.

Wound healing dominates the LPT literature but the majority of papers are in vitro or animal studies. In spite of being used for almost 50 years, the number of clinical studies is low and the overall quality is not high. Adding LPT in wound healing practice has a great savings potential. The annual cost of treating a chronic wound is around 4000 USD in Sweden.

Some of the observed effects of LPT in wound healing studies are:

- Upregulation of the growth factor TGF-ß, responsible for inducing collagen synthesis in fibroblasts [1149,1672]
- Increase of protein and mRNA levels of IL-1 alpha and IL-8 [584]
- Upregulation of cytokines responsible for fibroblast proliferation such as VEGF, bFGF, HGF and SCF [1673]
- Increase of platelet-derived growth factor (PDGF), transforming growth factor-ß (TGF-ß) and blood-derived fibroblast growth factor (bFGF) [1891].
- Transformation of fibroblasts into myofibroblasts [1270]
- Increase of prostaglandin E_2 production via the induction of cyclooxygenase-2 mRNA [1646]
- Reduction of PGE_2 [243,357,582, 718, 1008, 1276, 1461, 1560, 1800]
- Reduction of IL1-ß [188, 370, 1314, 1815, 1891]

Figure 4.37 Leg wound treated during four months. Patient instructed to stop using dressings. One LPT session in the clinic, ten days of home treatment, 100 mW, 808 nm.

Literature:

In vitro studies

In the work by Lilveria [1894], researchers evaluated mitochondrial respiratory chain complexes II and IV and succinate dehydrogenase activities in wounds after irradiation with laser. The animals were divided into two groups: group 1, the animals had no local nor systemic treatment and were considered as control wounds; group 2, the wounds were treated immediately after they were made and every day thereafter with a GaAs laser for 10 days. The results showed that LPT improved wound healing. Besides, the results showed that LPT significantly increased the activities of complexes II and IV, but did not affect succinate dehydrogenase activity. These findings are in accordance with other works, where cytochrome c oxidase (complex IV) seems to be activated by LPT. Moreover, researchers showed, for the first time, that complex II activity was also activated.

The aim of a study by Rigau [415] was to investigate the behaviour of the confluence monolayer fibroblast's culture when a central scratch of 0.4 - 1 mm and two irradiations are performed, by means of the study of the colony formation, haptotaxis (direction) and chemotaxis-chemokinesis (movement). An argon pumped DYE-laser, with a wavelength set at 633 nm, 2 J/cm² was used. The results indicate that all these phenomena appear sooner in the LPT cultures than in non-treated cultures.

In the study by Almeida-Lopes [906], human gingival fibroblasts were cultured in Petri dishes with different Fetal Bovine Serum concentrations, 5% or 10%. Four irradiations of 2 J/cm² were given at 12-hour intervals. Lasers with 670, 692, 780 and 786 nm were used. Cells in 5% FBS proliferated better than in all control groups, whereas the cells in the 10% FBS did not proliferate better than controls. The 670 and 692 nm visible lasers caused a higher improvement in cell proliferation than the infrared lasers. This study confirms the fact that cells in a less-than-optimal stage react bet-

ter to LPT than cells in an optimal nutritional stage. It also confirms that visible red is the best wavelength for superficial wound healing. The fibroblasts in the 10% solution did not proliferate better when irradiated. However, the irradiation caused a polarised cell pattern, forming bundles in different directions, a phenomenon also reported by Enwmeka [1161] and Tang [1162]. This may be a part of the explanation of the improved wound healing seen in laser surgery.

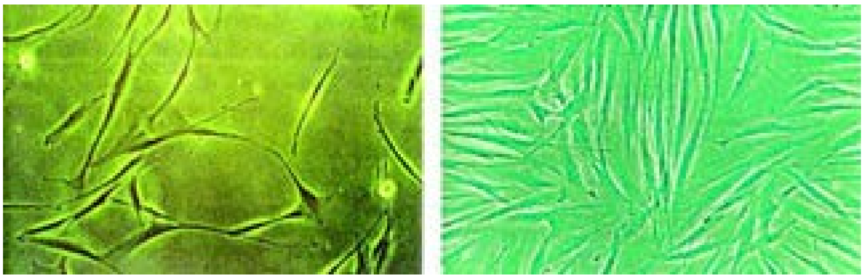


Figure 4.38 Fibroblasts in vitro before and after laser irradiation. Courtesy: Luciana Almeida Lopes

Webb [911] investigated the effect of a 660 nm, 17 mW laser diode at dosages of 2.4 J/cm² and 4 J/cm² on cell counts of two human fibroblast cell lines derived from hypertrophic scar tissue and normal dermal tissue explants. Estimation of fibroblasts utilised the methylene blue bioassay. Post-660 nm-irradiated hypertrophic scar fibroblasts had very significantly higher cell counts than controls.

In a study by Freitas [2267] seventeen volunteer subjects were stratified by age of their scars, and then randomly assigned to an experimental group (EG) - n= 9 -, and a placebo group (PG) - n= 8. Fifteen sessions were applied to both groups 3 times a week. However, in the PG the laser device was switched off. Scars' thickness, length, width, macroscopic aspect, pain threshold, pain perception and itching were measured. Results: After 5 weeks there were no statistically significant differences in any variable between both groups. Therefore, analysing independently each group, EG showed a significantly improvement in macroscopic aspect using LPT. Taking into account scars' age, LPT showed in EG a tendency to decrease older scars' thickness. The intervention with LPT appears to have a positive effect on the macroscopic scars' appearance, and on old scars' thickness, in the studied sample. However, it cannot be said for sure that LPT has influence on scar tissue.

Hubacek [1036] summarises the outcome of experimental data on HeNe wound healing: "HeNe laser emission 1.5 J/cm² applied five times during the course of one week improves wound healing through fibroblast stimulation in a directly irradiated wound, as well as in a remote wound. After irradiation with 1.8 J/cm² during a week, the production of collagen differs *depending on the phase of the healing wound. Early irradiation in the first week stimulates inflammatory type III collagen. Late irradiation in the third week inhibits the inflammatory reaction and improves deposition of type I collagen."*

van der Veen [675] studied the effect of 904 nm laser on the proliferation of mice fibroblasts. At an average power density of 3 mW/cm^2 there was a proliferation effect on the cultivated fibroblasts as compared to control. The BrdU-labeling showed an increased DNA activity. There was also a perfect match between the increased number of fibroblasts and the DNA activity.

Yu [586] studied the effect of 660 nm LPT on the production of basic fibroblast growth factor (bFGF). Fibroblasts irradiated with 2.16 J/cm^2 demonstrated increased cell proliferation and enhanced production of bFGF. At 3.24 J/cm^2, no proliferation or production of bFGF could be detected.

Yu [584] found that HeNe laser irradiation of keratinocytes in vitro stimulated interleukin-1 alpha and interleukin-8 production and their respective mRNA expression. Both these cytokines play a profound role in the enhancement of keratinocyte proliferation.

Hrnjak [676] irradiated human embryonic fibroblasts with 0.5, 1, 1.5 or 2 J/cm^2. A single HeNe laser irradiation exhibited a significant stimulation effect on the fibroblast proliferation.

In the important paper by Zhang [1416], the cDNA microarray technique was used to investigate the gene expression profiles of human fibroblasts irradiated by low-intensity red light. Proliferation assays showed that the fibroblast HS27 cells responded with a curve effect to different doses of low-intensity red light irradiation at a wavelength of 628 nm. An optimal dose of 0.88 J per cm^2 was chosen for subsequent cDNA microarray experiments. The gene expression profiles revealed that 111 genes were regulated by the red light irradiation and can be grouped into 10 functional categories. Most of these genes directly or indirectly play roles in the enhancement of cell proliferation and the suppression of apoptosis. Two signaling pathways, the p38 mitogen-activated protein kinase signaling pathway and the platelet-derived growth factor signaling pathway, were found to be involved in cell growth induced by irradiation of low-intensity red light. Several genes related to antioxidation and mitochondria energy metabolism were also found to react differentially upon irradiation. This study provides insight into the molecular mechanisms associated with the beneficial effects of red light irradiation in accelerating wound healing.

A study by Hawkins [1886] aimed to establish the behavior of wounded human skin fibroblasts (HSF) after HeNe laser irradiation using one, two, or three exposures of different doses, namely, 2.5, 5.0, or 16.0 J/cm^2 on each day for two consecutive days. Cellular responses to HeNe laser irradiation were evaluated by measuring changes in cell morphology, cell viability, cell proliferation, and damage caused by multiple irradiations. A single dose of 5.0 J/cm^2, and two or three doses of 2.5 J/cm^2, had a stimulatory or positive effect on wounded fibroblasts with an increase in cell migration and *cell proliferation while maintaining cell viability, but without causing additional stress or damage to the cells. Multiple exposures at higher doses (16 J/cm²) caused additional stress, which reduces cell migration, cell viability, ATP activity, and inhibits cell proliferation. The results show that the correct energy density or fluence (J/cm²) and number of exposures can stimulate cellular responses of wounded fibroblasts and promote cell migration and cell proliferation by stimulating mitochondrial activity and maintaining viability without causing additional stress or damage to the wounded cells. Results indicate that the cumulative effect of lower doses (2.5 or 5 J/cm²) determines the stimulatory effect, while multiple exposures at higher doses (16 J/cm²) result in an inhibitory effect with more damage.*

The experimental observations by Dixit [2296] suggest that helium-neon laser of 8 J/cm² facilitated photostimulation by tissue repair, but failed to show significant tissue hydroxyproline levels in excisional wound model.

Figure 4.39 Diabetic patient wounded by planer. Five sessions of LPT. Courtesy: Chrisse Bäckström

Animal studies

In a rabbit study by Nicolopoulos [721], a subtotal meniscectomy of the medial meniscus was performed in 24 animals. In group A, the operation was performed with a surgical blade, and in group B and C with CO_2 laser. The animals in group C received GaAlAs laser, 48 J/cm² every day until sacrificed. It was concluded that: 1) less damage was produced by the CO_2 laser than by the surgical blade; 2) the healing potential of rabbit meniscus following laser resection was accelerated by the use of LPT post-operatively.

Anneroth [41] could not observe any beneficial effects of GaAs irradiation, 0.24 J (0.5 mW for 8 minutes), on the wound healing quality in punched wounds on the back of healthy rats. The effects were observed from day 1 until day 14.

The purpose of a study by Kawalec [1423] was to evaluate therapy with a high power 980 nm laser for wound healing. Using genetically dia-

betic and non-diabetic mice, two 6 mm wounds were created on the back of each mouse by using a punch biopsy. The mice were assigned to one of four subgroups for laser treatment at different fluences and frequencies: 5 W (18 J/cm²) every 2 days, 5 W (18 J/cm²) every 4 days, 10 W (36 J/cm²) every 2 days, and 10 W (36 J/cm²) every 4 days. In addition, control mice were used and the wounds were allowed to heal naturally. Wound healing was evaluated on days 5, 12, and 19 by percentage of wounds healed and percentage of wound closure. A maximum of five mice per subgroup were killed on days 7, 14, and 21, and histology was conducted on the wound sites. For diabetic mice receiving 5 W every 2 days, the percentage of wounds healed after 19 days was 100% versus 40% in the control group. Only 20% of wounds in the 10 W diabetic subgroups achieved healing during the same period. For the subgroups whose wounds did not completely heal, all but the 10 W every 2-days subgroup had an average closure of >90%. The 100% closure for the 5 W every 2-days subgroup was significantly greater than the other subgroups. For non-diabetic mice, 100% of the wounds in the 5 W every 4-days and control subgroups were completely healed, whereas 90% of the wounds from the 5 W every 2-days and the 10 W every 4-days subgroups were completely healed. In the latter 2 subgroups, wound closure was 99.4% and 98.8%, respectively. These differences were not significant. The histology results confirmed these findings.

The objective of a study by Mendez [1498] was to histologically compare the effect of 830 nm, 35 mW and 685 nm, 35 mW lasers, alone or combined, with doses of 20 or 50 J/cm² on cutaneous wounds in the dorsum of the rat. Sixty rats were divided into seven groups: Group I - control (non-irradiated); Group II - 685 nm, 20 J/cm²; Group III - 830 nm, 20 J/cm²; Group IV - 685 nm and 830 nm, 20 J/cm²; Group V - 685 nm, 50J/cm²; Group VI - 830 nm, 50 J/cm²; and Group VII - 685 nm and 830 nm, 50 J/cm². The animals were sacrificed three, five and seven days after surgery. Light microscopic analysis using H&E and Picrosirius stains showed that, at the end of the experimental period, irradiated subjects showed an increased collagen production and organisation when compared to non-irradiated controls. Inflammation was still present in all groups at this time. Group IV (830 nm and 685 nm, 20 J/cm²) presented better results at the end of the experimental period.

Krypton laser light (670 nm) is rarely used for biostimulation. However, al-Watban [632] reports the results of wound healing experiments in rats. The optimal wound healing effect of 30% was found at 20 J/cm², zero stimulation was found at 100 J/cm², and a maximum 14% deceleration was found at 260 J/cm². The more widely used lasers showed better results than Krypton laser in the range of 9-20%.

al-Watban [471], [475] used several wavelengths (442, 514, 632, 670, 780, and 830 nm) in a study of wound healing in rats. It was found that 633 nm had the best effect, but all wavelengths had a positive effect. The doses should be decreased with increasing wavelengths. Depending on wavelength, *healing was accelerated from 15% to 29% in time, and from 32% to 50% in size reduction. Since wound healing in rodents is mainly through contraction, it is necessary to irradiate the entire wound with the beam, unlike in humans, where irradiation of the periphery is more important.*

In a study by Bisht [897], linear skin wounds were produced on either side of the dorsal midline in rats and immediately sutured. Wounds on the left side were irradiated daily with a helium neon laser at 4 J/cm^2 for five minutes, while those on the right side were not exposed and served as controls. The mean time required for complete closure in the control group was seven days, while irradiated test wounds took only five days to heal. The mean breaking strength, as measured by the ability of the wound to resist rupture against force, was found to be significantly increased in the test group. Early epithelisation, increased fibroblastic reaction, leukocytic infiltration and neovascularisation were seen in the laser-irradiated wounds.

In an experiment on 218 white rats, Efendiev [833] established an effect on the site of a future incision with the infrared laser irradiation in continuous mode. Output power ranging from 1 to 150 mW (dosage between 0.06 and 9.3 J/cm^2) induced a pronounced stimulation of the processes of collagen formation and a significant increase in the strength of scars. When the power density was increased, the reparative processes in the wounds were slowed and disturbed.

Figure 4.40 Burn wound after first and eighth session.
Courtesy: Chrisse Bäckström

The effect of low dose He-Ne laser on the healing of intestinal anastomosis in the albino rat was studied by Yew [1596]. A small piece of jejunum was removed from each rat and the ends sutured back with a simple inter-

rupted pattern. In the experimental animal, the anastomosis was irradiated through an optic fibre with a HeNe laser (1 mW) for 15 minutes, whereas in the control animal, the anastomosis was not irradiated. The differences between the two groups were compared by histology, transmission electron microscopy, scanning electron microscopy and autoradiography three and seven days after operation. The laser treated experimental animals demonstrated thicker collagen fibres and an increased quantity of collagen at the junction of the anastomosis compared to control animals. An increased uptake of labelled proline was also evident in the laser treated animals. These observations all point to a possible enhancement of collagen synthesis triggered by laser irradiation.

In the study by Pugliese [1535] on extra-cellular matrix elements, cutaneous wounds were performed on the back of 72 rats and a GaAlAs laser was punctually applied with different energy densities. The animals were killed after 24, 48, 72 hours and 5, 7 and 14 days. Tissues were stained with hematoxilin-eosin, sirius red, fast green and orcein and then analysed. It was observed that the treated group exhibited larger reduction of oedema and inflammatory infiltrate. The treated animals presented a larger expression of collagen and elastic fibres, although without statistical significance. Treatment with a dosage of 4 J/cm^2 exhibited more expressive results than that with 8 J/cm^2. In this study, the authors concluded that LPT contributed to a larger expression of collagen and elastic fibres during the early phases of the wound healing process.

Although LPT of wound healing is best used for non-healing wounds, the study by Medrado [1270] suggests that the quality of the wound healing process in perfectly healthy tissue is still influenced by LPT. Cutaneous wounds were performed on the back of 72 rats. Altogether 24 rats received one single irradiation of 4 J/cm^2, another 24 received 8 J/cm^2 and 24 served as control. The wavelength was 670 nm, 9 mW, and continuous mode. The lesions were analysed after 24, 48, 72 hours and 5, 7 and 14 days. After 14 days, all wounds had healed in a similar morphological fashion. However, histology and immuno-histochemistry in the three groups were different. Both laser groups revealed improved healing parameters compared to the control group, and all parameters were best in the 4 J/cm^2 group. During the first days, signs of acute inflammation were less intense and subsided earlier in the laser treated animals. The degree of oedema, vascular congestion and the exudation of neutrophilic polymorphonuclear leukocytes were particularly affected. After 72 hours, the laser groups showed prominent granulation tissue. The vascular proliferation was most apparent when immunohistochemically sections marked for smooth muscle actin were examined. Fibroblast proliferation and collagen deposition accompanied vascular proliferation. Collagen fibres appeared more regularly organised (in densely packed parallel bands) in the laser groups. This study seems to verify the common opinion that wounds in healthy tissue will heal in normal time, with or without laser. However, the symptoms of oedema and pain will be reduced.

Apart from the reduction of post-accident symptoms, the scar tissue will improve, which may have implications in aesthetic surgery. It is also worth observing that one single irradiation immediately after accident/surgery has a positive but not optimal effect.

In a study by Silveira [1725], the researchers evaluated mitochondrial respiratory chain complexes II and IV and succinate dehydrogenase activities in wounds after irradiation with LPT. The animals were divided into two groups: group 1, the animals had neither local nor systemic treatment and were considered as control wounds; group 2, the wounds were treated immediately after they were made and every day thereafter with a GaAs for 10 days. The results showed that LPT improved wound healing. Besides, the results showed that LPT significantly increased the activities of complexes II and IV, but did not affect the succinate dehydrogenase activity.

Figure 4.41 Diabetic wound, 8 sessions of LPT
Courtesy: Chrisse Bäckström

The aim of the study by Lima [2349] was to quantitatively evaluate blood corticosterone levels and tissue cytokine expression in cutaneous wounds of rats treated with LPT (9 mW, 670 nm, 0.031 W/cm^2, beam area 0.28 cm^2) and normal controls. A total of 36 male Wistar rats were used and randomly divided into two groups of 18 rats each. A standardised circular 6 mm-diameter wound was made in the dorsal skin region of each rat, and they were euthanised at 1, 6 and 12 h after cutaneous surgery. The blood was collected, and portions of cutaneous tissue and subcutaneous muscle were removed and cryopreserved. Corticosterone levels in the blood were measured by a radioimmunoassay technique; histological sections were submitted to the ELISA technique for analysis of tissue cytokine expression levels. At 6 h after surgery, a significant increase in corticosterone and a significant reduction in the levels of IL-1beta and IL-6 in tissues of irradiated wounds were observed when compared to controls. The levels of TNF-alpha and IL-

10 expression were not significantly different between the groups at different time intervals. Thus, this study strongly suggests a systemic and local biomodulation of LPT as indicated by the blood levels of corticosterone and the tissue expression of IL-1beta and IL-6, respectively.

Only heat?

The negligible effect of the presence of heat in LPT has been well demonstrated by Lanzafame [1447]. Pressure ulcers were created in mice by placing the dorsal skin between two round ceramic magnetic plates for three 12-h cycles. Animals were divided into three groups (n=9) for daily light therapy, 830 nm, 5.0 J/cm² on days 3-13 post ulceration in both groups A and B. A special heat-exchange device was applied in Group B to maintain a constant temperature at the skin surface (30 degrees C). Group C served as control, with irradiation at 5.0 J/cm² using an incandescent light source. Temperature of the skin surface, and temperature alterations during treatment were monitored. The wound area was measured and the rate and time to complete healing were noted. The maximum temperature change during therapy was 2.0 +/- 0.64 degrees C in Group A, 0.2 +/- 0.2 degrees C in Group B and 3.54 degrees C +/- 0.72 in Group C. Complete wound closure occurred on 18 +/- 4 days in Groups A and B and 25 +/- 6 days in Group C. The percentage of the wound closure on day 14 was 75. 4 +/- 7.2% and 77.7 +/- 5.6% for Groups A and B, respectively (NS differences). However, animals in Group C demonstrated a wound closure of 36.3 +/- 4.8%. These results demonstrate that the salutary effects of LPT on wound healing are temperature-independent in this model.

Mucosa and internal organs

The effects of low dose laser were studied by in vivo and in vitro systems by Mok [1598]. The experimental tissues that were used included bladders, tracheas and tongues as experimental tissues. Buddings (round surface projections) from the transitional epithelium of the bladder were frequently observed three days after laser treatment in both the in vivo and in vitro systems. The trachea and tongue were less affected. In both the in vivo and in vitro systems some epithelial cells of the trachea showed decreased microvilli and cilia three days after treatment, whereas the epithelial cells of the tongue revealed no response to laser treatment in either system. Low dose, however, appeared to promote the rate of healing of experimental tongue ulcer: healing occured about one day earlier in the laser treated animals compared to the non-treated animals, and vessel infiltration and epithelialisation were also detected earlier in the treated tissue.

Many Russian studies have reported a positive effect on gastric conditions, using an endoscopic technique. The effect has been confirmed in an experimental rat study by Shao [1754]. Sixty-three male adult rats were randomly divided into five groups, including a normal control group, a model control group and three groups treated with different dosages of HeNe laser.

The chronic atrophic gastritis (CAG) model in rats was made by pouring medicine, which was a kind of mixed liquor including 2% sodium salicylate and 30% alcohol, down the throat for eight weeks to stimulate rat gastric mucosa, combined with irregular fasting and compulsive sporting as pathogenic factors; 3.36, 4.80, and 6.24 J/cm² doses of HeNe laser were used, respectively, for three different treatment groups, once a day for 20 d. The pH value of diluted gastric acid was determined by acidimeter, the histopathological changes such as the inflammatory degrees in gastric mucosa, the morphology and structure of parietal cells were observed, and the thickness of mucosa was measured by micrometer under an optical microscope. In the model control group, the secretion of gastric acid was small, and pathologic morphological changes in gastric mucosa such as thinner mucous, atrophic glands, notable inflammatory infiltration were found. After a 3.36 J/cm² dose of HeNe laser treatment for 20 d, the secretion of gastric acid was increased, the thickness of gastric mucosa was significantly thicker than that in the model control group, and the gastric mucosal inflammation cells were decreased. Morphology, structure and volume of the parietal cells all recuperated or were close to normal. A 3.36 J/cm² dose of HeNe laser has a significant effect on CAG in rats.

Figure 4.42 Surgical wound where suturing has failed and remains open after two months of traditional therapy. Photos before LPT, and before session two and end at session eight.
Courtesy: Chrisse Bäckström

Gomez-Villamandos [425] induced duplicate pharyngeal mucosal ulcers in 12 horses. Using a fibroendoscope, one of the two injured sides was treated daily with a HeNe laser at 8 J/cm². On day 7, histological samples were taken from two horses. Irradiated lesions cicatrised after 10.5 days and *non-irradiated lesions after 18. A histological study showed coagulation, necrosis and oedema at the control site. However, in the samples from the irradiated lesions, no inflammatory oedema, numerous active fibroblasts, connective tissue or intensive epithelial regeneration were observed.*

Morrone [921] reports that 780 nm LPT showed better qualitative and quantitative healing in traumatised muscles as compared with controls in a rabbit experiment.

The regeneration of the liver after partial hepatectomy, followed by LPT, is reported by Castro e Silva [598]. Seventy percent of the liver in rats was removed by scalpel. Before suturing, a dye laser of 590 nm, 50 mW/cm^2, was used for five minutes in the experimental group. The animals in both the experimental group and the control groups were sacrificed at 24, 48 and 72 hours after the procedure. At 24 hours, there was a dramatic increase in ATP production per mg of mitochondrial protein in the laser group. At 48 and 72 hours there was no difference. The quantification of the liver regeneration was estimated by counting the nuclei stained in the PCNA immunohistochemical assay. The increase in the labeling index for the laser treated group was remarkable after 24 hours, but the difference was small at 48 and 72 hours. This study illustrates the regenerative effect of LPT and also the need for repeated irradiation to keep the process going.

The long term effects of LPT can involve mechanisms connected with activation of migration of stem cells towards damaged areas. Migration of stem cells was tested by Gasparyan [1627] under influence of laser light alone, as well as in a case of a combined influence of light and stromal cell-derived factor-1 alpha (SDF-1 alpha). This cytokine plays an important role in stem cell homing. Cells in group 1 were the control group, cells in group 2 received red laser light irradiation, cells in group 3 had IR laser light irradiation, cells in group 4 were treated with SDF-1 alpha, cells in group 5 were irradiated with red laser light in addition to SDF-1 alpha, and cells in group 6 by IR laser light and SDF-1 alpha. The count of migrated cells was 1496,5±409 (100%) in case of control. Red and IR laser light increased migration activity of stem cells up to 1892±283 (126%) and 2255,5±510 (151%) accordingly. Influence of SDF-1 alpha was more significant, than effects of light irradiation alone 3365,5±489 (225%). Combined effects of light irradiation and SDF-1 were significantly stronger: 5813±1199 (388%) for SDF-1 alpha and red laser light, and 6391,5±540 (427%) for SDF-1 alpha and IR laser light.

Souza [1718] divided 60 amputated worms into three study groups: a control group and two other groups submitted to daily one and three minutes long laser treatment sessions at approximately 910 W/m^2 power density. A 685 nm diode laser with 35 mW optical power was used. Samples were sent for histological analysis on the 4th, 7th and 15th day after amputation. A remarkable increase in stem cell counts for the 4th day of regeneration was *observed when the regenerating worms were stimulated by the laser irradiation.*

Figure 4.43 Scald injury treated with LPT. Note lack of post scarring at 4 months. Courtesy: Chrisse Bäckström

Burns

The effects of LPT on burns are described in [1029, 1048, 1049, 1050]. In a study by Schlager [1067], the effect of 635 and 690 nm on experimental burn wounds in rats was studied. There was no effect using the parameters of the study. This study has been criticised by al-Watban [1068] for lack of information about the procedures and parameters.

The paper by Bayat [1639] presents the results of a study on the effects of two different doses of LPT on healing of deep second-degree burns. Sixty rats were randomly allocated to one of four groups. A deep second-degree burn was inflicted in each rat. In the control group burns remained untreated; in two laser treated groups the burns were irradiated daily with a helium-neon laser with energy densities of 1.2 and 2.4 J/cm², respectively. In the fourth group the burns were treated topically with 0.2% nitrofurazone cream every day. The response to treatments was assessed histologically on days 7, 16 and 30 after burning, and microbiologically on day 15. The number of macrophages on day 16, and the depth of new epidermis on day 30, was significantly less in the laser treated groups in comparison with control and nitrofurazone treated groups (P=0.000). Staphylococcus epidermidis was found in 70% of rat wounds in the laser treated groups in comparison with 100% of rats in the control group. S. aureus was found in 40% of rat wounds in the nitrofurazone treated group, but was not found in either the wounds of laser treated groups or in control groups. It is concluded that LPT on deep second-degree burns caused a significant decrease in the number of macrophages and depth of new epidermis. In addition, it decreased the incidence of S. epidermidis and S. aureus.

A study by Vasheghani [2029] sought to investigate whether LPT with a HeNe laser would affect mast cell number and degranulation in second-degree burns in rats. Sixty-five rats were randomly allocated to one of five groups. A deep second-degree burn was inflicted on all rats except those in the control group. In the sham-exposed group burns remained untreated. In *the two laser-treated groups, the burns were irradiated every day by LPT, with energy densities of 1.2 and 2.4 J/cm^2. In the fifth group the burns were treated topically with 0.2% nitrofurazone cream every day. The unburned skin of the rats in the control group was used for baseline study. The effects on mast cell number and degranulation were assessed by counting the number of intact and degranulated mast cells in sections fixed in formalin and stained with toluidine blue. On the 7th and 16th days post-burn, the type 1 mast cell count in the 2.4-J/cm^2 laser-treated group was significantly higher than that of the control group. On the 30th day, the total number of mast cells in the laser-treated groups was lower than those in the control and sham-exposed groups. In conclusion, LPT of deep second-degree cutaneous burns in rats significantly increased the number of intact mast cells during the inflammatory and proliferative phases of healing, and decreased the total number of mast cells during the remodelling phase.*

Figure 4.44 Six months old burn wound, before first session and after two sessions of LPT. Courtesy: Chrisse Bäckström

The aim of an investigation by Meirelles [1880] was to compare by light microscopy the effects of laser at wavelengths of 660 and 780 nm on third-degree burns in Wistar rats. Fifty-five animals were used in this study. A third-degree burn measuring 1.5 × 1.5 cm was created on the dorsum of each animal. The animals were divided into three subgroups according to the type of laser they received (wavelength of 660 or 780 nm, 35 mW, area diameter 2 mm, and 20 J/cm^2). In the animals receiving treatment, it was begun immediately post-burn at four points around the burn (5 J/cm^2) and repeated at 24-h intervals for 21 d. The animals were humanely killed after 3, 5, 7, 14, and 21 d by an intraperitoneal overdose of a general anesthetic. The specimens were routinely cut and stained, and then analysed by light microscopy. The results showed more deposition of collagen fibres, larger amounts of granulation tissue, less oedema, a more vigorous inflammatory reaction, and increased revascularisation on all laser-treated animals. These features were more evident at early stages when the 660 nm laser was used, and were more evident throughout the experimental period for the animals receiving 780 nm LPT.

Mast cells have been shown to participate in the wound healing process. Bayat [1735] investigated the effects of LPT on mast cell numbers in the inflammation, proliferation, and remodelling phases of the wound healing process of experimental burns. Sixty rats subjected to third-degree burns were divided into four groups: two laser-treated, one control, and one nitrofurazone-treated group. In the two laser-treated groups, burned areas received LPT with a helium-neon laser at energy densities of 38.2 J/cm^2 and 76.4 J/cm^2, respectively. The effects on mast cell number and degranulation were assessed 7, 16, and 30 days postburn (inflammation, proliferation, and remodelling phases of wound healing, respectively). Intact and degranulated mast cells were counted. Five rats with no burns were used for baseline studies. On day 7 in the first laser group, the total number of mast cells was significantly higher than in the other groups. On day 16 in the nitrofurazone-treated group, the total number of mast cells was significantly higher than in the control, first laser, and normal groups. LPT on the experimental third-degree burns significantly increased the total number of mast cells during the inflammation phase of wound healing; also, topical application of 0.2% nitrofurazone ointment on the same burns significantly increased the total number of mast cells during the proliferation phase of burn healing.

A study by Fiorio [2240] investigated the effects of lasers on the tissue repair process of third-degree burns. Burns were produced on the backs of male Wistar rats. The animals were divided into four groups (n=12): control, injury, LPT 3 J/cm^2 , and LPT 4 J/cm^2. Each group was further divided into two subgroups; the rats in one subgroup were killed on day 8 and those in the other, on day 16 after injury. The animals in LPT 3 J/cm^2 and LPT 4 J/cm^2 were irradiated 1 h after injury, and irradiation was repeated every 48 h. Laser (660 nm, 35 mW) treatment at fluences of 3 and 4 J/cm^2 were used. After killing the rats, tissue fragments from the burnt area were removed for histological analysis. The LPT-treated groups showed a significant decrease in the number of inflammatory cells and increased collagen deposition compared to the injury group. Laser irradiation (both 3 and 4 J/cm^2) resulted in reduction in the inflammatory process and improved collagen deposition, thereby ameliorating the healing of third-degree burns.

A study by al-Watban [2114] was designed to assess and compare the efficacy of accelerating burn healing in diabetic rats using low-power visible and invisible lasers. Male Sprague-Dawley rats were used in the study. Streptozotocin was given for diabetes induction. A burn wound was created on the shaved back of the animals using a metal rod heated to 600 degrees C. The study was performed using 532-, 633-, 670-, 810-, and 980-nm diode lasers. Incident doses of 5, 10, 20, and 30 J/cm^2 and a treatment schedule of three times per week were used in the experiments. The percentage of burn healing on diabetic rats after LPT was 78.37% for the visible lasers and 50.68% for the invisible lasers. There was a significant difference between visible lasers and invisible lasers in the percentage of burn healing on diabetic rats after laser therapy.

A number of studies by al-Watban [2113] used 532, 633, 810, 980 and 10.600-nm lasers (visible to far infrared) and polychromatic LED clusters (510-872 nm, visible to infrared) as photon sources. Sprague-Dawley rats (n=893) were used. The improvements seen show that phototherapy with the 633 nm laser is quite promising for alleviating diabetic wound and burn healing, and exhibited the best results with 38.5% and 53.4% improvements, respectively. In this induced-diabetes model, wound and burn healing were improved by 40.3% and 45%, respectively, in 633 nm laser dosimetry experiments, and diabetic wound and burn healing was accelerated by phototherapy. This indicates that the healing rate was normalised in the phototherapy-treated diabetic rats. In view of these interesting findings, 633 nm laser therapy given three times per week at 4.71 J/cm^2 per dose for diabetic burns, and three times per week at 2.35 J/cm^2 per dose for diabetic wound healing are recommended as actual doses for human clinical trials, especially after major surgery in those with impaired healing, such as diabetics and the elderly.

In a study by Chagas-Oliveira [1903], this group of researchers compared the above findings with polarised light. The aim was to compare, by light microscopy, the effects of the use of laser photobiomodulation (LPBM) and polarised light (PL) on second-degree burns on rodents. Forty five rats were used in this study. A second-degree burn was created on the dorsum of each animal, and the animals were divided into four groups: PL (400-2000 nm, 40 mW, 2.4 J/cm^2/min); LPBM-1 (780 nm, 35/40 mW, area diameter 2 mm, 4 x 5 J/cm^2); LPBM-2 (660 nm, 35/40 mW, area diameter 2 mm, 4 x 5 J/cm^2); while untreated animals acted as controls. The treatment was started immediately post-burn at four points around the burned area (laser: 5 J/cm^2 per site). The illumination with PL was performed according to the manufacturer's instructions. Treatments were repeated at 24-h intervals for seven days. The animals were sacrificed on days three, five and seven post-burn. The specimens were routinely cut and stained and analysed by light microscopy using hematoxylin and eosin and Sirius red. The analysis of the results demonstrated that the damaged tissue was able to efficiently absorb and process the light at all tested wavelengths. LPBM at 660 nm showed better results at early stages of wound healing. However, the use of 780 nm laser light had beneficial effects throughout the experimental period, with the animals growing newly-formed tissue similar to normal dermis.

The aim of the study by Grbavac [1750] was to assess the effects of LPT and its possible dose dependency on the healing of CO_2 laser surgical wounds. Circular surgical wounds were created on the dorsum of rats, which were separated into three groups (A, B, and C). Group A acted as control and had no additional treatment. Groups B and C were irradiated with 685 nm laser light, either with 20 J/cm^2 (Group B) or 40 J/cm^2 (Group C). Laser-irradiated groups showed a healing process characterised by a more prominent fibroblastic proliferation, with young fibroblasts actively producing col-

lagen; no myofibroblasts were found. No statistically significant differences were observed when the different doses were compared.

Steroids are known to delay wound healing. In a study by Pessoa [1462], 48 rats were used, and after execution of a wound on the dorsal region of each animal, they were divided into four groups (n=12), receiving the following treatments: G1 (control), wounds and animals received no treatment; G2, wounds were treated with laser; G3, animals received an intraperitoneal injection of steroids, dosage (2 mg/kg of body weight); G4, animals received steroids and wounds were treated with laser. The laser emission device used was a 904 nm unit, in a contact mode, with 2.75 mW gated with 2.900 Hz during 120 sec. After a period of 3, 7, and 14 days, the animals were sacrificed. The results have shown that the wounds treated with steroid had a delay in healing, while laser accelerated the wound healing process. Also, wounds treated with laser in the animals receiving steroids presented a differentiated healing process with a larger collagen deposition and also a decrease in both the inflammatory infiltrated and the delay in the wound healing process. Laser accelerated healing, delayed by the steroids, acting as a biostimulative coadjutant agent, balancing the undesirable effects of cortisone on the tissue healing process.

The combination of steroids with LPT should therefore be avoided, if possible. This is confirmed in a study by Lopes-Martins [1456]. In this study, the classical experimental mice-model of carrageenan-induced pleurisy was used to investigate if the anti-inflammatory effect of low power LPT could be blocked by the steroid agent mifepristone. For the intervention group, mifepristone was injected into the pleural cavity an hour prior to the carrageenan injection. Pleurisy was then induced by an intrathoracic injection of carrageenan (0.5mg/cavity), or LPS from E. coli (250 ng/cavity) in mice. Laser irradiation (650 nm) was then carried out three times with hourly intervals on the skin of the injection site for both groups. Laser was administered with a previously established optimal accumulated dose of 7.5 J/cm^2. While laser after four hours effectively reduced inflammation almost to pre-injection levels of neutrophil cell counts, the anti-inflammatory effect was blocked after pre-injection of mifepristone.

In a study by Gál [2001], four round, full-thickness skin wounds were made on the backs of 48 rats that were divided into two groups (non-steroid laser-treated and steroid laser-treated). Three wounds were stimulated daily with a diode laser (daily dose 5 J/cm^2), each with a different power density (1 mW/cm^2, 5 mW/cm^2 and 15 mW/cm^2), whereas the fourth wound served as a control. Eight animals from each group were killed and samples were removed for histological evaluation 2 days, 6 days, and 14 days after surgery. In the non-steroid laser-treated rats, significant acceleration of epithelisation and collagen synthesis 2 days and 6 days after surgery were observed in laser-stimulated wounds. In steroid laser-treated rats, 2 days and 14 days after surgery, a decreased leucocyte/macrophage ratio and a reduction in the area of granulation tissue were recorded, respectively. LPT *improved wound healing in the non-steroid laser-treated rats, but it was not effective after corticosteroid treatment.*

Yang Li [1135] has observed that animals in wound healing studies frequently have reacted with a negative response if anaesthetics such as ketamine and ether have been used. It is speculated that there is some reagent competing against laser for the same receptor in the fibroblast.

Under general anesthesia, though, Vasilenko [2213] performed one full-thickness skin incision on the back of each rat (n=40) and immediately closed using an intradermal running suture. Rats were separated into five groups depending on treatment parameters: (1) sham irradiated control group (SIC); (2) 635 nm laser-treated group at 4 mW/cm^2 (L-635/4); (3) 635 nm laser-treated group at 15 mW/cm^2 (L-635/15); (4) 670 nm laser-treated group at 4 mW/cm(2) (L-670/4); and (5) 670 nm laser-treated group at 15 mW/cm^2 (L-670/15). The total daily dose was 5 J/cm^2 . Seven days after surgery each wound was removed for wound TS measurement. The lowest wound TS results were measured in the SIC rats. Higher wound TS results were measured in group L-670/15 and group L-635/4 rats, while significantly higher results were found in group L-670/4 and group L-635/15. The differences were significant between certain groups. Both red lasers significantly increased wound TS at selected parameters. Whereas the 635 nm laser significantly improved wound healing by using the higher power density, the 670 nm laser improved healing using a lower power density.

A promising concept of combining LPT and PDT (Photo Dynamic Therapy) is reported by Silva [1529]. That study analyses the effect of InGaAlP (685 nm) radiation, either alone or combined with a phthalocyanine-derived photosensitiser (PS) in a gel base delivery (GB) system, on the healing process of cutaneous wounds in rats. The rats were divided into six groups: control (untreated) (CG), gel base (GB), photosensitiser (PS), laser (LG), laser+photosensitiser (LPS), and laser+photosensitiser in a GB (LPSG). standardised circular wounds were made on the dorsum of each rat with a skin punch biopsy instrument. After wounding, treatment was performed once daily and the animals were killed on day eight. Tissue specimens containing the whole wound area were removed and processed for histological analysis using conventional techniques. Serial cross-sections were analysed to evaluate the organisation of the dermis and epidermis as well as collagen deposition. The animals of groups LG, PS, LPS, and LPSG presented a higher collagen content and an enhanced re-epithelialisation as compared to CG (control) and GB rats. Connective tissue remodelling was more evident in groups LPS and LPSG. The results clearly indicated a synergetic effect of light+photosensitiser+delivery drug on tissue healing. PDT did not cause any healing inhibition or tissue damage during the healing process.

Clinical studies

Guo [619] reports on the outcome of HeNe laser treatment in 53 cases of pediatric surgery. The results in children were better than in adults.

In a double-blind study, Palmgren [351] investigated the effect of LPT on infected abdominal wounds after surgery. 820 nm, 15 mW was used to treat nine patients, while nine patients were given sham irradiation. The dose was 1.6 J/cm^2. Healing time to half the wound size was significantly shorter in the laser group (6.8 days versus 14 days in the placebo group). The wound healing per day was 2.45 cm^2 in the laser group and 1.67 cm^2 in the placebo group.

In a study by Schaffer [907], three women with painful mastitis from irradiation after breast cancer with ionising radiation, and a male with a radiation ulcer, were treated with 780 nm, 5 J/cm^2. The healing of the ulcers was controlled using MRI measurement before and after treatment. In all patients, a complete clinical remission was noted following LPT. The results were confirmed by a decrease in inflammatory changes as depicted in MRI imaging.

The same indication is reported by Schindl [967]. Three patients with radiation ulcers following breast cancer therapy were treated with HeNe laser, 30 J/cm^2, three times weekly. At the 36-month control no patient showed any recurrence of the radiation ulcers or any neoplasm.

Almeida-Lopes [969] divided 150 patients who had undergone maxillofacial surgical CO_2 laser treatment into three groups: one control without LPT, one with 688 nm LPT, and one with 830 nm LPT. The LPT groups were irradiated immediately after surgery, and on days 7 and 14 with a fluence of 2 J/cm^2. The results showed that the LPT groups healed quicker than the non-irradiated group. There was no statistical difference between the 688 and the 803 nm group.

In the study by Gaida [1429], 19 patients with burn scars were treated with a 400 mW 670 nm laser twice a week over eight weeks. In each patient a control area was defined, which was not irradiated. Parameters assessed were the Vancouver Scar Scale (VSS) for macroscopic evaluation and the Visual Analogue Scale (VAS) for pruritus and pain. Photographical and clinical assessments were recorded in all the patients. A total of 17 out of 19 scars exhibited an improvement after treatment. The average rating on the VSS decreased from 7.10±2.13 to 4.68±2.05 points in the treated areas, whereas the VSS in the control areas decreased from 6.10±2.86 to 5.88±2.72. A correlation between scar duration and improvement through laser could be found. No negative effects were reported.

Soriano [1473] prospectively protocolised the local treatment of vasculitis ulcers for 10 years, using a GaAs laser, 904 nm, peak power 20 W, average power 40 mW, divergency angle 6°, cooled by a Peltier system. Punctual technique was used with a point spread of 2 cm and a punctual dose of 3 J/cm^2, irradiating the outer border, internal border and ulcer bed. Irradiation frequency being three times a week during alternating days. The ulcer was covered by a vaseline coated bandage for protection. The patients *had ambulatory freedom and if any infection was detected, they were treated with oral Ciprofloxacine. During the period of study, 46 patients were treated: 22 affected with systemic lupus, 14 rheumatoid arthritis, 3 scleroderma, 2 antiphospholipid antibody syndrome, 2 cryoblobulinemia, 1 mixed connective tissue disease, 1 lung neoplasia, 1 multiple myeloma. The majority showed multiple ulcers in both legs with intense pain and an average time of evolution of 38.86 weeks. All in all 6 (13.04%) patients suffered from local infections during the treatment, 28 (60.86%) patients healed completely in an average time of 13.78 weeks, 6 patients healed partially (13.04%), and 12 (26.09%) did not heal. The pain was relieved completely in 33 patients (71.74%)*

In the study by Kopera [1594], a 685 nm laser of 200 mW was used in a group of 44 patients with chronic venous ulcers. The outcome of the study is negative. ***Let us look at some possible reasons for the negative outcome. First of all, the only information given about dose and treatment technique is that the dose was 4 J/cm² and it is stated that the laser equipment calculated this dose acc. to the size of the wound. The accuracy of this cannot be estimated due to the lack of information about applied energy per point, total energy, continuous or pulsed, spot size and power density. As for treatment technique, we do not know if the wound area was treated or the periphery of the wound (where healing is initiated) or both and, if so, at what fluences. In the placebo group, an incoherent polychromatic commercial LED light source with a red glass window was used. No information is given about wavelength or power of the LED:s. It is known that LED:s can be used for superficial tissues such as wounds [1503, 1513, 1541, 1593, 1594], so the use of an LED array cannot be dismissed as a "placebo" light, unless very low powered. In fact, the study quotes Gupta [720] as a laser study on wound healing, but it is in fact a LED study. The possibility of getting a clinical effect from the LED unit used as placebo is further underlined by the fact that this group had a better mean outcome than the control (traditional therapy) and laser group. The treatment period consisted of 28 days. It is well-known that venous ulcers are difficult to treat and require an extended therapy time.***

Marino [951] treated 34 geriatric patients suffering from bed sores with HeNe scanning, 7.3 mW, 0.024 – 0.054 J/cm². Photographic and planimetric evaluations were performed every 15 days. Daily sessions were performed until at least 80% of the initial area was reduced. The number of sessions needed was related to the general clinical condition of the patient, and higher doses were more successful. ***Bed sores are normally difficult to heal, even with lasers, since the impetus of the pressure is not changed.***

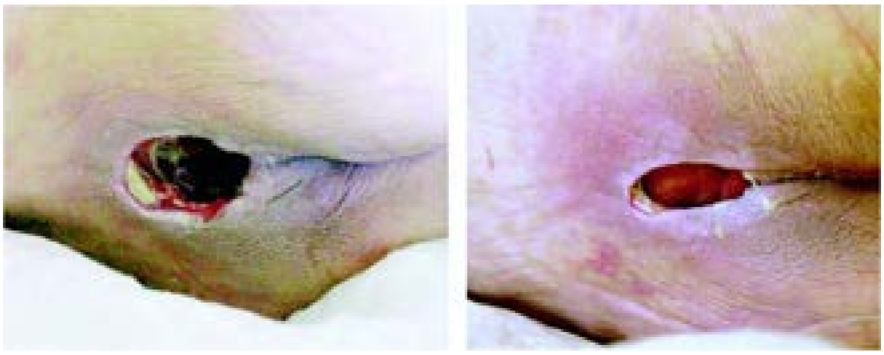


Figure 4.45 Improvement of bed sore after LPT. Courtesy: Chrisse Bäckström

A cumbersome task in wound healing therapy is the changing of dressings. If a dressing could be transilluminated by laser light without losing too much of the light energy, the therapy would be much facilitated. Lilge [1066] has addressed this problem.

Guirro [1474] measured the transmission through different dressings using wavelengths of 670, 830 and 904 nanometers. The results showed that the PVC Film was the material that presented the least attenuation of transmissivity at any of the wavelengths analysed, being 90%, 88% and 97% for the wavelengths of 670, 830 and 904 nm, respectively. Following the sequence of the same wavelengths, there was the adhesive Band-Aid® (60%, 64% and 81%), Micropore (36%, 33% and 62%), Adhesive tape (9%, 8% and 28%), Sabiá® porous plaster (4%, 5% and 20%) and lastly, the Band-Aid® cushion (2%, 2% and 6%). The results showed that the transmission of low power laser depends on the irradiated material as well as on the wavelength.

The aim of a study by Hemvani [1641] was to examine the effect of HeNe and nitrogen lasers on the apoptosis of polymorphonuclear cells (PMN) in normal versus burn patients. Inflammation is a major consequence of thermal injury, and PMN infiltration exacerbates the inflammatory process through the release of proinflammatory cytokines. The apoptotic death instead of necrotic death of PMN during the situation may help to resolve inflammation. Ten healthy volunteers and 10 burn cases (30-50% burn surface) were included in the study. The PMN was separated by dextran sedimentation and density gradient centrifugation before suspending in RPMI-1640 medium supplemented with autologous serum. The cell suspension aliquoted in microwells was exposed to nitrogen laser (wavelength of 337 nm, 3 mW) and HeNe (3 mW) lasers for 10 and 5 min. The wells not exposed to laser were used as controls. After 24-36 h of incubation, the apoptotic rates were measured. The percentage of apoptotic death increased from 32.9% in control PMN to 41.97% in PMN exposed to nitrogen laser for 5 min, and fur-

ther increased to 62.7% with nitrogen laser exposure for 10 min. HeNe laser exposure for 10 min increased the apoptotic cell percentage to 41.9%. Increased apoptosis in PMN exposed to nitrogen laser was statistically significant both for PMN from healthy subjects and burn cases. It was significantly elevated (p=0.005) only for PMN from healthy volunteers exposed to HeNe laser for 10 min, but not among HeNe exposed PMN from burn cases.

A systematic review of the literature by Lucas [1046] was limited to infrared studies. Only four randomised clinical trials were found and only one [13] showed any effect. A Meta analysis was performed for three of the studies and no significant effects could be found for decibitus ulcers, venous leg ulcers or other chronic wounds. ***The dosage calculation inaccuracy for the study [613] was not observed. In two of the three studies, the light sources are not lasers. One study [1063] is a non-coherent light study. Another study [1064] was excluded because of a different definition of the outcome, making a comparison difficult. It should, however, not have been included in the first place, since it is not a laser study but a study of the effect of combined laser and LED.***

Figure 4.46 Non healing venous ulcer where "everything" had been tried, after initiation with LPT. Healing is slow but pain reduction is rapid. Courtesy: Chrisse Bäckström

High powered lasers can easily be defocused and used within the regular therapeutic doses. In a study by Kubota [1116], a 1000 mW, 830 nm laser was used to treat skin ulcers. The power density was 669 mW/cm² and the dose 6.3 J/cm². Favourable results are reported.

In a triple-blind study on healthy persons, Hopkins [1486] found that non-irradiated wounds close to the actually irradiated wounds also healed better than control. ***This is a typical sign of the "systemic effect".***

A case of a large linear atrophic dog-bite scar on the chin was treated for three sessions at four to six week intervals with a 1450 nm diode laser in a case study by Jih Ming [1544].The wound had been present for more than two years. A 50-75% improvement in the appearance of the scar resulted after three treatments. No adverse effects were noted from the treatment. The patient subjective rating of scar improvement was more than 50%. A 1450-

nm diode laser may provide a non-invasive and effective alternative for the treatment of atrophic traumatic scars.

The study by Sari [2350] compared the effectiveness of matrix rhythm therapy, ultrasound treatment (UT), laser treatment (LT) used in the physiotherapy of burns. The case series comprised 39 individuals with second- and third-degree upper-limb burns, whose burn traumas ended approximately 1 to 3 months previously. Participants were separated into three groups: matrix rhythm treatment (MRT), UT and LT; each group was also applied a treatment protocol including whirlpool and exercise. Pain, range of motion (ROM), muscular strength, skin elasticity, and sensory functions were evaluated before and after the treatment. Pressure sense and passive ROM were higher in the MRT group than in the LT group. Pain was lower in the LT group than in the UT group, and passive ROM was higher in the UT group than the in LT group. Active ROM was found to increase in all treatment groups, whereas passive ROM increased only in the MRT and UT groups; pressure sense increased only in the MRT group, and pain decreased only in the LT group. MRT was found to be more effective in the restoration of sensory functions than LT, whereas LT was more effective in reducing pain than UT. No significant difference was observed in terms of skin elasticity according to the results of three treatment modalities.

The objective of the study by Santos [2366] was to evaluate the effects of LPT for perineal pain and healing after episiotomy. A double-blind, randomised, controlled clinical trial was performed, comparing perineal pain scores and episiotomy healing in women treated with LPT and with the simulation of the treatment. Fifty-two postpartum women who had had mediolateral episiotomies during their first normal delivery were randomly divided into two groups of 26: an experimental group and a control group. In the experimental group, the women were treated with LPT. Irradiation was applied at three points directly on the episiotomy after the suture and in three postpartum sessions: up to 2 hrs postpartum, between 20 and 24 hrs postpartum and between 40 and 48 hrs postpartum. The LPT was performed with 660 nm, spot size of 0.04 cm^2, energy density of 3.8 J/cm^2, radiant power of 15 mW and 10 s per point, which resulted in energy of 0.15 J per point and a total energy of 0.45 J per session. The control group participants also underwent three treatment sessions, but without the emission of radiation (simulation group), to assess the possible effects of placebo treatment. Comparing the pain scores before and after the LPT sessions, the experimental group presented a significant within-group reduction in mean pain scores after the second and third sessions and the control group showed a significant reduction after the first treatment simulation. However, the comparison of the perineal pain scores between the experimental and control groups indicated no statistical difference at any of the evaluated time points. There was no significant difference in perineal healing scores between the groups.

***Fortunately, the authors provide good details about the parameters, even in the PubMed** abstract. It is therefore easy* **to pinpoint the reason**

behind the lack of effect: much too low energies! 0.15 J per point and three points = total of 0.45 J for wound healing. Here again we find the misunderstanding of "the dose". 3.8 J/cm² is applied and this is close to 4 J/cm² which is a common "golden rule" for wound healing. But if the fibre is thin, "the dose" is reached very fast and with very low energies. At least ten times higher energies and a wider probe would have achieved a completely different result. Where are the proper advisors and where are the qualified peer reviewers?

Chavantes [1478] reports success in treating tracheal stenosis in entubated patients; 685 nm, 35 mW, 8 J/cm² was applied on the tracheal lumen.

Further literature: [704, 828, 935, 975, 976, 1149, 1164, 1165, 1246, 1248, 1273, 1290, 1291, 1292, 1457, 1458, 1498, 1514, 1523, 1586, 1690, 1691, 1751, 1752, 1839, 2017]

4.2 Zoster

Zoster (shingles) is a much-feared condition, not only for the acute pain that it causes, but also because it can lead to longer periods of pain after objective healing. This "postherpetic neuralgia" (PHN) is most common in older patients. The Norwegian and Danish word for zoster is "fire of hell", which is rather apt. Laser has an effect both on the acute zoster outbreak and on the post-herpetic pain. Shingles affects not only the midriff but also, for example, the trigeminal nerve. This can make it impossible to close the eye, or cause motor control difficulties, sores in the throat and oral cavity, and pulpitis sensation. In general, LPT relieves the symptoms, and a series of treatments reduces the patient's suffering considerably. It has been shown [404] that treatment in the acute phase reduces the risk of PHN. Apart from the therapeutic effect when treated in the acute phase, the reduced risk of post herpetic neuralgia may be the best argument for using LPT. A rather low percentage of zoster patients do develop post herpetic neuralgia, but we do not know in advance which ones, and for the unfortunate ones it may become a life-long “fire of hell”. One of the suggested effects of LPT on zoster is that it restores the intraneural blood flow, preventing the death of larger nerve fibres and thus arresting the development of PHN [692]. Red laser is recommended in the acute phase, infrared in the chronic phase.

Literature:

Moore [57] treated 20 patients suffering from PHN for whom conventional treatment had failed and who had experienced pain and discomfort for at least six months. Altogether 10 patients were treated with a GaAlAs laser. Another 10 received placebo laser treatment followed by GaAlAs laser light (a "cross-over study"). The experiment could thereby be conducted in a double-blind fashion while still administering equivalent treatment to all patients. The placebo group experienced little improvement after the first four treatment sessions, but after four "real" laser applications they came *very close to the results of the laser group. Pain intensity and spreading were measured. With 10 as a starting value for pain intensity, the average result was 2 and 3.3 respectively in the two groups. Pain distribution was initially set to 100, and the end result was 31 and 41. Of those treated, 15% experienced either little or no effect. When the experiment ended, the initial laser group had better scores than the second. This confirms the ongoing positive effect of LPT even after the end of a treatment period.*

In a retrospective report covering 300 patients over nine years, Moore [404] summarises: cephalic zoster patients experienced less pain reduction (61%) than thoracic patients (78%), with an equivalent difference in pain recurrence of 22% and 33% respectively. In a cost-efficiency calculation, LPT was some 28% less expensive. The use of LPT in the acute phase greatly reduces the incidence of postherpetic neuralgia.

In another study by Moore [476], comprising 20 PHN patients with malignant disease, all patients obtained at least 50% pain reduction after 8-10 treatment sessions. This patient category often does not tolerate the usual medication for PHN due to the high incidence of side effects. Power density was $3W/cm^2$.

McKibbin [58] treated 39 PHN patients with a GaAs laser. Patients estimated pain on a VAS scale of 1 to 10, the average value for the whole group being 8.5. At the end of the treatment period, the average value was 3.3, and one year after treatment it was 2.8 (44% were entirely free from symptoms).

Hong [59] reports on the outcome of the treatment of 20 PHN patients who had not responded to conventional therapy. Sixty percent of the cases were deemed to be successful after a year. The laser used was a GaAlAs.

Hachenberger [60] irradiated 41 cases of postherpetic neuralgia, 93 herpes simplex patients and 3 herpes progenitalis patients. He observed that these related complaints all responded well to HeNe laser treatment. None of the 93 herpes simplex patients experienced a recurrence in the same place during the observation period of three years.

Otsuka [421] also reports positive results of HeNe (with GaAlAs as an adjunct in difficult cases) during the acute phase of zoster.

In a double-blind study on the effect of GaAlAs laser on postherpetic neuralgia, Sato [398] found that the regional body temperature in the laser group increased from 31.9 °C to 32.6 °C, while it did not change in the placebo group.

Park [2227] recruited 28 consecutive Korean patients with acute herpes zoster ophthalmicus for a study. In the control group (group A), 14 subjects received oral famcyclovir. In the experimental group (group B), 14 subjects received oral famcyclovir and 830 nm LED phototherapy on days 0, 4, 7, and 10. In order to estimate the time for wound healing, the investigators measured the duration from the vesicle formation to when the lesion crust fell off. The Visual Analogue Scale (VAS) was used for the estimation of pain on days 4, 7, 10, and 14. The mean time required for wound healing was

13.14+/-2.34 days in group B and 15.92+/-2.55 days in group A. From day 4, the mean VAS score showed a greater improvement in group B, compared with group A. A marginal but not statistically significant difference in the VAS scores was observed between the two groups. In conclusion, LED at 830 nm for acute herpes zoster ophthalmicus leads to faster wound healing and a lower pain score.

Epidural or stellate ganglion blocks have been used to ease postherpetic pain. Otsuka [423] has also used LPT near the stellate ganglion and found effects similar to those of traditional injections. Thermograms illustrated a facial temperature increase. Irradiation near the carotid artery had a similar effect. The same author also reports a stimulative effect from stellate ganglion irradiation in patients with Raynaud's disease.

Hashimoto and Kemmutso [691, 692] have also shown that even irradiation of the stellate ganglion alone can have an effect on pain. In a double-blind study, patients with postherpetic neuralgia were treated with either 150 mW GaAlAs, 60 mW GaAlAs or placebo laser. Laser affected VAS pain scores and regional skin temperature, but there was no change in the placebo group. The pain reduction was dose dependent. It is suggested that laser irradiation of the stellate ganglion is a good alternative to traditional blocks.

Further literature: [183, 184, 418, 421, 1051]

4.3 Indications in the pipeline

Many indications have been tested clinically but still lack scientific support. Some of these are minor indications such as insect stings, nonetheless, some are important, such as osteoporosis, PMS and strawberry haemangiomas.

In every profession, unconfirmed reports and tales of pure fiction circulate. Let us look at some of the examples that now and again pop up in the therapeutic laser field. They may be a source of inspiration for further research.

4.3.1 Alzheimer's disease

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain. Current treatments only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease. As of 2012, more than 1.000 clinical trials have been or are being conducted to test various compounds in AD. Mental stimulation, exercise, and a balanced diet have been suggested as ways to delay cognitive symptoms in healthy older individuals, but there is no conclusive evidence supporting an effect. Is LPT one possibility?

Literature:

Apoptosis is a contributing pathophysiological mechanism of Alzheimer's disease (AD). In a study by Zhang, [1992] the techniques of fluorescence resonance energy transfer (FRET) and real-time quantitative RT-PCR were used to investigate the anti-apoptotic mechanism of LPT. Rat pheochromocytoma (PC12) cells were treated with amyloid beta 25-35 (A-beta(25-35)) to induce apoptosis before LPT treatment. The cell viability assays and morphological examinations show that a low fluence of LPT (0.156 J/cm^2-0.624 J/cm^2) could inhibit the cell's apoptosis. An increase of PKC activation was dynamically monitored in the cells treated with PMA (specific activator of PKC), LPT only or A-beta (25-35) followed by five minutes LPT treatment, respectively. However, the effect of LPT activating PKC could be inhibited by Go 6983 (specific inhibitor of PKC). Furthermore, LPT involved an increase in mRNA of the cell survival member bcl-xl and a decrease in the up-regulation of cell death member bax mRNA caused by A-beta(25-35). Further data shows that a low fluence of LPT could reverse the increased level of bax/bcl-xl mRNA ratio caused by A-beta (25-35) treatment. In addition, Go 6983 could inhibit the decreased level of bax/bcl-xl mRNA ratio. Taken together, these data clearly indicate that LPT inhibited A.beta(25-35)-induced PC12 cell apoptosis via PKC-mediated regulation of bax/bcl-xl mRNA ratio.

Rojas [2154] writes: Cerebral hypometabolism characterises mild cognitive impairment and Alzheimer's disease. LPT enhances the metabolic capacity of neurons in culture through photostimulation of cytochrome oxidase, the mitochondrial enzyme that catalyses oxygen consumption in cellular respiration. Growing evidence supports that neuronal metabolic enhancement by LPT positively impacts neuronal function in vitro and in vivo. Based on its effects on energy metabolism, it is proposed that LPT will also affect the cerebral cortex in vivo and modulate higher-order cognitive functions such as memory. In vivo effects of LPT on brain and behavior are poorly characterised. We tested the hypothesis that in vivo LPT facilitates cortical oxygenation and metabolic energy capacity and thereby improves memory retention. Specifically, we tested this hypothesis in rats using fear extinction memory, a form of memory modulated by prefrontal cortex activation. Effects of LPT on brain metabolism were determined through measurement of prefrontal cortex oxygen concentration with fluorescent quenching oximetry and by quantitative cytochrome oxidase histochemistry. Experiment 1 verified that LPT increased the rate of oxygen consumption in the prefrontal cortex in vivo. Experiment 2 showed that LPT-treated rats had an enhanced extinction memory as compared to controls. Experiment 3 showed that LPT reduced fear renewal and prevented the re-emergence of extinguished conditioned fear responses. Experiment 4 showed that LPT induced hormetic dose-response effects on the metabolic capacity of the prefrontal cortex. These data suggest that LPT can enhance cortical metabolic capacity and retention of extinction memories, and implicate LPT as a novel intervention to improve memory.

Von Leden [2259] summarises: Microglia exhibit a spectrum of responses to injury, with partial or full polarisation into pro- and anti-inflammatory phenotypes. Pro-inflammatory (M1 or classically activated) microglia contribute to chronic inflammation and neuronal toxicity, while anti-inflammatory (M2 or alternatively activated) microglia play a role in wound healing and tissue repair; microglia can fall anywhere along this spectrum in response to stimulation. The effect of LPT on microglial polarisation therefore was investigated using colourimetric assays, immunocytochemistry, proteomic profiling and RT-PCR in vitro after exposure of primary microglia or BV2 microglial cell line to LPT of differing energy densities (0.2, 4, 10, and 30 J/cm(2) , 808 nm wavelength, 50 mW output power). LPT has a dose-dependent effect on the spectrum of microglial M1 and M2 polarisation. Specifically, LPT with energy densities between 4 and 30 J/cm^2 induced expression of M1 markers in microglia. Markers of the M2 phenotype, including CD206 and TIMP1, were observed at lower energy densities of 0.2-10 J/cm^2. In addition, co-culture of LPT or control-treated microglia with primary neuronal cultures demonstrated a dose-dependent effect of LPT on microglial-induced neuronal growth and neurite extension. In conclusion, these data suggest that the Arndt-Schulz law as applied to LPT for a specific bioassay does not hold true in cells with a spectrum of responses, and that LPT can alter microglial phenotype across this spectrum in a dose-dependent manner. These data are therefore of important relevance to not only therapies in the CNS but also to understanding of LPT effects and mechanisms.

Downregulation of brain-derived neurotrophic factor (BDNF) in the hippocampus occurs early in the progression of Alzheimer's disease (AD). Since BDNF plays a critical role in neuronal survival and dendrite growth, BDNF upregulation may contribute to rescue dendrite atrophy and cell loss in AD. LPT has been demonstrated to regulate neuronal function both in vitro and in vivo. In a study by Meng [2335], the investigators found that LPT rescued neurons loss and dendritic atrophy via upregulation of BDNF in both A-beta-treated hippocampal neurons and cultured APP/PS1 mouse hippocampal neurons. Photoactivation of transcription factor CRE-binding protein (CREB) increased both BDNF mRNA and protein expression, since knockdown CREB blocked the effects of LPT. Furthermore, CREB-regulated transcription was in an ERK-dependent manner. Inhibition of ERK attenuated the DNA-binding efficiency of CREB to BDNF promoter. In addition, dendrite growth was improved after LPT, characterised by upregulation of Rac1 activity and PSD-95 expression, and the increase in length, branching, and spine density of dendrites in hippocampal neurons. Together, these studies suggest that upregulation of BDNF with LPT by activation of ERK/CREB pathway can ameliorate A-beta-induced neurons loss and dendritic atrophy, thus identifying a novel pathway by which LPT protects against A-beta-induced neurotoxicity.

Activated microglial cells are an important pathological component in brains of patients with neurodegenerative diseases. The purpose of the study by Song [2415] was to investigate the effect of 632.8 nm, 64.6 mW/cm² LPT a non-damaging physical therapy, on activated micro-glia, and the subsequent signalling events of LPT-induced neuroprotective effects and phago-cytic responses. To model microglial activation, the researchers treated the micro-glial BV2 cells with lipopolysaccharide (LPS). For the LPT-induced neuro-protective study, neuronal cells with activated microglial cells in a Transwell cell-culture system were used. For the phagocytosis study, fluorescence-labeled microspheres were added into the treated microglial cells to confirm the role of LPT. The results showed that LPT (20 J/cm²) could attenuate toll-like receptor (TLR)-mediated proinflammatory responses in microglia, characterised by down-regulation of proinflammatory cytokine expression and nitric oxide (NO) production. LPT-triggered TLR signalling inhibition was achieved by activating tyrosine kinases Src and Syk, which led to MyD88 tyrosine phosphorylation, thus impairing MyD88-dependent proinflammatory signalling cascade. In addition, we found that Src activation could enhance Rac1 ac-tivity and F-actin accumulation that typify microglial phagocytic activity. We also found that Src/PI3K/Akt inhibitors prevented LPT-stimulated Akt (Ser473 and Thr308) phosphorylation and blocked Rac1 activity and actin-based microglial phagocytosis, indicating the activation of Src/PI3K/Akt/Rac1 signalling pathway. The present study underlines the importance of Src in suppressing inflammation and enhancing microglial phagocytic function in activated microglia during LPT stimulation. We have identified a new and important neuroprotective signalling pathway that consists of regulation of microglial phagocytosis and inflammation under LPT treatment. This research may provide a feasible therapeutic approach to control the progression of neurodegenerative diseases.

Yang [2451] demonstrated that 632.8 nm laser was capable of suppressing cellular pathways of oxidative stress and inflammatory responses critical in the pathogenesis in AD. This study could prove to provide the groundwork for further investigations for the potential use of LPT as a treatment for AD.

Farfara [2530] recently reported that LPT to the bone marrow (BM) led to proliferation of mesenchymal stem cells (MSCs) and their homing in the ischemic heart suggesting its role in regenerative medicine. The aim of another study was to investigate the ability of LPT to stimulate MSCs of autologous BM in order to affect neurological behavior and beta-amyloid burden in progressive stages of Alzheimer's disease (AD) mouse model. MSCs from wild-type mice stimulated with LPT showed to increase their ability to maturate towards a monocyte lineage and to increase phagocytosis activity towards soluble amyloid beta (A beta). Furthermore, weekly LPT to BM of AD mice for 2 months, starting at 4 months of age (progressive stage of AD), improved cognitive capacity and spatial learning, as compared to sham-treated AD mice. Histology revealed a significant reduction in A beta *brain burden. These results suggest the use of LPT as a therapeutic application in progressive stages of AD and imply its role in mediating MSC therapy in brain amyloidogenic diseases.*

4.3.2 Botox failures

The widespread use of botulinum toxin type A (BTX-A) for aesthetic procedures in recent years has brought about some unwanted side effects that, though they are self-limited, cause inconvenience for patients. Injection of this paralytic toxin inactivates target muscle(s) for many months and unwanted facial movements will thus be prevented. Spreading of the toxin beyond the target muscles sometimes affects muscles necessary for other facial movements, such as the levator palpebrae, inactivation of which causes upper eyelid ptosis. Mild cases resolve after two to three weeks, but in severe cases the complication may last as long as the cosmetic results persist (three to four months), and until now there has been no medical intervention to accelerate healing.

Literature:

In an effort to achieve more rapid recovery from eyelid ptosis due to an overdose of BTX-A in the glabella, laser therapy was used by Majlesi [2024] in a 46-year-old woman with bilateral eyelid ptosis (partial on the right side and complete on the left) 12 d after injection. A GaAs laser was used and the protocol consisted of irradiation of three points on the upper lid just above the levator, and one point on the corrugator muscle on each side in contact mode, with three sessions per week (890 nm, peak power 94 W, average power 28 mW, pulse duration 200 ns, spot size 3 mm, pulse repetition rate 3000 Hz, duration of irradiation 40 sec per point, energy per point 1.1 J, total energy per session 8.8 J, dose 16 J/cm^2). The result was complete recovery from ptosis after 10 sessions, but the cosmetic results persisted for several months.

Figure 4.47 Rapid evolution of botox eylid prolaps. Courtesy: Gholamreza Majlesi

4.3.3 Cellulites

LPT has a stimulating effect on various pathological skin conditions. Whether or not cellulitis is a pathological condition is open to discussion. No documented reports on the effects of LPT for this indication have been published, but red laser machines can be seen demonstrated on TV and in other media.

4.3.4 Cholesterol reduction

In a study by Maloney [2096] 20 volunteers between the ages of 18 and 65 participated in a non-controlled, non-randomised study. Participants received LPT treatments three times per week for two weeks, with each treatment session lasting approximately 40 minutes. Treatments were administered across the abdomen and waist area wrapping around the lower back, an area which generally contains the most concentrated pockets of subcutaneous fat. The laser therapy used was a 17.5 mW, 635 nm diode. 75 % of study participants demonstrated an overall reduction in cholesterol serum levels, with the reduction ranging from -1.0 to -31.0 mg/dL and an average reduction of -16.1 points. For those participants demonstrating an overall reduction in cholesterol serum levels, 93 percent experienced a reduction in LDL levels (commonly referred to as "bad cholesterol"), with 47 percent revealing a reduction in LDL levels without experiencing a reduction in HDL levels (or "good cholesterol"). Of the 20 participants, 60 percent demonstrated a reduction in triglyceride levels.

4.3.5 Complex regional pain syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a chronic inflammatory pain syndrome that affects one or more extremities of the body. It is characterised by burning pain and abnormalities in the sensory, motor, and autonomic nervous systems. This condition is one of the many hard-to-treat pathologies where "everything has been tried" - except LPT! It is well illustrated by Taha [2545]: "There are no specific pharmacological drugs approved for the treatment of CRPS, and no reliable protocol is available for use in these patients. Although traditional therapies such as physiotherapy, range of motion exercises, and pain medications (e.g., antiepilepetics, antidepressants, opioids, antiinflammatories, bisphosphonates) offer temporary relief, they have not been shown to change significantly the overall course of the syndrome. These poor results may be due to poor therapeutic mechanisms, the diversity of the symptoms, or diverse patient responses."

Taha well describes the situation for many chronic pain patients. It seems that “anything goes” for these patients, even in traditional medical circles. LPT, being a possible alternative with no side effects is not even “anything”, which is sad for these patients. The authors of this book have contact with therapists reporting promising results for CRPS and LPT can be recommended, even in spite of its poor scientific backing for this condition.

Literature:

The aim of a study by Kocic [2453] was to evaluate and compare, by using thermovison, the effects of LPT and therapy with interferential current in treatment of CRPS I. The prospective randomised controlled clinical study included 45 patients with unilateral CRPS 1, after a fracture of the distal end of the radius, of the tibia and/or the fibula. The group A consisted of 20 patients treated by LPT and kinesy-therapy, while the patients in the group B (n=25) were treated by interferential current and kinesy-therapy. The regions of interest were filmed by a thermovision camera on both sides, before and after the 20 therapeutic procedures had been applied. Afterwards, the quantitative analysis and the comparing of thermograms taken before and after the applied therapy were performed. There was statistically significant decrease of the mean maximum temperature difference between the injured and the contralateral extremity after the therapy in comparison to the status before the therapy, with the patients of the group A as well as those of the group B. The decrease was statistically significantly higher in the group A than in the group B.

4.3.6 Eczema

Although no scientific papers on this indication can be found on PubMed, it doesn’t mean that LPT is ineffective - just that the indication has not been investigated in a scientific setting. The photos below underline the fact that eczema is a good indication.

Courtesy: Chrisse Bäckström

4.3.7 Erectile dysfunction

A company has produced a laser especially designed for treatment of erectile dysfunction [1692]. All in all 44 volunteers were randomly assigned to treatment with placebo or 808 nm GaAlAs laser light. Altogether 39 patients completed all treatments and follow-up visits: 18 patients in the treatment group (A) and 21 in the placebo group (B). The treatments were delivered for 19 minutes, twice a week, with a total of six treatment sessions. The laser unit used has two rows of five treatment points each and the unit is applied on the dorsal aspect of the penis, every row corresponding to the corpus cavernosum of the penis. Treatment was given for 20 minutes, twice a week, six to eight times. Power of each diode was 150 mW. Questions three and four, as well as the Erectile Function Domain from the International Index of Erectile Function (IIEF), assessed the improvement in Erectile Dysfunction. The improvement duration on average was six months.

4.3.8 Familiar amyotrophic lateral sclerosis (FALS)

Familiar amyotrophic lateral sclerosis (FALS) is a neurodegenerative disease characterised by progressive loss of motor neurons and death. Mitochondrial dysfunction and oxidative stress play an important role in motor neuron loss in ALS. Light therapy (LPT) has biomodulatory effects on mitochondria. Riboflavin improves energy efficiency in mitochondria and reduces oxidative injury.

Literature:

The purpose of a study by Moges [2085] was to examine the synergistic effect of LT and riboflavin on the survival of motor neurons in a mouse model of FALS. G93A SOD1 transgenic mice were divided into four groups: Control, Riboflavin, Light, and Riboflavin+Light (combination). Mice were treated from 51 days of age until death. A single set of LT parameters was *used: 810 nm diode laser, 140 mW output power, 1.4 cm^2 spot area, 120 seconds treatment duration, and 12 J/cm^2 energy density. Behavioral tests and weight monitoring were done weekly. At end stage of the disease, mice were euthanised, survival data was collected and immunohistochemistry and motor neuron counts were performed. There was no difference in survival between groups. Motor function was not significantly improved with the exception of the rotarod test which showed significant improvement in the Light group in the early stage of the disease. Immunohistochemical expression of the astrocyte marker, glial fibrilary acidic protein, was significantly reduced in the cervical and lumbar enlargements of the spinal cord as a result of LPT. There was no difference in the number of motor neurons in the anterior horn of the lumbar enlargement between groups. The lack of significant improvement in survival and motor performance indicates study interventions were ineffective in altering disease progression in the G93A SOD1 mice. These findings have potential implications for the conceptual use of light to treat other neurodegenerative diseases that have been linked to mitochondrial dysfunction.*

4.3.9 Glomerulonephritis

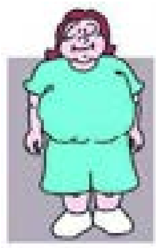
Glomerulonephritis, also known as glomerular nephritis, is a term used to refer to several renal diseases. Many of the diseases are characterised by inflammation either of the glomeruli or small blood vessels in the kidneys, but not all diseases necessarily have an inflammatory component.

Literature:

The goal of a study by Yamato [2198] was to investigate the anti-inflammatory effect of daily external LPT in an animal model of crescentic glomerulonephritis. Crescentic glomerulonephritis was induced in male Wister Kyoto rats by intravenous injection of antibody for glomerular basement membrane (GBM). The rats were irradiated with a low- level laser, 830 nm, from the shaved skin surface once a day for 14 days (irradiation spot size on the skin surface, 2.27 cm^2 ; power intensity 880 mW/cm^2 ; irradiation mode, continuous mode; irradiation time 250 s; energy 500 J; energy density 220 J/cm^2) After laser irradiation for 14 days, animals were killed, and the extent of inflammation was evaluated. Expression of gene for inflammatory cytokines including interleukin (IL)-1beta and tumour necrosis factor alpha (TNF-alpha) was assessed by reverse transcription polymerase chain reaction. Crescent formation in glomeruli and infiltration of macrophages and lymphocytes were assessed by histochemical observation. Injection of anti-GBM antibody induced severe glomerulonephritis with crescent formation. Histological observations indicated that LPT suppressed crescent formation and infiltration of ED1+ macrophages and CD8+ lymphocytes into the glomeruli. LPT attenuated the levels of IL-1beta and TNF-alpha messenger RNA in the renal cortex. Externally directed LPT suppresses the activity of *rat anti-GBM crescentic glomerulonephritis in rats. LPT has the potential to be used for direct treatment of glomerulonephritis.*

Regardless of the aetiology, chronic kidney disease (CKD) involves progressive widespread tissue fibrosis, tubular atrophy, and loss of kidney function. This process also occurs in kidney allograft. At present, effective therapies for this condition are lacking. Oliveira [2417] investi-gated the effects of LPT on the interstitial fibrosis that occurs after experimental UUO in rats. The occluded kidney of half of the 32 Wistar rats that underwent UUO received a single in-traoperative dose of LPT (780 nm, 22.5 J/cm^2, 30 mW, 0.75 W/cm^2, 30 sec on each of nine points). After 14 days, renal fibrosis was assessed by Sirius red staining under polarised light. Immuno-histochemical analyses quantitated the renal tissue cells that expressed fibroblast (FSP-1) and myofibroblast (alpha-SMA) markers. Reverse transcriptase polymerase chain reaction (RT-PCR) was performed to determine the mRNA expression of interleukin (IL)-6, monocyte chemotactic protein-1 (MCP-1), transforming growth factor (TGF)-beta1 and Smad3. The UUO and LPT animals had less fibrosis than the UUO animals, as well having decreased expression inflammatory and pro-fibrotic markers. For the first time, it was shown that LPT had a protective effect regarding renal interstitial fibrosis. It is conceivable that by attenuating in-flammation, LPT can prevent tubular activation and trans-differentiation, which are the two processes that mainly drive the renal fibrosis of the UUO model.

4.3.10 Obesity



Obesity has been reported to be affected by LPT. When treating a person with GaAs on an area of the abdomen, therapists have been able to observe a slight "depression" in the fat layer where the probe has been held - the laser has in some way affected the tissue. However, the patient has not lost any weight, and furthermore, where would all the fat have gone if no weight was lost?

However, what we usually regard as “fat” is not just fat. The “fat” in a thigh contains only about 30% fat – the rest is water and glycogen. In some cases it can be regarded, more or less, as an oedema. As laser treatment of oedema can be very effective, local treatment of “fat” can appear to be effective as well.

The use of laser therapy prior to liposuction remains controversial, as can be seen from the different outcomes in the studies below.

Literature:

Support for the effect on fat cells is given by Neira [1317, 2025]. This study examined whether 635 nm lasers had an effect on adipose tissue in vivo and the procedural implementation of lipoplasty/liposuction techniques. The experiment investigated the effect of 635 nm, 10 mW diode laser irradiation.

Total energy values of 1.2 J/cm^2, 2.4 J/cm^2, and 3.6 J/cm^2 were applied on human adipose tissue taken from lipectomy samples of 12 healthy women. The tissue samples were irradiated for zero, two, four and six minutes with and without tumescent solution, and were studied using the protocols of transmission electron microscopy and scanning electron microscopy. Non-irradiated tissue samples were taken for reference. More than 180 images were recorded and professionally evaluated. All microscopic results showed that without laser exposure, the normal adipose tissue appeared as a grape-shaped node. After four minutes of laser exposure, 80% of the fat was released from the adipose cells; at six minutes of laser exposure, 99% of the fat was released from the adipocyte. The released fat was collected in the interstitial space. Transmission electron microscopic images of the adipose tissue taken at x60,000 showed a transitory pore and a complete deflation of the adipocytes. The laser energy affected the adipose cell by causing a transitory pore in the cell membrane to open, which permitted the fat content to go from inside to outside the cell. The cells in the interstitial space and the capillaries remained intact.

In a study by Brown [1428], this observation could not be confirmed. To explore published data on the effects of LPT on fatty tissue, Brown initiated a series of in vitro experiments on human preadipocytes in a porcine model. Using a 635 nm laser of 1.0 J/cm^2, these studies were designed to determine whether alterations in adipocyte structure or function were modulated after LPT. Cultured human preadipocytes after 60 minutes of laser irradiation did not change appearance compared with non-irradiated control cells. In the porcine model, LPT (30 minutes) was compared with traditional lipoplasty (suction-assisted lipoplasty) and ultrasound-assisted lipoplasty. From histologic and scanning electron microscopic evaluations of the lipoaspirates, no differences were observed between LPT-derived and suction-assisted lipoplasty-derived specimens. Using exposure times of 0, 15, 30, and 60 minutes in the presence or absence of superwet wetting solution and in the absence of lipoplasty, a power output of 0.9 mW was delivered to tissue samples at three increasing depths from each experimental site. No histologic tissue changes or specifically in adipocyte structure were observed at any depth with the longest LPT (60 minutes with superwet fluid). Three subjects undergoing large-volume lipoplasty were exposed to superwet wetting fluid infiltration 14 minutes before and 12 minutes after. Tissue samples from infiltrated areas were collected before suction-assisted lipoplasty and lipoaspirates from suction-assisted lipoplasty. No consistent observations of adipocyte disruptions were observed in the histologic or scanning electron microscopy photographs.

In a study by Medrado [1697], dorsal fat pads of normal adult rats were submitted to laser irradiation applied locally through intact skin with four different dose schedules (4, 8, 12 and 16 J/cm^2), with a further group being sham-irradiated. Histology, morphometry, immunofluorescence, and electron microscopy were all used to analyse irradiated tissues. Changes *were restricted to the brown fatty tissue, in which a tendency was shown for multivacuolar cells to be transformed into the unilocular type. The number of cells which exhibited enlargement and fusion of small vacuoles was greater in the 4 J/cm² and 16 J/cm² groups. Increased vascular proliferation and congestion was another more evident finding in laser-treated animals compared to non-treated animals. Laser irradiation at therapeutic levels cause brown adipose fat droplets to coalesce and fuse. Additionally, it stimulated proliferation and congestion of capillaries in the extracellular matrix.*

The aim of a study by Senhorino [1901] was to evaluate the influence of LPT on the morphometry of adipose cells in rats. The sample consisted of 20 rats randomised into four groups. The dorsal fat pads of the animals were exposed to the InGaAlP laser with fluencies of 2, 8, 16 and 0 J/cm² for L1, L2, L3 and L4 respectively. The average morphometry, in pixels, was: 3741 ±704.14, 3762 ±947.54, 3737 ±1076.92 and 4619 ±781.52 for L1, L2, L3 and L4, respectively, without any significant differences amongst the groups. The application of LPT with different fluencies did not influence the morphometry of white adipose cells differently.

A study by Mvula [2111] investigated the effects of LPT and epidermal growth factor (EGF) on adult adipose-derived stem cells (ADSCs) isolated from human adipose tissue. Isolated cells were cultured to semi-confluence, and the monolayers of ADSCs were exposed to low-level laser at 5 J/cm² using 636 nm diode laser. Cell viability and proliferation were monitored using adenosine triphosphate (ATP) luminescence and optical density at 0 h, 24 h and 48 h after irradiation. Application of low-level laser irradiation at 5 J/cm² on human ADSCs cultured with EGF increased the viability and proliferation of these cells. The results indicate that low-level laser irradiation in combination with EGF enhances the proliferation and maintenance of ADSCs in vitro.

Obesity and associated dyslipidemia is the fastest growing health problem throughout the world. The combination of exercise and LPT could be a new approach to the treatment of obesity and associated disease. In the work by Aquino [2197], the effects of LPT associated with exercises on the lipid metabolism in regular and high-fat diet rats were verified. The authors used 64 rats divided in eight groups with eight rats each, designed: SC, sedentary chow diet; SCL, sedentary chow diet laser, TC, trained chow diet; TCL, trained chow diet laser; SH, sedentary high-fat diet; SHL, sedentary high-fat diet laser; TH, trained high-fat diet; and THL, trained high-fat diet laser. The exercise used was swimming during 8 weeks/90 min daily and LPT, 830 nm, 4.7 J/point and total energy 9.4 J per animal, applied to both gastrocnemius muscles after exercise. They analysed biochemical parameters, percentage of fat, hepatic and muscular glycogen and relative mass of tissue, and weight percentage gain. LPT decreased the total cholesterol triglycerides, low-density lipoprotein cholesterol and relative mass of fat tissue, suggesting increased metabolic activity and altered lipid pathways. The combination of exercise and LPT increased the benefits of exercise alone. How-

ever, LPT without exercise tended to increase body weight and fat content. LPT may be a valuable addition to a regimen of diet and exercise for weight reduction and dyslipidemic control.

In a review of the literature Avci [2244] writes: LPT is a non-invasive, non-thermal approach to disorders requiring reduction of pain and inflammation and stimulation of healing and tissue regeneration. Within the last decade, LPT started being investigated as an adjuvant to liposuction, for non-invasive body contouring, reduction of cellulite, and improvement of blood lipid profile. LPT may also aid autologous fat transfer procedures by enhancing the viability of adipocytes. However the underlying mechanism of actions for such effects still seems to be unclear. It is important, therefore, to understand the potential efficacy and proposed mechanism of actions of this new procedure for fat reduction. A review of the literature associated with applications of LPT related to fat layer reduction was performed to evaluate the findings from pre-clinical and clinical studies with respect to the mechanism of action, efficacy, and safety. The studies as of today suggest that LPT has a potential to be used in fat and cellulite reduction as well as in improvement of blood lipid profile without any significant side effects. One of the main proposed mechanisms of actions is based upon production of transient pores in adipocytes, allowing lipids to leak out. Another is through activation of the complement cascade which could cause induction of adipocyte apoptosis and subsequent release of lipids. Although the present studies have demonstrated safety and efficacy of LPT in fat layer reduction, studies demonstrating the efficacy of LPT as a stand-alone procedure are still inadequate. Moreover, further studies are necessary to identify the mechanism of action.

The aim of a study by Savoia [2344] was to evaluate the application of a 635 nm and 40 mW power per multiple diode laser in combination with vibration therapy for the application of non-invasive reduction of circumference in patients with localised adiposity and cellulite. The study enrolled men and women (n=33) aged 18-64 years with localised adiposity or fibrous cellulite. The evaluation parameters were: photographic evaluation, perimetric evaluation, blood tests, ecographic evaluation, histological evaluation, and subjective and objective tests. The results produced were statistically analysed and resulted in a significant reduction of fat thickness when compared to the measurement prior to the treatment. Moreover, subjective and objective tests, as well as ecographic and histological evaluations, confirmed the reduction of fat thickness.

4.3.11 Orofacial granulomatosis

Orofacial granulomatosis (and also termed granulomatous cheilitis, cheilitis granulomatosa, cheilitis granulomatosis, and oral granulomatosis), is a condition characterised by persistent enlargement of the soft tissues of the mouth, lips and the area around the mouth on the face. The enlargement does not cause any pain.

Merigo [2420] reports a case of orofacial granulomatosis successfully treated with LPT with the use of a 4-cm defocalised lens and power of 1 W. Treatment was administered in sessions of 5 irradiations of 1 minute each, with a 1 minute interval between 2 subsequent irradiations (power density 0.08 W/cm²; fluence/application 4.8 J/cm²; fluence/session: 24 J/cm²). LPT was repeated 12 times (3 times per week). After 2 weeks of LPT applications, the patient reported an improvement of symptomatology as well as a decrease of labial swelling. Complete healing was observed after 1 month. The patient was followed for 2 years. No recurrence of swelling was observed during the follow-up.

4.3.12 Parkinson's disease

Several new indications for LPT are preliminary but deserve attention, even though the documentation still is scarce. The papers below create an embryo for further research.

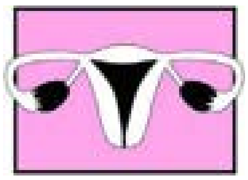
Literature:

Komelkova [1851] studied the influence of LPT on the course of Parkinson's disease in 70 patients. This influence appeared adaptogenic both in the group with elevated and low MAO B and Cu/Zn SOD activity. LPT resulted in a reduction of the neurological deficit, normalisation of the activity of MAO B, Cu/Zn-SOD and immune indices. There was a correlation between humoral immunity and activity of the antioxidant enzymes (SOD, catalase).

The effect of HeNe laser on the activity of MAO B, Cu/Zn-SOD, Mn-SOD, and catalase in blood cells from patients with Parkinson's disease was studied in vivo and in vitro by Vitreshchak [1852]. The effects of intravenous in vivo irradiation were more pronounced than those observed in similar in vitro experiments.

It has been hypothesised that reduced axonal transport contributes to the degeneration of neuronal processes in Parkinson's disease (PD). Mitochondria supply the ATP needed to support axonal transport and contribute to many other cellular functions essential for the survival of neuronal cells. Furthermore, mitochondria in PD tissues are metabolically and functionally compromised. To address this hypothesis, Trimmer [2050] measured the velocity of mitochondrial movement in human transmitochondrial cybrid "cytoplasmic hybrid" neuronal cells bearing mitochondrial DNA from patients with sporadic PD and disease-free age-matched volunteer controls (CNT). The absorption of LPT by components of the mitochondrial electron transport chain (mtETC) enhances mitochondrial metabolism, stimulates oxidative phosphorylation and improves redox capacity. PD and CNT cybrid neuronal cells were exposed to near-infrared laser light to determine if the velocity of mitochondrial movement can be restored by LPT. Axonal transport of labeled mitochondria was documented by time lapse microscopy in dopaminergic PD and CNT cybrid neuronal cells before and after illumina-

tion with an 810 nm laser (50 mW/cm^2) for 40 seconds. Oxygen utilisation and assembly of mtETC complexes were also determined. The velocity of mitochondrial movement in PD cybrid neuronal cells was significantly reduced compared to mitochondrial movement in disease free CNT cybrid neuronal cells. For two hours after LPT, the average velocity of mitochondrial movement in PD cybrid neurites was significantly increased and restored to levels comparable to CNT. Mitochondrial movement in CNT cybrid neurites was unaltered by LPT. Assembly of complexes in the mtETC was reduced and oxygen utilisation was altered in PD cybrid neuronal cells when compared to CNT cybrid neuronal cells. PD cybrid neuronal cell lines with the most dysfunctional mtETC assembly and oxygen utilisation profiles were least responsive to LPT. The results from this study support the proposal that axonal transport is reduced in sporadic PD and that a single, brief treatment with near-infrared light can restore axonal transport to control levels.



4.3.13 Post-menstrual stress

PMS is a problematic condition for many women. It can be treated with oestrogene but the side effects are potentially serious. The authors have limited but very positive experience of using a GaAs multiprobe over the projection of the ovaries. This therapy has reduced symptoms and in one case eliminated the need for hormones. Further indications related to women´s health, reported by Behling [1939], are Endometriosis, Ovarian Cysts, Fibrocystic Breast conditions, Dysmenorrhea, Herpes - Genital and Oral, Infertility/Optimal Fertility, Fibromyalgia, Vulvadynia.

Earlier studies show that one in three Swedish women suffer from menstrual pain. Although, analgesics may to some extent reduce the pain, the side effects of such treatments are not ignorable and thus other safe approaches must be sought. Twenty volunteer women suffering from painful menstruation participated in a pilot study by Kim [2105]. Every individual were treated 15 minutes per week for 8 weeks each time with a total of 200 joules energy using a GaAs multiprobe laser. Approximately 80% of treated individuals experienced milder pain during menstruation. The consumption of analgesics was considerably reduced during menstruation. This results show that laser therapy is efficient in reducing menstrual pain and may potentially replace analgesics.

Further literature: [143]

4.3.14 Pemphigus vulgaris

Pemphigus vulgaris is a chronic autoimmune mucocutaneous disease that initially is manifested by painful intraoral erosions and ulcers which spread to other mucosa and the skin, generally more than 5 months after oral lesion manifestation. The treatment consists of prednisone alone or in combination with an immunosuppressive agent, and the clinical response is perceived within 2 to 4 weeks. Minicucci [2416] reports two cases of pemphigus vulgaris that received systemic treatment associated with LPT for oral and cutaneous lesions. Prompt analgesic effect in oral lesions and accelerated healing of oral and cutaneous wounds was observed. This suggests LPT as a non-invasive technique that should be considered as an adjuvant therapy in oral and skin disorders in patients with PV.

Further reference: [2529]

4.3.15 Sleeping disorders

In a previous study, Wu [2487] found that the LPT stimulation at the palm with a frequency of 10 Hz was able to induce significant brain activation in normal subjects with opened eyes. However, the electroencephalography (EEG) changes to LPT stimulation in subjects with closed eyes have not been studied. In the present study, the laser array stimulator was applied to deliver insensible laser stimulations to the palm of the tested subjects with closed eyes (the laser group). The EEG activities before, during, and after the laser stimulation were collected. The EEG amplitude powers of each EEG frequency band at 19 locations were calculated. The authors found a pronounced decrease in the EEG power in alpha-bandwidth during laser simulation and then less decrease in the EEG power in delta-bandwidth in normal subjects with laser stimulation. The EEG power in beta-bandwidth in the right occipital area also decreased significantly in the laser group. It is suggested that laser stimulation might be conducive to falling into sleep in patients with sleep problems.

Similar effects have been reported using LED [2192].

4.3.16 Withdrawal periods

In the study by Mirzaii-Dizgah [1901] the effects of LPT on naloxone-induced withdrawal signs of morphine-dependent rats were examined. A GaAlAs laser with a power density of 12.5 J/cm^2 was used. One-way ANOVA showed that the LPT applied immediately or 15 min prior to naloxone injection significantly decreased total withdrawal score (TWS). These results suggest that LPT prior to naloxone injection attenuates the expression of withdrawal signs in morphine-dependent rats.

4.3.17 Wrinkles

Wrinkles are the LPT critic's favourite subject. We have not been able to find the source of the assertion that therapeutic lasers can remove wrinkles. The assertion is probably as incorrect as the critic's explanation of the alleged effect: "The laser can possibly cause a local inflammatory reaction in the skin which leads to local oedema, which in turn temporarily flattens out the wrinkles". LPT does not cause any local inflammatory reaction in the skin. But the critics have obviously seen a temporary smoothing of wrinkles, as they are theorising about the underlying cause.

However, as mentioned previously (see chapter 3.6.1 “Laser therapy with carbon dioxide lasers” on page 148), it has been demonstrated that superficial burning ("laser peeling") with a CO_2-laser beam or an Er:YAG laser is effective in skin resurfacing for the treatment of wrinkles. Chernoff [294, 295] performed over 50 exfoliations to smooth out perioral, lip, and periorbital wrinkles and scars. The thermal damage depth was between 75 and 150 µm. The result is astonishing (far better than what can be achieved with chemical peeling and mechanical dermabrasion). There is no question that biostimulation is a decisive factor in the process.

This is even more strongly underlined in the recent reports about so called “non-ablative skin rejuvenation”. Here, laser powers and fluencies have been used at levels that do not cause pain, and often not even a heat sensation. Examples of such lasers are: 590 nm pulsed dye-laser [1145], 1064 nm Nd:YAG-laser [1146], 1320 nm Nd:YAG-laser [1147] and 1540 nm Nd:glass laser [1146]. This is obviously a question of adjuvant biostimulation effects (See chapter 1.20.1 “The CO2 laser (carbon dioxide laser)” on page 44).

4.3.18 Consumer lasers

Several medical conditions require repeated treatments, others are chronic and require lifelong treatment. A laser for home care is therefore a useful product. Such a laser should ideally be provided or recommended by a competent therapist, be it a medical doctor, dentist, physiotherapist or other professionals. After initial diagnosis and treatment plan, the therapist can initiate the treatment and find a working protocol. This protocol can include a home care period in between sessions, to support the treatment. Such a schedule will not only save time but be environmental friendly through reduced transports. For chronic conditions, therapist and patient agree upon the future protocol, with regular check-ups.

Home care lasers are also useful for a number of recurrent or accidental conditions such as herpes simplex and aphthous ulcers. Herpes simplex is ideally treated in the prodromal stage and to have a home care laser readily at hand is then optimal. Indeed, patients with risk of herpes simplex outbreaks should have the laser at hand whenever going for vacation in areas where they are exposed to sunlight. This is in particular important for persons experiencing recurrent HSV attacks, since constant use of the laser in the prodromal stage will prolong the interval between occurrences.

A home care laser should be comparatively low powered, not exceeding 100 mW. But the actual output is not as important as the size of the laser aperture. By using a large aperture, the power density is reduced and the minimal risk of eye damage is further reduced. To add to safety, there should be a light or sound signal when the beam is on and a short period of irradiation per activation. For superficial conditions, home care units containing LEDs are also useful.

Literature

The aim of a study by Nylander [2302] was to compare two different methods of LPT, a method in which the patients are treated in the clinic and another method in which patients treat themselves at home. The study included 9 patients and the study lasted 6 months. The patients were randomised into 3 groups. Group 1 (control group): Initial LPT twice a week for three weeks by irradiating the salivary glands. After three weeks, a new saliva sample. Thereafter no further treatment, only follow up with saliva samples every month for five months. Group 2: Initial treatment twice a week for three weeks by irradiating the salivary glands. After three weeks, a new saliva sample. Then the patient comes to the clinic for saliva sampling and treatment with LPT. The same mode of operation, once a month for five months. Group 3: Initial treatment twice a week for three weeks by irradiating the salivary glands. After three weeks, a new saliva sample. Then the patients were trained to treat themselves with a home care laser three times a week for the rest of the time the study lasted. Patients came to the clinic for saliva sampling every month. Mode of operation: Treatment in the clinic, 810 nm, 60 mW, 1800 Hz. Probe diameter 4 mm in skin/mucosa contact. Gl. parotis 7.2 J, gl. submandibularis 4.8 J and gl. lingualis 3 J on both sides, total energy of 15 J per side. Self-treatment: Skin/ mucosa contact, 808 nm, 75 mW, CW, probe diameter 8 mm. Gl. parotis 6.75 J, gI. mandibularis 4.5 J and gl. linguals 3 J, bilaterally. Both sides received a total energy of 14 J. After treating the patients for three weeks the investigator could see an increase in salivary secretion in each patient. The result after 6 months showed an increase in salivary flow in group B and C. In group A, the same trend could not be seen. LPT of hyposalivation leads to an increase in saliva and the study suggests that a supportive treatment with LPT provides a continued increase in saliva for up to 6 months. Supportive treatment can be performed equally well in the clinic as by patients treating themselves at home.

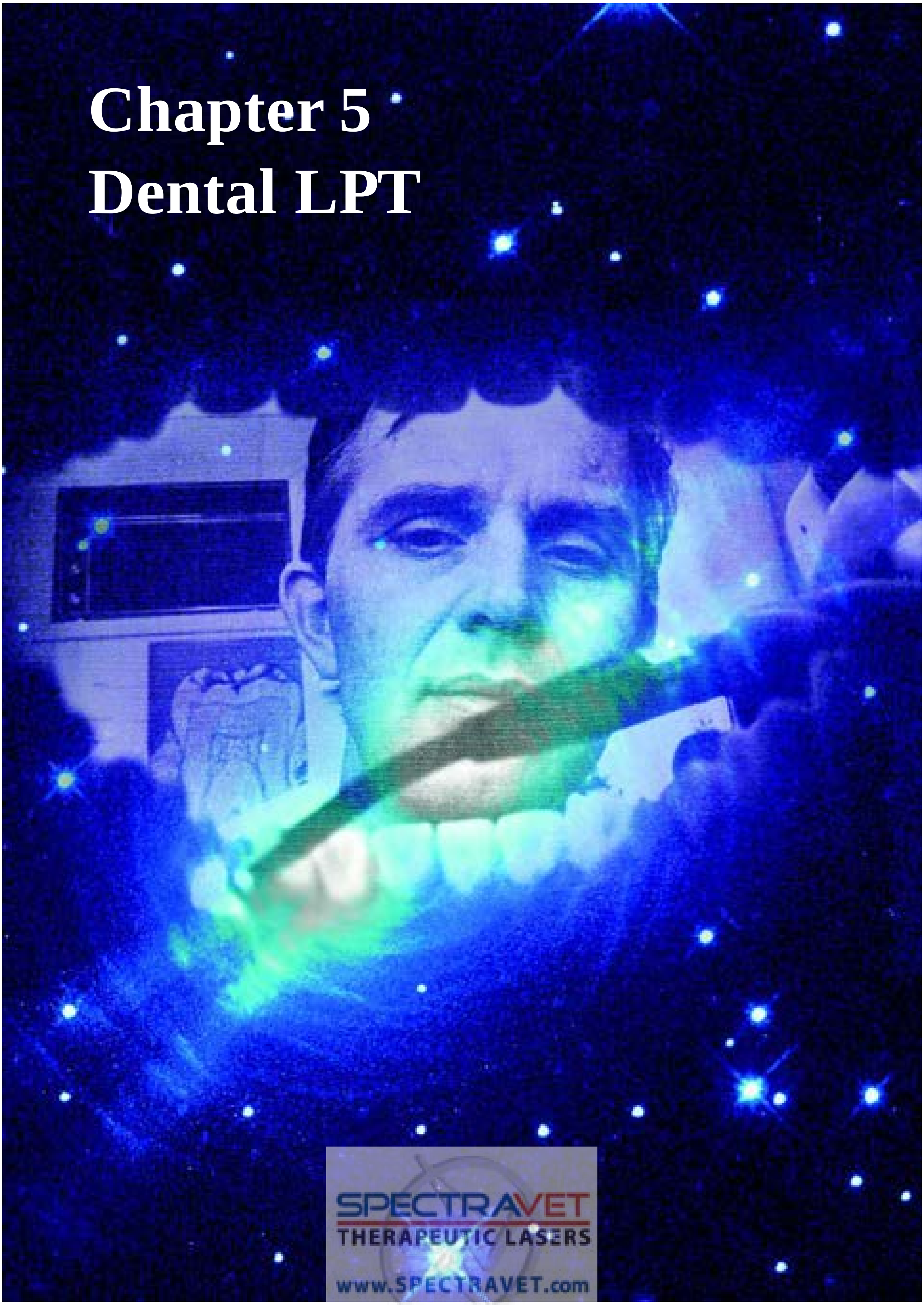
Irradiation of
gl. parotis

Irradiation of
gl. lingualis

Irradiation of
gl. submandibularis

Courtesy: Mikael Nylander

Chapter 5
Dental LPT



The therapeutic laser is just one of many modern tools which we can use in our everyday work. It is also a fairly new tool which relatively few dentists have acquired yet. But in the not too distant future we may come to see it as a natural part of our equipment, no more unusual than the curing light or the ultrasonic scaler.

Dentists often say that the use of LPT is so complicated and that they do not understand all the difficult terms and parameters involved. But if you take the courage of looking closer at these seemingly difficult matters, you (I hope) will find that there is not much to it that you did not already learn. The laser light has very unique properties, that is why it is so useful, but it is still "only" light. And we are already using light daily in our clinics - the curing light. So let us compare the two lights - the well-known curing light and the therapeutic laser, and see what we already know!

First we have the **wavelength**. The curing light is broad banded, whether from a light emitting diode (LED) or a filtered halogen lamp. The peak of this blue light is around 460 nanometres, where the optimal curing property of the camphorquinone is. Some filling materials need light peaks at slightly different wavelengths but they are all in the visible blue range. I am sure you already knew this, maybe not the exact wavelength peak, but that is not important in daily practice. So the curing light is blue, the beginning of the colour of the rainbow: blue, green, yellow and red. These are the colours that we can see and they are in the range of about 400-800 nanometres, after which the invisible infrared comes. The lasers commonly used in laser therapy are in the red and infrared spectrum, 650-904 nm.

Let us look at the **power** of our lights. The output of the curing lamp differs depending on its design: filtered halogen lamp or blue LED. But what comes out of the curing wand is not measured in watts like in the lamps used in your ceiling. The intensity is rather given in the specifications from the manufacturer, and it is expressed in mW per cm^2. OK, you remember that you used to have a curing lamp of "500" but upgraded to "1200" something. And yes, the upgrading was the milliwatts per square cm (mW/cm^2). This tells you exactly this: the number of mW irradiated over each square cm, measured at the opening of the wand. Maybe you own some sort of "turbo" probe to obtain faster cure? If so, it is a probe with a thinner aperture. The power (number of photons) stays the same but now they are forced into a smaller area and the intensity (mW/cm^2) increases. Just like we do with a magnifying glass where the rays from the sun are focused into a very small spot and the intensity of the pleasant sun suddenly can start a fire. The same goes for the lasers. If the probe opening is small, the power density is higher than if the probe has a larger diameter. This is an important aspect of laser therapy. The output of one laser may be high, but the intensity of the beam also depends upon the size of the "laser eye".

The curing **depth** of our curing devices is generally considered to be 2 mm for light shades. So if 10 seconds is fine for shade A2, you would probably irradiate for 20 seconds when using A4. The same is true for lasers: fat and mucosa are rather transparent, bone less transparent and muscles even less so. The main absorber of the light is the haemoglobin. The obvious fact that different materials have different penetration indices is obvious and we have to consider this when using lasers. We must think of dose at target, not just the dose. Because of the gradual loss of light intensity in the tissue, we must make a slight calculation, based upon the depth of our target. To give the same dose at target to the apex of a lower molar we must use a higher energy than for an upper lateral incisive.

Now back for a while to the wavelength. The wavelength of the curing light is set once and for all to fit the material that you are using. With lasers the wavelength is also fixed for each instrument, but there are different instruments with various wavelengths. Which wavelength is "best"? There is no such thing as an "optimal" wavelength, so now things become a bit more complex that the curing light. Red light is best for superficial tissues such as mucosa and skin. Teeth are very transparent, too. The penetration rate increases as the wavelength increases and around 800 nm we are very "transparent". So infrared lasers have a better ability to reach areas such as the IAN, maxillary sinuses and apices. But this does not mean that they are not useful for superficial tissues, only that they are not optimal and dosage has to be slightly adapted.

So we have reached "the hot spot" - **dosage**! With the curing light we count seconds and that is very convenient. We can do so because the materials we are using are very similar and have the same photoacceptors. With the laser we can also use seconds, but first we have to make a little calculation, because the "material" that we are irradiating differs from point to point: mucosa, bone, muscles etc. I will not bother you with the basics of such calculations. As with the curing light it is up to the manufacturer to supply you with a precise manual, indicating the number of joules given per each second of irradiation and the dose then applied per second, when the laser probe is held in contact with tissue. Such an easy-to-read manual should be part of any laser investment in your clinic. Anyway, the problem is to understand the difference between **"joule"** and **"dose"**. Joule (J) means energy. If the output of the laser is 50 mW and you irradiate for 10 seconds, the energy applied is 50 x 10 = 500 millijoules (mJ) = 0.5 J. A laser of 100 mW used for 5 seconds produces 100 x 5 = 500 mJ = 0.5 J. This calculation is easy. But joule is not the dose! The dose is the energy in joules, divided by the irradiated area. So if the energy is 4 J and the area is 1 cm^2 , we have 4/1 = 4 J/cm^2. But if the area is only 0.25 cm^2 , then the calculation is 4/0.25 = 16 J/cm^2! This is because the intensity increased; all those photons were added to a smaller area. This is a little complicated, admittedly. If you are going to perform a scientific study, these matters are very important. In the clinical situation, however, we can use the less exact term "energy per point". A "point" is then about 0.5 cm^2 and we only count the energy in joules added to that imaginary point. In your clinical records you can just add "J per point".

What about the mechanisms behind laser therapy? Well, I cannot say that they are easy to understand. But on the other hand, do you know the mechanisms behind composite curing, ultrasound and electrosurgery? If you do, congratulations, but as for myself I only have faint knowledge about these things but I find no problems in applying these techniques daily. A deeper understanding of the mechanisms behind everything we do is an advantage but not always necessary for having good results. Many dentists using therapeutic lasers started with a rather limited understanding of the mechanisms but along a successful road of therapies later on had a reborn interest in looking into these matters in detail.

5.1 The dental laser literature

In a 2004 survey of the dental LPT literature, performed by the authors, nearly 400 studies were found. Studies were classified as dental if the indication studied was dental or if the researcher was a dentist. The studies originated from more than 100 faculties in 38 countries. The number of studies was not very high and the quality varied. However, more than 90% of these studies reported positive effects, so it is still a good indicator for the efficacy of the therapy. A similar survey today would end up in considerably more studies, and studies of better quality. In recent years, about 350 LPT studies have been published on PubMed annually, whereas there were only 20 in the year 2000.

A literature search on Medline was performed by Carroll [2518] on laser and light treatments in a range of dental/orofacial applications from 2010 to March 2013. The search results were filtered for LPT relevance. The clinical papers were then arranged to eight broad dental/orofacial categories and reviewed. The initial search returned 2778 results, when filtered this was reduced to 153. 41 were review papers or editorials, 65 clinical and 47 laboratory studies. Of all the publications, 130 reported a positive effect in terms of pain relief, fast healing or other improvement in symptoms or appearance and 23 reported inconclusive or negative outcomes. Direct application of light as a therapeutic intervention within the oral cavity (rather than photodynamic therapies, which utilise photosensitizing solutions) has thus far received minimal attention. Data from the limited studies that have been performed which relate to the oral cavity indicate that LPT may be a reliable, safe and novel approach to treating a range of oral and dental disorders and in particular for those which there is an unmet clinical need. The potential benefits of LPT that have been demonstrated in many healthcare fields and include improved healing, reduced inflammation and pain control, which suggest considerable potential for its use in oral tissues.

5.2 On which patients can LPT be used?

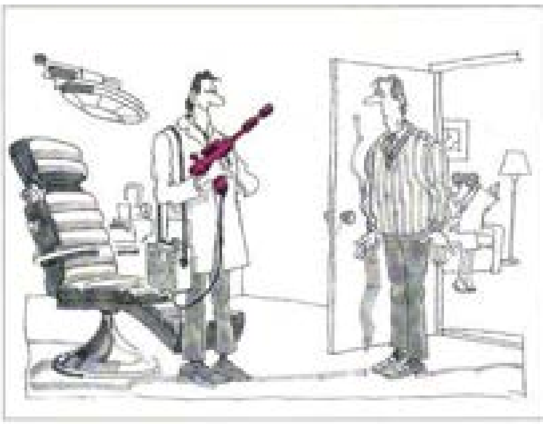
LPT can be used, with few exceptions, on all patients but we should remember that this form of treatment is no different from other forms of medical treatment. Not all patients react in the same way to LPT, and one patient may not always react the same way, depending on the condition of the tissue and immune system.

Let us look at anaesthetic injections by way of comparison. Some patients are thought to need double quantities of anaesthetic, while others need very little. In some cases, the effects disappear very quickly, in others they remain for an unusual length of time. Even a patient who normally finds it easy to be fully anaesthetised may suffer when the dentist treats his deep pulpitis - it may be that nothing helps.

In general terms, we can expect up to 80% of patients to respond positively to LPT. If a patient does not respond to treatment, bear in mind that the degree of success of the treatment is contingent on a number of parameters. A poor result can be due to too small a dosage, too great a dosage, incorrect diagnosis, too few treatment sessions, power density, etc. Remember: the more experienced the practitioner, the more success he or she will have with LPT.

Experience shows that practitioners use LPT not only on patients, but on themselves, on relatives, staff and on friends, and maybe even treat complaints outside their own domain. The next step could be that practitioners may even begin treating their patients for seemingly non-odontological problems, in which case they will appear to their patients as unusually skilled professionals, even if, by definition they are working outside their normal sphere of business. Experience also shows that many practitioners have too much respect for the new tool in the beginning. Remember that it is only light! Bearing the few relative contra indications and caveats in mind, a great new field is now opening up. Many dental conditions are not limited to the oral cavity and TMD certainly often extends way down to the trapezius. The upper trapezius and the neck would then be in the dental sphere.

In the following text, as well as in chapter 4, the indication of "dose" is sometimes joules, sometimes J/cm^2. This comes from the fact that we quote data from the literature, where sometimes energy (joules) and sometimes dose (J/cm^2) is indicated, not always both. This lack of full reporting of the laser parameters remains a problem. In the clinical setting the use of "joule per point" is a convenient method, although not completely accurate.



5.3 Dental indications

This chapter may seem like rather heavy reading, as it contains numerous short summaries of articles in different LPT fields. We prefer this structure, despite its drawbacks, as the aim of this book is not just to inform the dental profession about the uses of LPT but to show that there is a great deal more scientific documentation on the subject than most people realise.

The following is a body of information (in alphabetical order by subject) about a number of areas of use for LPT. The text is intended as a source of inspiration for the laser user, not a set of detailed treatment instructions. Several "dental" areas are to be found in chapter 4 as well as there is no defined boundary between medicine and dentistry.

The suggested dosages should be seen as average doses, and clinical judgment should always be the basis for dosage calculation. It should also be noted that most conditions require repeated treatment. This is often difficult from a practical point of view. The patient may not be motivated enough to visit every other or every third day, or the dentist may think it difficult to charge for such drawn-out treatment if assisting personnel is unable to administer it. In practice then, laser treatment often takes place in connection with the patient's ordinary appointments, in which case treatment is hardly ever optimised. "Home lasers" are available on the market and very useful as an adjunctive therapy. Once the dentist has made the diagnosis, made a laser application and found the response level of the patient, the patient can treat himself at home until the next dental session [2302].

In spite of the higher cost of the Nd:YAG and Er:YAG lasers, more dentists seem to be looking at these semi-surgical lasers rather than at the therapeutic lasers. It should be born in mind that all dental lasers have a biostimulative effect and can be adopted for biostimulation if the dosage is adjusted accordingly. The “surgical” diode lasers operating between 810-980 nm can be adjusted to reasonable biostimulators, although the thin fibre should not be used with these.

5.3.1 Alveolitis

LPT directly after extraction helps to prevent alveolitis. If alveolitis is already established, 4-5 J before and after the alveolus is debrided and plugged with medication is recommended. Irradiate the alveolus and the surrounding area directly. If the alveolitis is very painful, do not hesitate to use 15-20 J. The local lymph nodes can be irradiated at advantage [1531, 2303].

Literature:

A study by Hedner [43] has shown that 47% of patients with "dry socket" manifested a reaction of herpes simplex type 1 after the extraction of the third molar in the lower jaw. This raises an interesting hypothesis: does the alveolitis-preventive effect of LPT depend in part on the anti-viral effect of the laser?

The purpose of a study by Korany [2130] was to evaluate the effect of LPT in enhancing bone repair in irradiated sockets of albino rats. Thirty male Swiss Albino rats were used in this study. The animals were subjected 6 gray gamma radiations. Three days post irradiation, right and left mandibular first molars were extracted. The sockets of the left sides were irradiated by (GaAlAs) diode laser device immediately after extraction, while the sockets of the right side were not exposed to the laser and served as control. The rats were randomly assigned into three groups (10 rats each) according to the date of sacrifice, 3, 7 and 10 days into groups I, II and III, respectively. The two sides of each mandible were separated. Each group was further subdivided into subgroups A and B (10 specimens each), where A represents the right side of the mandible and B represents the left side. LPT accelerated bone healing, while, radiotherapy induced delay of bone healing along the three experimental groups. This acceleration was assessed histologically by the presence of mature collagen fibre bundles and early new bone formation in the lased groups. Histomorphometric analysis revealed an increase in the area percentage of bone trabeculae in the lased sockets compared to the control ones in group II. This increase was statistically significant. The increase in the area percentage of bone trabeculae between the lased and control sockets of group III was also statistically insignificant.

The aim of a randomised prospective clinical trial by Kaya [2435] was to compare the effects of alvogyl, the SaliCept patch, and LPT in the management of alveolar osteitis. The study population included 104 patients who had been referred to the clinic with complaints of alveolar osteitis. The patients were randomly assigned to 1 of 4 groups: group 1, curettage and irrigation alone; group 2, curettage and irrigation followed by alvogyl applied directly to the socket; group 3, curettage and irrigation followed by a

SaliCept patch applied directly to the socket; and group 4, curettage and irrigation followed by LPT (808 nm, 100 mW, 60 seconds, 6J, 7.64 J/cm^2). The treatment procedures were repeated after 3 days. The clinical signs and symptoms for each patient were recorded at diagnosis, at 3 days after the diagnosis, and at 7 days after the diagnosis. In addition, the pain intensity levels for each patient were recorded at diagnosis and daily for 7 days after the initial treatment. No statistically significant differences in the management of alveolar osteitis were observed between groups 2 and 3. However, the management of alveolar osteitis was significantly better in group 4 than in the other 3 groups.

Further literature: [106, 111, 116, 218, 544, 1943, 2027]

5.3.2 Anaesthetics

Some patients are difficult to anaesthetise. By administering 2-3 J over the apex, circulation is increased and the anaesthetic is more quickly absorbed. This also means, of course, that duration is reduced. The duration of the numbness in the lip after anaesthesia can therefore be reduced by LPT. This can be advantageous in pediatrics.

Teeth with a large volume of pulp can be successfully anaesthetised with a defocused surgical laser such as the argon, Nd:YAG and Er:YAG. Lasers with an output within the biostimulative power density range cannot give this full anaesthetic dosage but can still be used to raise the pain threshold. When treating caries in young teeth, the following method can be tested. The enamel should be drilled as usual - this does not usually present any problems as far as pain is concerned. The laser should then be applied into the cavity and 8-10 J administered. The pulp will not be anaesthetised but the pain threshold will be raised. The method can be used on co-operative patients. For pediatric restorative dentistry, 4-6 J at the gingival level and over the projection of the apex of the decidious tooth will very often be sufficient for pain-free drilling and filling.

An injection per se rarely causes complications, and the perforation of the mucous membrane is hardly noticed if thin 30 gauge hypodermic needles are used. 2-3 J over the injection area can further reduce the patient's awareness of the injection.

Unfortunately, we now and again hit a vessel with the needle, and in addition to the usual treatment with pressure and cooling, 6-8 J can reduce the oedema and the subsequent pain. Treatment is administered both extraorally and intraorally.

Intraligamental anaesthesia can lead to postoperative pain if the injection is given too rapidly. 3-4 J under the papilla reduces the pain. Prophylactic treatment before the anaesthesia wears off is recommended.

Literature:

Vélez-Gonzáles [105, 504] injected a salicylic solution subcutaneously in rats and compared absorption between irradiated and non-irradi-

ated animals. Using HeNe laser with doses ranging from 1.9-4.9 J/cm², absorption was found to increase in a dose-dependent fashion.

Tamachi [44] administered HeNe to rats that had been given experimental cancer. The uptake of the cytotoxin 5 FU in the cancer cells was higher in the group treated with a HeNe laser than in the group that received only 5 FU.

Omura [1047] discusses the problem of insufficient drug uptake in some patients. The situation can, in the author's experience, be improved by using several treatment modalities, such as acupuncture, electrical stimulation and LPT.

Yang Li [1135] has observed that animals in wound healing studies frequently have reacted with a negative response if anaesthetics such as ketamine and ether have been used. It is speculated that there is some reagent competing against laser for the same receptor in the fibroblast.

Koultchavenia [1442] found that transcutaneous IR laser increased the uptake of the anti-tuberculosis drug isoniasid in the kidney. The concentration was confirmed by surgical PAD in the concomitant surgery and was compared to a group not receiving laser preoperatively.

The study by Tanboga [2397] was carried out on 10 children aged 6 to 9 years old for a total of 20 primary molar teeth. For laser preparation an Er:YAG laser was used. Half of the preparations were treated by LPT before laser preparation and the remaining half without LPT (non-LPT) before laser preparation. All cavities were prepared by Er:YAG laser, restored with light-cured composite resin following the application of acid etching and bonding agent. Children were instructed to rate their pain on the Visual Analogue Scale from 0 to 5 points. VAS Median (min-max) scores were 1 (0-2) for LPT and 3 (1-4) for the non-LLT treated children. Between LPT and non-LPT groups results were statistically significant. The use of LPT before cavity preparation with laser decreased pain in paediatric dental patients.

5.3.3 Aphthae

Aphthous stomatitis (recurrent aphthous stomatitis, RAS) is a common cause of benign and non-contagious mouth ulcers (canker sores). This condition is characterised by the repeated formation of ulcers on the mucous membrane of the oral cavity (the lining of the mouth), in otherwise healthy individuals. These ulcers occur periodically and heal completely between attacks. Symptoms range from a minor nuisance to interfering with eating and drinking. The cause is not completely understood, but may involve a T cell mediated immune response which is triggered by a variety of factors. Different people may have different triggers, including nutritional deficiencies, local trauma, stress, hormonal influences, allergies, and a genetic predisposition. The condition is very common, affecting about 20% of the general population. There is no cure, and treatments are aimed at reducing pain and speeding the healing process.

Aphthae are not as easy to treat as herpes simplex. The symptoms of most patients can, however, be alleviated by laser treatment, and the healing period can be reduced. Carbon dioxide, Er:YAG and Nd:YAG lasers can also alleviate symptoms if a defocused beam is used. The dosage is determined by the patient's response to pain relief. When the patient feels a distinct reduction in pain, you are on the way to the "right" dosage. Several treatment sessions are often necessary to prevent any discomfort to the patient until the aphthae have disappeared. 4-6 J is a good “starting point”.

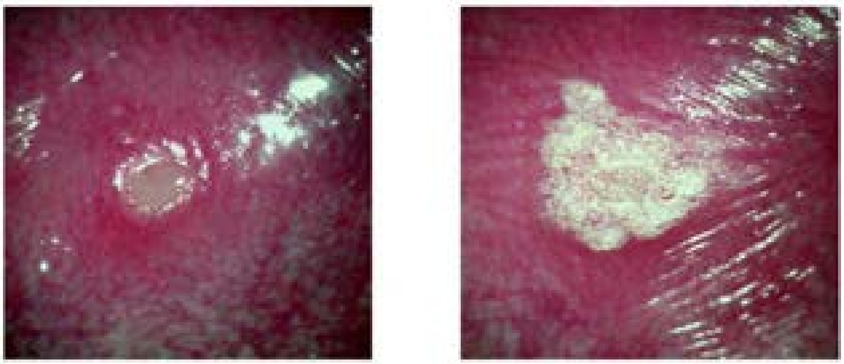


Figure 5.1 Aphthae treated with Er:YAG laser, before and immediately after irradiation.
Courtesy: Continuum Lasers

Literature:

Guang Hua Wang [64] demonstrated a pain-alleviating effect when a HeNe laser was used on aphthous ulcers. A 1% and a 10% KCl solution were applied to the aphthous ulcer, after which the SRT (Shortest Response Time) was measured. The procedure was repeated three times, after which the SRT was 100%, i.e. an immediate response. The trial group (25 people) was irradiated with a HeNe laser immediately after the third application of KCl solution. The SRT increased markedly in the trial group but not in the control group. The application was repeated every five minutes for 45 minutes. The laser output was 25 mW, and the treatment time was ten seconds.

Manne [222] treated 12 cases of aphthae with a GaAs laser. In 11 cases the aphthae disappeared three days after a single treatment session, and in the last case five days after two sessions.

Fagnoni [486] treated 32 aphthae cases with a HeNe laser, 300 mJ/cm^2. Approximately 22% of the lesions healed within one day, 41% in two days and 31% in three days.

Takashi [238] reports the positive effect on aphthae using a HeNe laser.

Guerra [1420] used a 20 mW GaAlAs laser to treat apthae. In this observed blind and randomised study the laser group received 1.8 J altering *days acc. to the evolution of the aphthae. The control group received Lidocaine 2% gel, analgesics and alimentary counseling. Cases were classified acc. to size and the two groups were almost identical in this respect. Total scarring within different time frames was as follows, with control group within brackets: <48 hrs 17(0), 48 hrs-4 days 8(0), 5-7 days 1 (21), >7 days 0 (5). One ulcer of the large type healed with laser within 4 days and another within 5 days while one case of herpetifom ulcer healed only after 7 days.*

In an extended study by Sánchez [2255], 208 consecutively received patients were divided into either study group or control group. The laser used had a wavelength of 670 nm, output power 40 mW. Each ulcer received 40 seconds of irradiation, 1.6 J, 2.04 J/cm^2, 51 mW/cm^2, spot size 0.79 cm^2 and irradiation from a distance of about 0.5 cm. All patients were controlled daily, and if not fully healed, the patients in the LPT group received another irradiation on the third day. The time for wound closure was chosen as the end point of observation. In the study group, 68 small lesions healed within 48 hours and the remaining 24 healed within 48 hours to 4 days, except for 4 cases of herpetiform wounds, which healed within 7 days. In the control group no ulcer healed within 4 days; 82 ulcers healed after 5 to 7 days. The distribution of aphthous stomatitis in the different age groups was found to be in accordance with previous reports in the literature.

Tezel [2129] reports fair results using Nd:YAG.

The study by Fekrazad [1568] was performed as a clinical trial on 138 patients with aphthous ulcers. The patients were randomly assigned into three groups, as follows: (1) treatment with a focalised beam; (2) treatment with a non-focalised beam and (3) placebo treatment. The specifications of the laser treatment were as follows: Nd:YAG laser, power 3 W, energy 100 mJ, pulse repetition rate 30 Hz, time 60 sec. A HeNe laser was used for marking the beam of the Nd:YAG area (power 5 mW). In group (1) the laser beam was administered from a distance of 6 mm from the centre of the ulcer and up to 1 mm of its outer border without using a clear and defined point of irradiation. In group (2) a well-defined point beam of the laser was irradiated from a distance of 2 mm from the centre of the ulcer, in a helical fashion and covering up to 1 mm of the ulcer's outer border. In group (3) the HeNe laser was used as placebo at a long distance and not covering the aphthe itself, while the Nd:YAG laser beam was off. In group (1) and (2) a significant reduction in pain was observed compared to group (3). The duration of pain and the duration of the recovery period were shortest in group (2).

A prospective clinical study was performed by Prasad [2254], using defocused CO_2 laser on 25 patients with minor recurrent aphthous stomatitis. Pre-treatment pain levels were recorded using a numerical rating scale. Ulcers were randomised to either receive treatment or placebo. Pain levels were assessed immediately after treatment and after 24 h. Healing was assessed on days 3 and 4, and once every 2 days thereafter for 2 weeks. Mean pain scores in the laser group were significantly reduced immediately after treatment compared with pre-treatment. In contrast, the placebo group *showed little difference in pain scores between pre-treatment and immediately after treatment. In the laser group, significant improvements in healing times were observed.*

A total of 30 patients who presented with two separate aphthous ulcers were included in the study by Aggarwal [2513]. Each lesion was randomly allotted to either the active treatment group or the sham control group. Lesions which were included in the active group were treated with LPT in a single sitting, which was divided into four sessions. Lesions in the sham control group were subjected to similar treatment without activating the laser unit. Each patient was evaluated for pain, lesion size, and complete healing at the following intervals: immediately post LPT and one day, two days, and three days follow up. Complete resolution of the ulcers in the active group was 3.05 ± 1.10 days as compared to 8.90 ± 2.45 days in the sham control group. Immediately, post the LPT application, complete pain relief was observed in 28 of the 30 patients of the active group.

The aim of the study Albrektsson [2516] was to determine whether LPT has an analgesic effect in patients with recurrent aphthous stomatitis (RAS). A randomised single-blinded placebo-controlled trial was conducted with LPT (wavelength, 809 nm; power, 60 mW; pulse frequency, 1800 Hz; duration, 80 seconds per treatment; dose, 6.3 J/cm^2 in 40 patients with RAS. The intervention group was treated with LPT on 3 occasions, with a 1-day interval. The control group was treated similarly, without any laser power. Pain perception (Visual Analogue Scale rating) and patients' experience of eating, drinking, and brushing teeth was registered. VAS rating decreased (day 0 until day 2) from 84.7 to 31.5 (LPT) and from 81.7 to 76.1 (placebo). LPT also relieved the difficulty of drinking, eating, and brushing teeth. LPT reduced the pain and the inconvenience of eating, drinking, and brushing teeth for patients with RAS, compared with placebo.

Anand [2357] reports on two cases of RAS successfully treated withn 940 nm laser.

Zand [2128] reports good result when treating aphthae with a CO_2 laser, irradiating through a transparent gel.

As with HSV-1, it appears that laser treatment of RAS is not wavelength sensitive.

Further literature: [56, 525, 531, 623, 635, 1036, 2127, 2256, 2281]

5.3.4 Bleeding

A laser is useful in the treatment of postoperative bleeding. Although the mechanism behind this is unclear, the literature shows that LPT brings about an initial vasoconstriction, but that it is followed by a vasodilatation [44, 121, 152, 479, 630]. Logically speaking, this should lead to increased bleeding, but clinical experience shows the opposite, which is why other mechanisms must be involved. HeNe laser or InGaAlP radiation is absorbed better in haemoglobin than GaAlAs and GaAs and thus seems most suitable. The low power of most HeNe lasers is an obstacle, however. 3-4 J is administered in and around each alveolus directly after the extraction. GaAlAs has been shown to counteract the appearance of fibrin networks [96], which could be one reason why HeNe and InGaAlP laser have a better effect on this indication.

Patients on Warfarin and similar pharmaceuticals are not a contraindication for the use of LPT. However, patients with hereditary coagulation disorders should be a caveat, due to limited knowledge.

Figure 5.2 a) directly after extraction; b) after 3 minutes of HeNe irradiation; c) the following day. Courtesy: Talat Qadri

Literature:

Brill [1083] suggests that HeNe laser irradiation inhibits platelet activation and aggregation through the involvement of intracellular secondary messengers – cGMP and/or NO.

Fine [305] studied the effect of ruby and Nd:YAG laser on the bleeding of heparinised mice.The tails of the animals were cut and the effect of laser irradiation on the bleeding was monitored. The bleeding stopped after a period between 10 seconds to 5 minutes in mice irradiated at 60 J, focused on a spot of 3-8 mm in diameter. The animals in the control group were exsanguinated.

Trelles [262] reports that vasodilatation of both arterioles and venules is one of the biological effects characterising the action of LPT on tissue. Vasodilatation does not occur immediately but a few minutes after irradiation and then continues even if the affected tissue is cooled.

Kubota [479] used the laser speckle method to measure the microcirculation in flaps. The blood flow rate was reduced immediately following one-minute irradiation with 830 nm. 30 minutes later the flap perfusion was greater than in the control flap.

Juri [505] summarises a rodent study as follows: It is concluded that HeNe laser radiation blocks the usual increment of plasma fibrinogen level after tissue injury, probably by interfering with the interaction of PGE1 + Bradykinin.

Iakovleva [834] studied the effect of HeNe laser exposure, power 1 mW, at the tip of the light-guide, on the blood anticoagulant system in narco-

tised mongrel dogs during the postresuscitation period after 4-min clinical death from massive blood loss. The anticoagulant system of the blood plasma was depleted during the reanimation period (the activities of plasmin and fibrinogen-heparin complexes and the level of heparin dropped). Intravascular laser exposure of the blood (for 30 min. during blood loss after drop of the mean arterial pressure to 40 mm Hg and at the beginning of the second hour of the postreanimation period) boosted the activities of plasmin and fibrinogen-heparin complexes but failed to increase the level of heparin in the postreanimation period.

Further literature: [106, 1448, 2130]

5.3.5 Bisphosphonate Related Osteonecrosis of the Jaw

Bisphosphonates have been introduced to treat osteoporosis. These substances can be administered orally or intravenously. The bisphosphonates have a high affinity to hydroxyapatite and are accumulated in bony structures. During bone remodelling, osteoclasts are exposed to large concentrations of bisphosphonates with consequent apoptosis of the osteoclasts. An uncommon but problematic side effect of bisphosphonates is local necrosis of the bone, particularly in the mandible. This is called Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ). However, other substances such as denosumab can cause bone necrosis and a more appropriate term would therefore be Osteonecrosis of the Jaw (ONJ).

Patients affected by BRONJ may present areas of exposed necrotic bone, particularly after surgical oral procedures. The main symptom is pain that is poorly controlled by common analgesic drugs. Different lasers have been used to treat ONJ and seem to have a potential for this condition.

Literature:

In vitro studies

The purpose of a study by Bayram [2181] was to investigate the effects of LPT on cell proliferation and alkaline phosphatase (ALP) activity of human osteoblast-like cells (Saos-2) treated with different doses of zoledronate, the most potent bisphosphonate. Saos-2 cells were treated with different concentrations of zoledronate and were irradiated with diode laser (808 nm, 10 s, 0.25 or 0.50 W). Cell numbers and ALP activity of the cells were determined. LPT mildly increased the proliferation rate or ALP activity, while zoledronate reduced both. When applied together, LPT lessened the detrimental effects of zoledronate and improved cell function and/or proliferation. Based on the results of this study, it was concluded that LPT has biostimulative effects on Saos-2 cells, even after treatment with zoledronate. LPT may serve as a useful supportive method for BRONJ treatment through enhancement of healing by osteoblasts

Animal studies

The purpose of a study by Diniz [2187] was to verify the effect of laser therapy in combination with bisphosphonate on osteopenic bone structure. The 35 Wistar female rats used were divided into five groups: (1) sham-operation rats (control), (2) ovariectomised (OVX'd) rats with osteopenia, (3) OVX'd rats with osteopenia treated with laser, (4) OVX'd rats with osteopenia treated with bisphosphonate and (5) OVX'd rats with osteopenia treated with bisphosphonate and laser. Groups 3 and 5 were given daily 6 mg doses of bisphosphonate orally. Groups 4 and 5 underwent low level laser therapy, 830 nm, 50 mW and 4 J/cm^2, on the femoral neck and vertebral segments (T13-L2). Both treatments were performed over an 8-week period. Rats from the osteopenic control and osteopenic + laser groups presented marked osteopenia. In the osteopenic + bisphosphonate group, the trabecular bone volume in vertebra L2 was significantly greater than in the osteopenic control group. Notably, in the association between laser and bisphosphonate, the trabecular bone volume was significantly greater in vertebrae L2 and T13 and was similar to that in the sham-operation control group. It was concluded that the laser therapy associated with bisphosphonate treatment was the best method for reversing vertebral osteopenia caused by the ovariectomy.

The purpose of a study by Garcia [2183] was to analyse histologically the effect of LPT in combination with bisphosphonate on bone healing in surgically created critical size defects (CSD) in rat calvaria. One hundred Wistar female rats sham operated (sham) and ovariectomised (Ovx) were maintained untreated for 1 month to allow for the development of osteopenia in the Ovx animals. A CSD was made in the calvarium of each rat, and the animals were divided into five groups according to following treatments: (1) sham rats (control), (2) Ovx rats, (3) Ovx rats treated with LPT, (4) Ovx rats treated with bisphosphonate, and (5) Ovx rats treated with bisphosphonate and LPT. Groups 4 and 5 were irrigated with 1 ml of bisphosphonate, and groups 3 and 5 were submitted to 660 nm, 24 J, and 0.4285 W/cm^2 on the CSD. Ten animals of each treatment were killed at 30 and 60 days. Histomorphometric assessments, using image analysis software, and histological analyses were performed. No defect was completely regenerated with the bone. Histometrically, it can be observed that groups 3 and 5 showed a significant bone neoformation when compared to groups 1 2 and 4 in all experimental periods. It was possible to conclude that the LPT associated or not with bisphosphonate treatment was effective for stimulating bone formation in CSD in the calvaria of rats submitted to ovariectomy.

Clinical studies

The aim of a study by Martins [2142] was to compare retrospectively the effect of three different treatments on the healing outcome of BRONJ in cancer patients. Twenty-two cancer patients were treated for BRONJ with one of the following protocols: clinical (pharmacological therapy), surgical (pharmacological plus surgical therapy), or PRP plus LPT (pharmacologi-

cal plus surgical plus platelet rich plasma (PRP) plus LPT. The laser treatment was applied with a continuous 660 nm laser, using punctual and contact mode, 40 mW, spot size 0.042 cm^2, 6 J/cm^2, 6 s and total energy of 0.24 J per point. The irradiations were performed on the exposed bone and surrounding soft tissue. The analysis of demographic data and risk factors was performed by gathering the following information: age, gender, primary tumor, bisphosphonate (BP) used, duration of BP intake, history of chemotherapy, use of steroids, and medical history of diabetes. Most BRONJ lesions occurred in the mandible (77%) after tooth extraction (55%) and in women (72%). A significantly higher percentage of patients reached the current state of BRONJ without bone exposure (86%) in the PPR plus LPT group than in the pharmacological (0%) and surgical (40%) groups after 1-month follow-up assessment. These results suggest that the association of pharmacological therapy and surgical therapy with PRP plus LPT significantly improves BRONJ healing in oncologic patients.

Kan [2143] presents the successful management of two dental patients who had high potentials for BRONJ development as a result of chemo and radiotherapy combined with IV zoledronic acid application. Multiple consecutive teeth extractions followed with primary wound closure and LPT applications were performed under high doses of antibiotics prophylaxis. Satisfactory wound healing in both the surrounding soft and hard tissues was achieved. LPT application combined with atraumatic surgical interventions under antibiotics prophylaxis is a preferable approach in patients with a risk of BRONJ development, according to the authors. Adjunctive effect of LPT in addition to careful infection control on preventing BRONJ was reported and concluded.

Twelve patients affected by BRONJ were monitored in a study by Romeo [2144]. Among these patients, only seven had pain in necrotic areas and were recruited for LPT. Laser applications were performed with double diode laser simultaneously emitting at two different wavelengths (650 nm and 904-910 nm, spot size 8 mm). All of the patients were irradiated with a fluence of 0.053 J/cm^2 for 15 min five times over a period of 2 weeks, in a non-contact mode, 1 mm from the pathologic area. The patient's maximum and minimum pain was recorded using a numeric rating scale (NRS) evaluation before and after the treatment. Six patients showed significant pain reduction, and only one patient indicated a worsening of the symptoms, which was probably related to a reinfection of the BRONJ site, which occurred during the study. A statistically significant difference was found between the NRS rates before and after the protocol.

One hundred ninety patients affected by BRONJ were observed by Vescovi [2145] between January 2004 and November 2011 and 166 treated sites were subdivided in five groups on the basis of the therapeutical approach (medical or surgical, traditional or laser-assisted approach, with or without LPT. Clinical success has been defined for each treatment performed as clinical improvement or complete mucosal healing. Combination of antibiotic *therapy, conservative surgery performed with Er:YAG laser and LPT applications showed best results for cancer and non-cancer patients. Non-surgical approach performed on 69 sites induced an improvement in 35 sites (50.7%) and the complete healing in 19 sites (27.5%), while surgical approach on 97 sites induced an improvement in 84 sites (86.6%) and the complete healing in 78 sites (80.41%). Improvement and healing were recorded in 31 (81.5%) and 27 (71.5%) out of the 38 BRONJ sites treated in non-cancer patients and in 88 (68.75%) and in 69 (53.9%).*

The aim of a retrospective study by Atalay [2180] was to compare the effects of laser surgery with biostimulation to conventional surgery in the treatment of BSP-induced avascular bone necrosis on 20 patients who have been treated in our clinic. BRONJ was evaluated in patients with lung, prostate, and breast cancer under intravenous BSP treatment. Twenty patients in this study developed mandibular or maxillary avascular necrosis after a minor tooth extraction surgery or spontaneously. Bone turnover rates were evaluated by serum terminal C-telopeptide levels (CTX) using the electrochemiluminescence immunoassay technique and patients were treated with laser or conventional surgical treatments and medical therapy. Ten patients were treated with laser surgery and biostimulation. An Er:YAG laser, very long pulse (VLP) mode (200 mJ, 20 Hz) using a fiber tip 1.3 mm in diameter and 12 mm in length was used to remove the necrotic and granulation tissues from the area of avascular necrosis. Biostimulation was applied postoperatively using an Nd:YAG laser. LPT was applied to the tissues for 1 min from 4 cm distance using an Nd:YAG laser with a R24 950-µm fiber handpiece long-pulse (LP) mode, 0.25-W, 10 Hz power/cm^2 from the mentioned distance the spot size was 0.4 cm^2, and power output was 2.5 J. Energy density from the mentioned distance was calculated to be 6.25 J/cm^2. The other ten patients were treated with conventional surgery. Treatment outcomes were noted as either complete healing or incomplete healing. There were no statistically significant differences between laser surgery and conventional surgery. CTX values also did not affect the prognosis of the patients. Treatment outcomes were significantly better in patients with stage II osteonecrosis than in patients with stage I osteonecrosis. These findings suggest that dental evaluation of the patients prior to medication is an important factor in the prevention of BRONJ. Laser surgery is a beneficial alternative in the treatment of patients with this situation.

One hundred and twenty-eight patients (33 males, 95 females; 52 with diagnosis of multiple myeloma, 53 with diagnosis of bone metastasis, and 23 with diagnosis of osteoporosis) affected by BRONJ were evaluated by Vescovi [2182] between January 2004 and July 2009. Overall number of BRONJ sites was 151, and number of treated sites was 101. In order to assess the efficacy of different treatments, sites were subclassified as follows: Group 1 (G1): 12 sites treated with medical therapy; Group 2 (G2): 27 sites treated with medical therapy associated with low level laser therapy (LPT); Group 3 (G3): 17 sites treated with a combination of medical and surgical *therapy; Group 4 (G4): 45 sites treated with a combination of medical therapy, surgical (including laser-assisted) therapy, and LPT. Outcome of treatment was assessed using the staging system proposed by Ruggiero et al. Transition from a higher stage to a lower one for at least 6 months was considered as clinical improvement and suggestive of a successful treatment. Clinical improvement was achieved in 3 out of 12 (25%) BRONJ sites in G1. Sites if G2 with an improvement were 18 out of 27 (66%). Nine out 17 BRONJ sites (53%) in G3 had a transition to a lower stage after treatment. For sites in G4, a clinical improvement was recorded in 40 out of 45 cases (89%). In the experience of the research group, the percentage of success obtained with a combined approach based on medical therapy, surgical (including laser-assisted) therapy, and LPT (G4) is significantly higher than the percentage of improvement obtained in G1, G2, and G3.*

de Guarda [2184] reports about an 82-year-old man taking intravenous bisphosphonate presented with ONJ-BP after tooth extraction. The patient was treated by LPT using 860 nm; 70 mW; spot size 4 mm2. An energy density of 4.2 J/cm^2 per point was applied in a punctual contact manner every 48 h for 10 days, in association with antibiotic therapy and curettage of the necrotic bone. Reduction in painful symptoms was reported after the second irradiation session, and tissue healing was complete at the end of the third week following oral curettage. The patient was followed up for 12 months and exhibited good oral health and quality of life.

Scoletta [2185] studied a prospective cohort of 20 patients affected by ONJ-BP, who received biostimulation with a GaAs laser. Patients were exposed to a 904 nm infrared laser (50 kHz, 28.4 J/cm^2 energy density, 40% duty cycle, spot size 0.8 cm). Outcome variables were the size of lesions, oedema, visual analogue score of pain, presence of pus, fistulas, and halitosis. Preoperative results were compared with the postoperative outcome and statistically evaluated. Four weeks after LPT, a statistically significant difference was observed for reported pain clinical size oedema and presence of pus and fistulas.

Vescovi [2186] describes preliminary results with 19 patients affected by bisphosphonate-associated osteonecrosis of the jaws who were treated conventionally with surgical or medical treatment alone or in combination with Nd:YAG laser. Clinical variables such as symptoms, presence of pus, and closure of mucosal flaps before and after treatment were evaluated to establish the effect of the laser irradiation. Researchers treated nine patients with LPT with or without surgical treatment, and in this group there were eight clinical successes and one symptomatic improvement, with a clinical finding better than ones without laser biostimulation (ten patients, five clinical successes, and one symptomatic improvement).

5.3.6 Caries

Every operation on the hard tissue of teeth involves trauma for the dental pulp. It is subjected to thermal variations, vibrations and then chemical influence from insulating and filling materials. The normally very short-term symptoms a patient experiences after an operation involving the hard tissue can be eliminated by administering 1-2 J per root and 2 J into the cavity, after the operation. 1-2 J can also be given over the papilla to eliminate postoperative irritation from wedging. This kind of prophylactic operation may seem trivial to the dentist - perhaps we ourselves should sit a little more often in the dentist's chair in order to feel more motivated to treat this "insignificant" discomfort that we cause.

Hyperaemia after composite fillings and the cementation of ceramic inserts is an all too common problem. In most cases, the problem is of a transitory nature, but who wants a hyperaemic tooth for several weeks? The majority of these problems can be avoided if the tooth is given 2-3 J per root immediately after filling/cementation. A number of telephone calls are also avoided. More serious hyperaemia should be treated repeatedly, but this is clearly preferable to root treatment on a tooth that was problem-free before we started to treat it!

Several studies have shown that CO_2 and various YAG lasers have the ability to decrease the solubility of enamel. Hsu [838] has shown that even rather low intensities of CO_2 laser (85-170 J/cm^2) can induce this effect and that it is dramatically increased in the presence of fluoride. The interesting question is - how low intensities are necessary? Early Russian studies indicate that HeNe laser in combination with a fluoride varnish will decrease the decay. Later studies in the USA and South Africa seem to confirm these findings.

Figure 5.3 Pulp recation after drilling in rat molars with and without LPT. Courtesy: Aldo Brugnera Jr.

Literature:

In vitro studies

Hicks [837] evaluated the effect of combining low level argon laser treatment and acidulated phosphate fluoride treatment on caries initiation and progression in human root surfaces. The combination of laser and fluoride treatment increased the caries resistance of root surfaces when compared with no treatment and with laser irradiation treatment alone.

Therapeutic laser light doses also seem to have a positive effect on the bonding mechanisms between dental substances and composite bonding materials, according to Kunin [1103].

The enhancement of the fluoride effect when using LPT has also been noted by Liu [1104].

van Rensburg [836] used a GaAlAs laser with an energy of 5.45 J (30 mW for 180 seconds) and an energy density of 27.54 J/cm² to irradiate two fluoride containing orthodontic bonding materials. SEM evaluation showed that the laser irradiation had no superficial physical ultrastructural effects on either of the two materials. However, the fluoride release of one material could be enhanced for up to seven months by a sole application of laser. Fluoride release from the other material was also increased but was not statistically significant.

Okamoto [841] has demonstrated that cariogenic bacterias are sensitive to HeNe laser light, but only in the presence of various dyes, mainly phenylmethane dyes. There was a dose dependent suppressive effect on the bacteria and it is suggested that HeNe laser may be suitable for clinical applications in preventive dentistry.

A study by Ferreira [1882] investigated the biomodulatory effect of the 670 nm laser in pulp cells on reactional dentinogenesis, and on the expression of collagen type III (Col III), tenascin (TN), and fibronectin (FN) in irradiated dental tissues and controls (not irradiated). Sixteen human premolar teeth were selected (after extraction due to orthodontal reasons) and divided into irradiated and control groups. Black class V cavity preparations were accomplished in both groups. For the irradiated group, laser (670 nm, 50 mW) with an energy density of 4 J/cm² was used. Soon after, the cavities were restored with a glass ionomer and the extractions made after 14 and 42 days. Histological changes were observed by light microscopy; less intense inflammatory reaction in the irradiated group was found when compared to the controls. Only the irradiated group of 42 days exhibited an area associated with reactional dentinogenesis. After immunohistochemical analysis, the expression of Col III, TN, and FN was greater in the irradiated groups. : These results suggest that a laser with energy density of 4 J/cm² and wavelength of 670 nm causes biomodulation in pulp cells and expression of collagen, but not collagen of the extracellular matrix, after preparation of a cavity.

Nammour [2131] reports that the use of argon laser at low energy density (10.74 J/cm²) significantly increased the fluoride retention in lased enamel that had approximately 400 times more fluoride than the unlased enamel.

The study by Oliveira [2406] evaluated the transdentinal effects of different LPT doses on stressed odontoblast-like pulp cells seeded onto the pulpal side of dentin discs obtained from human third molars. The discs were placed in devices simulating in vitro pulp chambers and the whole set was placed in 24-well plates containing plain culture medium (DMEM). After 24 *h incubation, the culture medium was replaced by fresh DMEM supplemented with either 5% (simulating a nutritional stress condition) or 10% fetal bovine serum (FBS). The cells were irradiated with doses of 15 and 25 J/cm² every 24 h, totalling three applications over three consecutive days. The cells in the control groups were removed from the incubator for the same times as used in their respective experimental groups for irradiation, though without activating the laser source (sham irradiation). After 72 h of the last active or sham irradiation, the cells were evaluated with respect to succinic dehydrogenase (SDH) enzyme production (MTT assay), total protein (TP) expression, alkaline phosphatase (ALP) synthesis, reverse transcriptase polymerase chain reaction (RT-PCR) for collagen type 1 (Col-I) and ALP, and morphology (SEM). For both tests, significantly higher values were obtained for the 25 J/cm² dose. Regarding SDH production, supplementation of the culture medium with 5% FBS provided better results. For TP and ALP expression, the 25 J/cm² presented higher values, especially for the 5% FBS concentration. Under the tested conditions, near infrared laser irradiation at 25 J/cm² caused transdentinal biostimulation of odontoblast-like cells.*

Animal studies

Iwase [77] studied plaque build-up in 20 hamsters fed on a sucrose-rich diet. One molar in each of the animals was given HeNe laser treatment for two minutes, five times a week, for five weeks. Prior to this, plaque had been allowed to build up freely for four weeks. After a total of eight weeks, the amount of plaque around the treated tooth was measured and compared with the amount of plaque on the contralateral tooth. In 19 of the 20 cases, there was a smaller amount of plaque on the treated tooth, and in the last case a greater amount.

In a study by Müller [1847] dental caries were induced in molars of 40 rats divided into five groups: control group (CG), the teeth were not submitted to any treatment; laser group (LG), teeth were irradiated with a red laser, power of 30 mW and dose of 5 J/cm²; fluoride group (FG), teeth were treated with topical acidulated phosphate fluoride (APF) 1.23% applied for 4 min; laser + fluoride group (LFG), teeth were irradiated with LPRL followed by APF; fluoride + laser group (FLG), teeth were treated with APF followed by LPRL. The animals were killed after 48 days, and the first and second molars were extracted to analyse the caries lesion area, microhardness, and calcium and phosphorus ratio. There were no statistical differences among FG, LFG, and FLG regarding to caries area and microhardness, although the caries area were smaller in LFG. Ca/P ratio did not show significant differences among all groups. Although laser irradiation before APF application appeared to diminish the caries progression, laser irradiation did not present any additional benefit compared with acidulated phosphate fluoride on the prevention of induced-dental caries in rats.

Arany [2517] showed that LPT can be used as a minimally invasive tool to activate an endogenous latent growth factor complex, transforming *growth factor-beta1 (TGF-beta1) that subsequently differentiates host stem cells to promote tissue regeneration. LPL treatment induced reactive oxygen species (ROS) in a dose-dependent manner, which, in turn, activated latent TGF-beta1 (LTGF-beta1) via a specific methionine residue (at position 253 on LAP). Laser-activated TGF-beta1 was capable of differentiating human dental stem cells in vitro. Further, an in vivo pulp capping model in rat teeth demonstrated significant increase in dentin regeneration after LPL treatment. These in vivo effects were abrogated in TGF-beta receptor II (TGF-betaRII) conditional knockout mice or when wild-type mice were given a TGF-betaRI inhibitor. These findings indicate a pivotal role for TGF-beta in mediating LPL-induced dental tissue regeneration. More broadly, this work outlines a mechanistic basis for harnessing resident stem cells with a light-activated endogenous cue for clinical regenerative applications.*

Clincal studies

Kazmina [410] investigated the caries-preventive action of a HeNe laser. 350 children and 50 adults were divided into three groups. All groups were treated conventionally to restore oral health. Normal preventive measures were taken. The first group received no further treatment and the second group received additional treatment with a fluoride lacquer, three sessions, repeated twice a year. The third group had the same treatment as group two but had additional treatment with a HeNe laser twice a year. The laser employed had a power output of 17 mW (from a tube) and a bundle diameter of 5 mm and was thus able to irradiate the entire tooth. Each tooth was irradiated for one minute per session. At the four-year control the CFE index was used (Caries-Filling-Extraction). The index for the untreated group one was 1.0, indicating one new carious lesion per patient. The fluoride lacquer group had an index of 0.29 and the lacquer/LPT group had an index of 0.02.

Kunin [625] used a HeNe or GaAs laser in combination with fluoride lacquers. Percentual reduction in enamel solution rate was studied in four groups. Group 1 received fluoride varnish only, group 2 semiconductor laser treatment only, group 3 HeNe and varnish, group 4 semiconductor laser and varnish. The reductions were 12.7, 19.5, 27.2 and 23.8 respectively.

Two female volunteers with 8 premolars indicated for extraction for orthodontic reasons were recruited in the study by Godoy [1781]. Class I cavities were prepared and the teeth were randomly divided into two groups. The first group received treatment with a GaA1As laser, 660nm, 30mW and energy dose of 2J/cm^2, directly and perpendicularly into the cavity in a single visit. After the irradiation, the cavities were filled with composite resin. The second group received the same treatment, except by the LPT. 28 days post-preparation, the teeth were extracted and processed for transmission electron microscopy analysis. Two sound teeth, without cavity preparation, were also studied. The irradiated group presented odontoblast process and all posterior occurrences of odontoblastic to odontoblast in higher contact with *the extracellular matrix and the collagen fibrils and all posterior occurrences of fibres to fibrils appeared more aggregated and organised than those of the control group. These results were also observed in the healthy teeth. These findings suggest that laser irradiation accelerates the recovery of the dental structures involved in the cavity preparation at the predentine region.*

The study by Moosavi [2517] aimed to investigate the efficacy of low-level laser irradiation when applied just before placement of resin composite on reducing postoperative sensitivity of class V lesions. In this randomised clinical trial, 31 patients with 62 class V cavities were included (two teeth in each participant). The teeth were randomly assigned into laser and placebo groups. After cavity preparation, the teeth in the experimental group were subjected to irradiation from 630 nm, 28 mW, continuous wave, 60 s, 1.68 J, which was applied for 1 min on the axial wall of the cavity. In the control group, the same procedure was performed but with laser simulation. Then, a self-etch adhesive was applied and the cavities were restored with a microhybrid resin composite. Before treatment and on days 1, 14, and 30 after treatment, tooth sensitivity to a cold stimulus was recorded using a Visual Analogue Scale. Although both groups experienced a significant improvement in pain and discomfort throughout the follow-up periods, the changes in Visual Analogue Scale (VAS) scores between baseline and each follow-up examination were significantly greater in the laser than the placebo group. LPT before placement of resin composite could be suggested as a suitable approach to reduce postoperative sensitivity in class V restorations.

Further literature: [842, 1510, 1785]

5.3.7 Dentitio dificilis (pericoronitis)

Pericoronitis is inflammation of the soft tissues surrounding the crown of a partially erupted tooth, including the gingiva and the dental follicle. Most commonly pericoronitis occurs with a partially erupted or partially erupted and impacted mandibular third molar (lower wisdom tooth). Periocoronitis is a common dental problem, often occurring in young adults since this is roughly the age when the wisdom teeth are erupting into the mouth.

Conventional treatment is supplemented with local LPT over the operculum, buccal and lingual bony wall and any tender points in the musculature. Complementary use of LPT leads to a much faster reduction of discomfort than conventional treatment on its own. LPT is also effective in alleviating pain during the eruption of deciduous teeth. The submandibular lymph nodes should be included in the treatment [915, 1470]. Herpes virus is suspected to be involved in the symptoms during eruption of deciduous teeth [1743], which would further explain the good effect of LPT. If the patient shows signs of an infection spreading down beyond the submandibular areas, LPT should be postponed until full antibiotic protection is obtained, since LPT will open the circulatory system into an area where it is not supposed to go.

Literature:

Manne [222] treated 12 cases of juvenile pericoronitis with GaAs. In eleven cases, there were quick positive reactions, while one case was unsuccessful despite two applications within the space of 24 hours, and extraction was necessary.

The purpose of a study by Sezer [2132] was to evaluate the effect of LPT as an adjunct to standard therapy in acute pericoronitis. Eighty acute pericoronitis patients were randomly assigned to one of four LPT groups: Nd:YAG, n=20, 8 J/cm², 0.25 W, 10 Hz, 10 sec; 808 nm, n=20, 8 J/cm², 0.25 W, 10 sec; 660 nm, n=20,8 J/cm², 40 mW, 60 sec; or a placebo laser control group: n=20. After standard treatment, LPT or a placebo laser were applied to the treatment area at a distance of 1 cm from the buccal site. Interincisal opening, pain perception, and oral health-related quality of life were evaluated at baseline, 24 h,and 7 days after laser application. It was found that the trismus and the OHRQoL in the Nd:YAG and the 808 nm groups were significantly improved when compared with the 660 nm and control groups at 24 h. No statistically significant differences were detected on day 7 among the groups with regard to any of the parameters evaluated.

Further studies: [2133]

5.3.8 Endodontics

A pain reaction can arise after over-instrumentation in root canals when treating both vital and non-vital pulp. This pain is short in duration but still causes the patient discomfort. 2-3 J over the apex eases the symptoms in most cases. This treatment can be administered prophylactically to some advantage when it is known that over-instrumentation has occurred.

In other respects, LPT can be recommended for pulp capping and pulp amputation of milk teeth. LPT appears to stimulate the odontoblast calcium and collagen production, leading to secondary dentine formation.

Literature:

Ohbayashi [1107] isolated human dental pulp cells and irradiated the cells with two doses of GaAlAs laser. In the laser groups there was an increased collagen production, increase in the calcified nodules and enhancement of osteocalcin and alkaline phosphate activity.

Paschoud [109] exposed pulp horns and studied the effects of HeNe laser light in direct pulp capping with three different pulp capping preparations, all based on calcium hydroxide. Pulp capping preparations only were used in three control groups. When capping with Pulpdent and Contrasil, a dentine bridge was developed over a shorter period by those treated with a HeNe laser than by the control group. No positive results were achieved in combination with Dycal.

Figure 5.4 Endodontics

The conclusions drawn were that calcium hydroxide preparations can create a dentine bridge during pulp capping, and that HeNe laser light further stimulates new formation of dentine. The properties of the preparation itself are central to the result. The intrapulpal temperature was also taken during this experiment. After two minutes it had increased by 0.5 °C, after which it increased no further.

The results of the study by Utsunomiya [1010] suggest that laser irradiation accelerates wound healing of the pulp and the expression of the lectins and collagens. Furthermore, D-glucose-, D-mannose-, N-acetyl-D-galactosamine-, and N-acetyl-neuraminic acid-binding sugars and type I, III, and V collagens play an important role in the healing of pulp.

Nagasawa [107] has observed that Nd:YAG and argon laser irradiation within LLL doses strongly stimulates the formation of secondary dentine.

Dcabrowska [714] performed 30 pulp cappings or amputations in combination with calcium hydroxide and LPT. 36 teeth were treated with calcium hydroxide only. The laser treated group had a more favourable outcome.

Thwee [1118] performed pulpotomy in rats and exposed the open pulp to HeNe laser irradiation. After irradiation, the pulp was coated with a calcium hydroxide coating. A large amount of dentine-like calcified barrier was formed in the laser irradiated group.

Kurumada [577, 1549], on the other hand, used GaAs laser light without calcium hydroxide on vital pulpotomies. Laser irradiation induced enhancement of calcification in the wound surface and stimulated formation of calcified tissue.

In a study by Sousa [2080] the aim was to analyse the effect of LPT on the secretory activity of macrophages activated by interferon-gamma (IFN-gamma) and lipopolysaccharide (LPS), and stimulated by substances leached from an epoxy resin-based sealer (AH-Plus) and a calcium hydroxide-based sealer (Sealapex). Cytotoxicity was indirectly assessed by measuring mitochondrial activity. Macrophages were stimulated by the leached substances or not (controls), and the groups were then irradiated or not. The secretion of pro-inflammatory cytokines (TNF-alpha and MMP-1) was analysed using ELISA. Two irradiations at 6-h intervals were done with 780 nm, *70 mW, spot size 4.0 mm², 3 J/cm², for 1.5 sec) in contact mode. The sealers were non-cytotoxic to macrophages. The production of TNF-alpha was significantly decreased by LPT, regardless of experimental group. The level of secretion of MMP-1 was similar in all groups. Based on the conditions of this study the authors conclude that in activated macrophages, LPT impairs the secretion of the pro-inflammatory cytokine TNF-alpha, but has no influence on MMP-1 secretion.*

The effect of bone repair in periapical lesions has been studied by Sousa [1238]. 15 patients with a total of 18 periapical lesions were divided into two groups. One group received endodontic treatment and/or periapical surgery. The patients in the other group were submitted to the same procedure and in addition the lesions were irradiated by GaAs laser, 11 mW average power, 9 J/cm². This therapy was performed during 10 sessions with an interval of 72 hours. Bone regeneration was evaluated through X-ray examination. The results showed a significant difference between the laser and the control group in favour of the laser group.

The aim of the study by Kreisler [1501] was to evaluate the effect of laser application on postoperative pain after endodontic surgery in a double blind, randomised clinical study. Fifty-two healthy adults undergoing endodontic surgery were included into the study. Subsequently to suturing, 26 patients had the operation site treated with an 809 nm at a power output of 50 mW and an irradiation time of 150 s. Laser treatment was simulated in further 26 patients. Patients were instructed to evaluate their postoperative pain on 7 days after surgery by means of a Visual Analogue Scale (VAS). The results revealed that the pain level in the laser group was lower than in the placebo group throughout the 7 day follow-up period. The differences, however, were significant only on the first postoperative day.

Liu [1114] confirms the pain-relieving effect of laser after post-endodontic filling pain.

Seventy-two endosurgery cases on incisors and premolars were included in a study by Payer [1616]. After PDT therapy over the dental apex regular LPT was performed over the sutured area. The cases were split randomly into a laser test group, a placebo group, and a control group. In the laser group irradiation was performed 1, 3, and 7 days after surgery. In the placebo group, irradiation was performed without laser activation. In the control group, neither laser nor placebo therapy was used. Swelling, wound healing, and pain were evaluated by a blinded investigator 1, 3, and 7 days postoperatively. The laser had a wavelength of 680 nm, 75 mW, energy density 3-4 J/cm². The irradiated area was approx. 4 cm². No statistically relevant differences between the laser and the placebo groups were found. Patients in the control group reported statistically stronger pain.

Propopowisch [1553] treated a total of 120 teeth in 90 patients endodontically. The teeth were divided into three groups: (1) Simulated laser, (2) 2 J/cm² into the canal opening and 1 J/cm² over the apical area and (3) 2 Jcm² over the apical area only. After 24 hours and 7 days the degree of post-

operative pain was evaluated. Group (2) had significantly less pain that the other two groups.

Further references: [1550]

5.3.9 Extraction

After extraction, the alveolus is irradiated along with the lingual and buccal bony wall. Faster coagulation, less postoperative discomfort and quicker healing can be expected. A normal consequence of using elevators during extraction is that neighbouring teeth become sensitive, which makes chewing difficult. 2-4 J over the apex usually reduces this discomfort, and the treatment can be administered prophylactically immediately after the extraction.

For reduction of oedema, relatively high doses of GaAs or GaAlAs light are needed on a large area around the wound. The laser decreases the permeability of the lymphatic vessels and induces dilatation of these vessels.

It has not yet been possible to determine the "best" wavelength, although a HeNe/InGaAlP laser seems to be the best option for coagulation, which is vital for continued healing. GaAlAs and GaAs lasers have more effect on postoperative pain and swelling than red light.

When removing impacted wisdom teeth, or after operations involving stress on the maxillary joint, 6-8 J over the joint directly after the operation is a reasonable energy. For postoperative oedema and pain, energies of 15-25 J are needed locally and extraorally. The energy must be correlated to the amount of trauma.

Most studies have irradiated the immediate area around the extraction socket. This is fine for reducing bleeding (red) and inflammation (infrared) in the local area, but complicated extractions such as lower molars involve a large area of the jaw and cheek. Thus, high energies can at advantage be applied with infrared extraoralllly, 15-20 J at 3-4 sites.

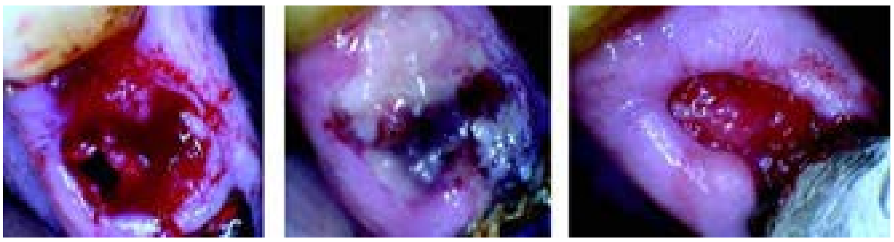


Figure 5.5 Tooth extraction directly postop, at 15 and at 30 days.

Figure 5.6 Same patient, contra-lateral side; with red laser treatment directly postop, at 15 and 30 days. Courtesy: Talat Qadri

Literature:

Animal studies

Filho [399] extracted the upper left incisor of 24 rats. 12 of the extraction wounds were given HeNe laser with 3 J/cm². Clinically, the rats exposed to the laser beam showed a better healing rate than the unlased rats from the control group.

Park [2325] attempted to investigate the effects of irradiation time on the healing of extraction sockets by evaluating the expressions of genes and proteins related to bone healing. The left and right first maxillary molars of 24 rats were extracted. Rats were randomly divided into four groups in which extraction sockets were irradiated for 0, 1, 2, or 5 min each day for 3 or 7 days. Specimens containing the sockets were examined using quantitative real-time reverse transcription polymerase chain reaction and western blotting. LPT increased the expressions of all tested genes, Runx2, collagen type 1, osteocalcin, platelet-derived growth factor-B, and vascular endothelial growth factor, in a time-dependent manner. The highest levels of gene expressions were in the 5-min group after 7 days. Five minutes of irradiation caused prominent increases of the expression of all tested proteins after both 3 and 7 days. The expression level of each protein in group 4 was higher b almost twofold compared with group 1 after 7 days. Laser irradiation for 5 min caused the highest expressions of genes and proteins related to bone healing. In conclusion, LPT had positive effects on the early stages of bone healing of extraction sockets in rats, which were irradiation time-dependent. LPT

Takeda [110] studied the effects of a GaAs laser on tooth extraction. 24 rats were used in the experiment, in which irradiation was administered immediately after extraction. The wound was then studied under a microscope on days 0, 2, 4 and 7. Five minutes after the extraction there was no histological difference as compared with the control group. On day 2, fibroblasts had begun to proliferate from the remaining periodontal membrane in the clot. This proliferation was more pronounced in the laser group than in the control group. The ossification process was more advanced in the laser group on day 4, and on day 7 the laser group's trabeculae were thicker and greater in number.

Clinical studies

Fernando [216] compared the effects of 830 nm laser light during the simultaneous extraction of two similarly impacted lower wisdom teeth. Post-operative pain and swelling were studied. 4 J was applied directly into the empty socket. In a double-blind study, no difference was observed between the treated and untreated sides.

Verplanken [128] treated 44 patients with GaAs laser immediately after tooth extraction, with a control group of 27 patients. The distance between the bucco-lingual and mesio-distal wound walls, the colour of the coagulum, and postoperative pain and swelling were measured. The author summarised the results as follows: "We could observe a significant stimulation of the healing process as a result of LPT."

Wahl [693] was not able to find any effect of a 6 mW HeNe laser on the postoperative outcome after removal of the third molar.

Tay [1137] studied the effect of LPT following third molar surgery. 55 patients with bilateral and similarly impacted third molars were selected for surgery under general anaesthesia by one surgeon at one sitting. A 30 mW GaAlAs laser was used. The patients were divided into laser and placebo laser groups. The laser group received 10 J at four sessions during the first 24 hours postoperatively, a total of 40 J. The contralateral side served as control. There was a significant reduction of pain in the laser group, with the greatest reduction found after the initial dose of 10 J.

C-reactive protein plasma concentration can be monitored to evaluate the degree of inflammation in tissue. CRP plasma concentration is usually low, increases quickly at the onset of acute inflammatory processes and quickly falls when effective control of the process occurs. Freitas [1268] used this method to monitor the possible anti-inflammatory effect of 830 nm laser after the removal of impacted third molars. 12 patients were irradiated with 4.8 J per session 24 and 48 hours after surgery. A control group (n=12) was treated with sham laser. CRP values were more symmetric and better distributed for the irradiated group 48 hours after surgery but there was no statistical difference between the groups.

The aim of the study by Neckel [1597] was to evaluate the effect of LPT on the bony regeneration of extraction sockets. 40 extraction sockets of first mandibular molars were randomly selected into four test groups.

1. Control group: 10 sockets. No additional therapy.

2. Test group I: 10 sockets: LPT immediately postoperative, 3 days, 6 days, 9 days and 12 days postoperatively; 24 mW, 150 sec, 7.5 J/cm^2.

3. Test group II: 10 sockets: LPT immediately postoperative, 3 days, 6 days, 9 days and 12 days postoperatively; 36 mW, 150 sec, 11.3 J/cm^2.

4. Test group III: 10 sockets. LPT immediately postoperative, 3 days, 6 days, 9 days and 12 days postoperatively; 48 mW, 150 sec, 15.1 J/cm^2.

Clinical and radiological re-evaluation took place after 8 weeks. Intraoral radiographs were compared in subtraction radiography and the changes in *bone density evaluated. LPT showed statistically significant better results than the control group.*

The aim of the study by Markovic [1766] was twofold: (1) to evaluate the postoperative analgesic efficacy, comparing long-acting and intermediate-acting local anaesthetics; and (2) to compare the use of laser irradiation and the non-steroid anti-inflammatory drug diclofenac, which are claimed to be among the most successful aids in postoperative pain control. A twofold study of 102 patients of both sexes undergoing surgical extraction of LTM (lower Third Molar) was conducted. In the first part of the study, 12 patients with bilaterally impacted lower molars were treated in a double-blind cross-over fashion; local anaesthesia was achieved with 0.5% bupivacaine plain or 2% lidocaine with 1:80.000 epinephrine. In the second part of the study, 90 patients undergoing lower molar surgical extraction with local anaesthesia received postoperative laser irradiation (30 patients) and a preoperative single dose of 100 mg diclofenac (30 patients), or only regular postoperative recommendations (30 patients). The results of the first part of the study showed a strikingly better postoperative analgesic effect of bupivacaine than lidocaine/epinephrine (11 out of 12; 4 out of 12, respectively, patients without postoperative pain). In the second part of the study, LPT irradiation significantly reduced postoperative pain intensity in patients premedicated with diclofenac, compared with the controls. Provided that basic principles of surgical practice have been achieved, the use of long-acting local anaesthetics and LPT irradiation enables the best postoperative analgesic effect and the most comfortable postoperative course after surgical extraction of lower molars.

The aim of another study by Markovic [1911] was to compare the effectiveness of LPT and dexamethasone after surgical removal of impacted lower third molars under local anaesthesia. There were 120 healthy patients divided into four groups of 30 each. Group 1 received LPT irradiation immediately after operation (4 J/cm^2, 50 mW, 637 nm); group 2 also received intramuscular injection of 4 mg dexamethasone into the internal pterygoid muscle; group 3 received LPT irradiation supplemented by systemic dexamethasone 4 mg i.m. in the deltoid region, followed by 4 mg of dexamethasone intraorally 6h postoperatively; and the 4th (control) group received only the usual postoperative recommendations (cold packs, soft diet, etc.). Laser irradiation with local use of dexamethasone (group 2) resulted in a statistically significant reduction of postoperative oedema in comparison to the other groups. No adverse effects of the procedure or medication were observed.

The purpose of a study by Aras [2062] was to compare the effects of extraoral and intraoral LPT on postoperative trismus and oedema following the removal of mandibular third molars. Forty-eight patients who were to undergo surgical removal of their lower third molars were studied. Patients were randomly allocated to one of three groups: extraoral LPT, intraoral LPT, or placebo. In the study, 808 nm was used, and the laser therapy was applied by using a 1 x 3-cm handpiece. The flat-top laser beam profile was *used in this therapy. For both of the LPT groups, laser energy was applied at 100 mW for a total of 120 s, 12 J. Patients in the extraoral-LPT group (n= 16) received 12 J, 4 J/cm^2, and the laser was applied at the insertion point of the masseter muscle immediately after the operation. Patients in the intraoral-LPT group (n=16) received 12J (4 J/cm^2 intraorally at the operation site 1 cm from the target tissue. In the placebo group (n = 16), the handpiece was inserted intraorally at the operation site and then was touched extraorally to the masseter muscle for 1 min at each site (120 s total), but the laser was not activated. The size of the interincisal opening and facial swelling were evaluated on the second and seventh postoperative days. At the second postoperative day, trismus and swelling in the extraoral-LPT group were significantly less than in the placebo group. Trismus in the extraoral-LPT group at the seventh postoperative day was also significantly less than in the placebo group. However, at the seventh postoperative day in the intraoral-LPT group, only trismus was significantly less than in the placebo group. This study demonstrates that extraoral LPT is more effective than intraoral LPT for the reduction of postoperative trismus and swelling after extraction of the lower third molar using these parameters.*

A prospective, randomised, and double-blind study was undertaken in 20 healthy patients with two symmetrically impacted lower third molars by López-Ramírez [2134]. The application of a LPT was made randomly on one of the two sides after surgery. The experimental side received 5 J/cm^2, a wavelength of 810 nm, 0.5 W. On the control side, a handpiece was applied intraorally, but the laser was not activated. Evaluations of postoperative pain, trismus, and swelling were made. The sample consisted of 11 women and nine men, and mean age was 23.35 years (18-37). The pain level in the first hours after surgery was lower in the experimental side than in the placebo side, although without statistically significant differences. Swelling and trismus at the 2nd and 7th postoperative days were slightly higher in the control side, although not statistically significant differences were detected. The application of a LPT with the parameters used in this study did not show beneficial effects in reducing pain, swelling, and trismus after removal of impacted lower third molars.

The study by Ferrante [2135] has contrasting results with higher energies. Thirty patients were randomised into two treatment groups, each with 15 patients-group test (LPT) and a group control (no-LPT) and were told to avoid any analgesics 12 h before the procedure. In group test, a 980 nm diode-laser was applied, intraorally (lingual and vestibular) at 1 cm from the involved area and extraoral at the insertion point of the masseter muscle immediately after surgery and at 24 h. The group control received only routine management. Parameters used for LPT were: 300 mW for a total of 180 s, 54 J). Group test showed improvement in the interincisal opening and remarkable reduction of trismus, swelling and intensity of pain on the first and the seventh postoperative days. The authors correctly conclude: Although LPT has been reported to prevent swelling and trismus following *the removal of impacted third molars, some of these studies reported a positive laser effect while others did not. All references to the use of laser therapy in the postoperative management of third molar surgery employ different methodologies and, in some, explanations as to selection of their respective radiation parameters are not given.*

In a randomised clinical setting by Saber [2166], 100 patients were assigned to two groups of 50 in each. Every patient underwent surgical removal of one mandibular third molar (with osteotomy). After suturing the flap, the laser was applied to every patient. In group I laser radiation was applied by the dental assistant with output power of 100 mW, in continuous mode with sweeping motion, in group II, the laser hand piece was only brought into position without releasing energy, so that no patient knew which group he belonged to. The patient was given a pain evaluation form where they could determine their individual pain level and duration. The statistical tests showed significant difference in pain level between laser and control group but no significant difference found in pain duration in the two groups.

In a study by Kazancioglu [2276], patients were randomised into three treatment groups of 20 patients each: two study groups (group 1 = LPT), group 2 = ozone therapy) and a control group (no-LPT or ozone therapy). Twenty teeth extractions were performed in each group. Evaluations of postoperative pain, the number of analgesics tablets taken, trismus, swelling, and quality of life were made. The pain level and the number of analgesics tablets taken were lower in the ozonated and LPT applied groups than in the control group. This study showed that ozone and LPT therapies had a positive effect on the patients' quality of life. Trismus in the LPT group was significantly less than in the ozonated and control groups. Ozone application showed no superiority in regards of postoperative swelling; however, LPT group had significantly lower postoperative swelling. This study demonstrates that ozone and laser therapies are useful for the reduction of postoperative pain and they increase quality of life after third-molar surgery. Although the ozone therapy had no effect on postoperative swelling and trismus after surgical removal of impacted lower third molars, LPT had a positive effect.

The purpose of the literature study by Bjordal [1782] was to investigate if the observations about the anti-inflammatory and pain reducing effects of LPT found in the literature can be translated into clinical situations, like the classical model of third molar extraction. Systematic reviews of randomised controlled trials (RCT) with Meta-analysis of pain (continuous data) within 0-24 hours after surgery were gathered. Methodological assessments of trials were made according to Jadad´s scale. Subgroup analyses were planned for wavelength, irradiance and energy dose. The literature search yielded 9 RCTs, of which 8 RCTs with acceptable quality and a total of 658 patients reported pain data within 0-24 hours after surgery. There was a significant pain reduction from all 8 RCTs combined at 7.8 mm measured on a 100 mm VAS. Subgroup analysis revealed no significant interaction between effect and wavelength (red/infrared) or irradiance. But in 3 *trials administering low energy doses (0.37-0.96 Joules), the overall effect was not significantly different from placebo at 1.2 mm on VAS, while high energy doses (6-7.5 Joules) in 5 RCTs induced significant pain relief at 9.6 mm on VAS. In one RCT, there was no significant difference between high dose LPT and the anti-inflammatory drug diclofenac. In conclusion, LPT with red/infrared wavelengths and energy doses of 6 -7.5 Joules, is effective in reducing acute inflammatory pain.*

In a study by Halon [2358], 89 teeth were extracted; 45 sockets were exposed to 6 J laser radiation (820 nm, 200 mW, 6 J/cm^2, spot size 38 mm^2, CW) for five consecutive days following tooth extraction, and the remaining extraction wounds were left to heal spontaneously without laser irradiation. Antigen CD34 was assessed by immunohistochemistry as a marker of angiogenesis, and its expression was examined by computer-assisted histomorphometric image analysis. As a result, LPT in HIV-infected patients of varying degrees of immunodeficiency greatly accelerated post-extraction neoangiogenesis, regardless of the patient's gender, tooth position, number of roots, or number of CD4 lymphocytes in the blood. Application of LPT for the treatment of tooth extraction wounds in HIV positive patients greatly enhanced the formation of new blood vessels, which in turn promoted wound healing.

Comment: 6 J or 6 J/cm^2 - that is the question. The reporting of parameters seems to be incorrect overall.

A systematic review and Meta-analysis by He [2436] demonstrated that LPT was effective in reducing pain, trismus, and swelling after mandibular third molar surgery. Intra-oral irradiation over the surgical field as well as extra-oral irradiation over the masseter seem to produce the best effects. However, because of the heterogeneity of intervention and outcomes assessment and risk of bias of included trials, the efficacy was proved with limited evidence. In the future, the authors underline, larger and better-designed RCTs will be needed to draw a stable conclusion.

Further literature: [1132, 1193, 1293, 2136]

5.3.10 Gingivitis

Gingivitis is a non-destructive periodontal disease. The most common form of gingivitis, and the most common form of periodontal disease overall, is in response to bacterial biofilms (called plaque) adherent to tooth surfaces, termed plaque-induced gingivitis. In the absence of treatment, gingivitis may progress to periodontitis, which is a destructive form of periodontal disease. While in some sites or individuals gingivitis never progresses to periodontitis, data indicates that periodontitis is always preceded by gingivitis.

LPT can be used as supplementary treatment for gingivitis. In combination with conventional treatment, LPT quickens healing and reduces postoperative pain. The need for complete debridement and good oral hygiene must be emphasised. Preoperative LPT reduces pain associated with scaling.

Literature:

In vitro studies

Chomette [71] also studied the healing process in 14 patients from whom gingiva biopsies had been taken. In patients with no gingivitis before the biopsy, (laser group) cicatrisation took place within 14 days, and in the control group (no gingivitis, no laser treatment) within 21 days. Even in the presence of gingivitis, the laser groups exhibited quicker and better cicatrisation.

Loevschall [75] examined the effects of GaAlAs laser on human oral fibroblasts. This study showed increased incorporation of thymidine in the fibroblasts, which suggests that LPT can stimulate DNA synthesis.

Kim [948] conducted an in vitro study of the GaAlAs laser's stimulating effect on gingival fibroblasts from human subjects. The cell cultures were treated daily for four days, and the treatment period in the three groups was 30, 60 and 90 seconds. The number of cells in the experimental group rose with increased exposure to laser irradiation, although the rise was not statistically significant in comparison with the control group. It was also found, when comparing the protein content of the different cultures, that a very significant increase had taken place in the experimental group treated with 90 seconds GaAlAs irradiation. In terms of DNA content, the only significant difference was in the group that had received 60 seconds GaAlAs irradiation.

In the study by Sakurai [1008] laser irradiation inhibited PGE_2 by LPS in hGF cells through a reduction of COX-2 mRNA level. The findings suggest that LPT may be of therapeutic benefit against the aggravation of gingivitis and periodontitis through bacterial infection

Animal studies

Kubota [479] measured the microcirculation in skin flaps using the laser speckle method. One minute after irradiation the perfusion was less, and 30 minutes later it was greater than in the control flap.

In a histopathological study, Abramovici [640] studied the effect of a HeNe laser on the healing process of open gingival wounds in cats. The irradiation initiated a massive inflammatory cell exudate together with an anti-oedematic effect after the second postoperative day. A substantial acceleration of the healing process was noted on the sixth day. The biostimulatory effect seemed to act photodynamically at both the intracellular and extracellular levels, thus promoting the proliferatory capacity of fibroblasts and the capillary bud formation necessary for a rapid differentiation of connective tissue.

A study by Ghahroudi [2382] aimed to assess the effect of LPT irradiation and Bio-Oss graft material on the osteogenesis process in the rabbit calvarium defects. Twelve white male New Zealand rabbits were included in this study. Four 8 mm diameter identical defects were prepared on each rabbit's calvarium. One site was left as an untreated control (C), the second site was filled with Bio-Oss (B), the third site was treated with laser irradiation

(L), and the fourth site treated with Bio-Oss and laser irradiation (B + L). In the laser group, a diode laser (810 nm, 300 mW, CW, 4 J/cm²) was applied immediately after surgery and then one other day for the next 20 days. After 4 and 8 weeks, the animals were sacrificed and histological and histomorphometric examinations were performed. Significant differences were not found regarding inflammation severity, foreign body reactions, and vitality of newly formed bone on 4th and 8th week after operation. The mean amount of new bone was 15.83 and 18.5 % in the controls on the 4th and 8th week; 27.66 and 25.16 % in the laser-irradiated group; 35.0 and 41.83 % in Bio-Oss and 41.83 and 47.0 % in the laser + Bio-Oss treated specimens with significant statistical differences.

Clinical studies

Rydén [42] studied the effect of a GaAs laser on experimental gingivitis in 10 healthy human volunteers. After three weeks plaque accumulation, one side was given a total dose of 1 J, divided between day 21 and day 24. The degree of gingivitis was examined by identifying the vessels in the area, using photography, on day 0, day 21, day 28 and day 42. No statistical difference was found between the laser group and the control group with respect to the number of vessels.

A study conducted by Yarita [182] found no change of morphology in the initial stages of gingivitis in humans. In a group that had received laser treatment, however, increased blood flow was observed.

Kozlov [368] has studied the microcirculation in patients with periodontal disease of various degrees, using biomicroscopic techniques and laser Doppler flowmetry. The intensified tissue blood flow observed after HeNe laser irradiation was caused by intensification of blood microcirculation and the activation of neovascularisation. Tissue blood flow stimulation was caused by precapillary dilatation and opening of "reserved" capillaries. Doses between 10 and 30 J/cm² had adverse effects. The best effect was observed in patients with moderate periodontal disease. The key to the four studies above is the condition of the tissue. Experimental gingivitis in healthy subjects reacts differently to LPT than a true disease would.

Lee [136] examined the gingivitis of 13 dental students. GaAlAs laser light was administered to one side of the jaw on days 1, 3, 5 and 7. A histological evaluation was carried out on day 4. The sulcus bleeding index decreased on the experimental side, but the pocket depth and plaque index were unchanged. On the side treated with laser, a reduction in motiles and spirochetes was observed, along with an increase in non-motiles. From a histological point of view, the inflammatory infiltration decreased in density and extent after LPT.

Amorim [1225] selected seven patients who were to undergo gingivectomy on both sides of the jaw. In these patients LPT (685 nm, 50 mW, 4 J/cm²) was applied on one side only, the other side serving as control. The healing process was monitored clinically and biometrically, using photo-

graphs for a period of 35 days. The analysis was performed by three specialists in periodontology. Biometrical evaluation showed improvement of the healing for the period of 21 and 28 days in the laser group. Clinical evaluation showed better reparation mainly after the third day.

The aim of the split-mouth controlled clinical trial by Ozcelik [1822] was to assess the effects of LPT on healing of gingiva after gingivectomy and gingivoplasty. Twenty patients with inflammatory gingival hyperplasias on their symmetrical teeth were included in this study. After gingivectomy and gingivoplasty, a diode laser (588 nm, 120 mW, 5 minutes per session, 36 J per session, during 7 consecutive days) was randomly applied to one side of the operation area for 7 days. The surgical areas were disclosed by a solution to visualise the areas in which the epithelium is absent. Comparison of the surface areas on the LPT-applied sites and controls were made with image-analysing software. While there were no statistically significant differences between the stained surface areas of the LPT applied and the control sites immediately after the surgery, LPT-applied sites had significantly lower stained areas compared with the controls on the post-operative third, seventh and 15th day. Within the limitations of this study, the results indicated that LPT may enhance epithelisation and improve wound healing after gingivectomy and gingivoplasty operations. This study has the highest energy used in any similar study.

A comparative study of the influence details of low-intensity pulse and continuous laser radiation of red and infrared parts of spectrum upon microcirculation indices in comprehensive treatment of chronic parodontitis of light and middle severity was performed by Krechina [2011]. The predominantly activating influence upon microcirculation in gingival tissues of the pulsed laser radiation in the red part of spectrum was established.

In the study by Qadri [1185] a combination of 635 nm diode laser and GaAlAs laser were used to treat gingivitis and periodontal disease. 17 patients received laser on one side of the upper arch and placebo laser on the other side, after the teeth having been debrided. 635 nm diode laser 0.9 J was applied at the base of the interdental papilla and GaAlAs 3.5 J at the projection of the alveolar bone margin. The results were as follows (laser side/placebo side): gingival index 0.54/1.4, plaque index 0.26/0.68, pocket reduction 0.92/0.16. The gingival exsudate was reduced on the laser side, 0,04 µl vs. 0.14 µl. The metalloproteinase-8 (MMP-8) was slightly reduced on the laser side and elevated on the placebo side. There was no difference in elastase activity or of the amount of IL-1β, nor any significant changes in microbiology.

The aim of another study by Qadri [1634] was to study whether or not the length of coherence is of importance in phototherapy. Laser light is coherent but the length of coherence of gas lasers such as a HeNe laser is much greater than that of a diode laser of the same wavelength. The biological significance of the length of coherence has hitherto not been investigated. 20 patients with light to moderate periodontitis were selected. After instruc-

tion about oral hygiene, scaling and root planing (SRP), one side of the upper jaw of each patient was randomly selected for HeNe (632.8 nm, 3 mW) or InGaAlP (650 nm, 3 mW) laser irradiation, using the same power and dose, irradiating once of week during six weeks. One week after the SRP the following parameters were measured: pocket depth, gingival index, plaque index, GCF volume, MMP-8, IL-8 and microbiology in the pocket. The irradiation (180 seconds per point, 0.54 J/cm^2) was then performed by a dental hygienist and the selection of side was blinded to the evaluators. After six weeks renewed measurements revealed that all clinical parameters had improved significantly better on the HeNe side. MMP-8 was more reduced on the HeNe side while there was no difference for IL-8 or pathogens. Coherence is an important factor in phototherapy but even the length of the coherence appears to be of importance.

The aim of a study by Igic [2010] was to determine the efficiency of a LPT in the therapy of chronic gingivitis in children. The study included 100 children with permanent dentition and suffering from chronic gingivitis. They were divided into two groups: group I-50 children with chronic gingivitis, who underwent the basic therapy; group II-50 children with chronic gingivitis, who underwent the basic therapy and also LPT. Evaluation of the condition of oral hygiene, the health of gingiva and periodontium was done using appropriate index before and after the therapy. For the plaque index (PI) following results were obtained: in the group I PI = 1.94, and in the group II PI = 1.82. After the therapy in both groups PI was 0. In the group I sulcus plaque index (SPI) was 2.02 before the therapy and 0.32 after the therapy. In the group II SPI was 1.90 before the therapy and 0.08 after the therapy. In the group I Community Periodontal Index of Treatment Needs (CPITN) was 1.66 before the therapy and 0.32 after the therapy, and in the group II CPITN was 1.60 before the therapy and 0.08 after the therapy. Chronic gingivitis in children can be successfully cured by the basic treatment but the use of LPT can significantly improve this effect.

The purpose of another study by Igic [2137] was to determine the level of gingival inflammation and the prevalence of periodontopathogenic microorganisms in adolescents with chronic gingivitis, as well as to compare the effectiveness of two approaches in gingivitis treatment-basic therapy alone and basic therapy + adjunctive LPT. After periodontal evaluation, the content of gingival pockets of 140 adolescents with gingivitis was analysed by multiplex PCR for the presence of P. gingivalis, A. actinomycetemcomitans, T. forsythensis and P. intermedia. Subsequent to bacteria detection, the examinees were divided into two groups with homogenous clinical and microbiological characteristics. Group A was subjected to basic gingivitis therapy, and group B underwent basic therapy along with adjunctive LPT. A statistically significant difference between the values of plaque-index (PI) and sulcus bleeding index (SBI) before and after therapy was confirmed in both groups, though more pronounced in group B. Following therapy, the incidence of periodontopathogenic microorganisms decreased considerably.

The best result was obtained in P. gingivalis eradication by combined therapy.

Further literature: [70, 72, 76, 77, 164, 165, 166, 641, 1185, 2138]

For more studies, see "Periodontitis"

5.3.11 Herpes zoster

(See chapter 4.2 "Zoster" on page 477)

5.3.12 Hypersensitive dentine

Painful necks of teeth often respond well to laser treatment. Recent desensitising agents have greatly reduced the problem of hypersensitive dentine. While these products effectively reduce minor sensitivities, LPT is superior for cases with more profound pulpitis. The seriousness of the hypersensitivity decides the dosage and number of sessions needed. The tooth neck should be treated until the patient feels a distinct improvement (check with the air syringe). With GaAlAs/GaAs lasers and its greater penetration, it is possible to irradiate directly over the apex, through mucous membrane and bone. With HeNe laser it is only possible to use the tooth neck, except for the upper incisors. A combination irradiation over the coronary pulp, tooth neck and apex is recommended. A hypersensitive tooth that does not respond to 4-6 J per root in 2-3 sessions is a candidate for endodontics.

Figure 5.7 Patient's reaction to the air syringe before and after LPT. Courtesy: Per Hugo Christensen

With the advent of porcelain inlays/onlays and large composite fillings, the number of postoperative complaints has increased. The patients are disappointed and some of them have to undergo endodontics. Such postoperative sensations can be eliminated or reduced by using LPT after preparation and before cementing or filling. If post-operative problems appear, the laser could solve many of them in one or a few sessions. This is indeed much more profitable than free endodontics.

There are many studies in this field. For a literature review, the article by Kimura [1055] is recommended. These studies also confirm the safety of the therapy.

Literature:

Brugnera [1127] evaluated the histological reaction of the pulp in rats after LPT. Thirty-two upper molars from albino rats with mechanically exposed occlusal pulps (~1 cm^2) were treated. The parameters of the laser were HeNe 6 mW, beam cross section 1.8 mm^2, and exposure time 240 s, 1.44 J/cm^2, in scanning mode. The animals were divided into four different groups, each with its own control group, and were given weekly applications. The results showed that irradiated animals presented an increased production of dentine and shutting of dentinal tubuli. On the other hand, non-irradiated subjects still showed signs of intense inflammatory reactions and even necrosis for the same experimental times. Irradiated teeth did not show cell degeneration. The irradiation was shown to be efficient in the stimulation of odontoblast cells, producing reparative dentin and closing dentin tubuli.

In a double-blind study, Gelskey [610] studied the effect of HeNe or HeNe + Nd:YAG on patients with dentine hypersensitivity on both sides. One was treated with HeNe laser (guide light, dose not stated) and one with a combination of HeNe and Nd:YAG. Surprisingly enough, HeNe reduced dentine hypersensitivity to air by 63% and to mechanical stimulation by 61% over three months. The HeNe + Nd:YAG treatment reduced sensitivity to air by 58% and to mechanical stimulation by 61%. All teeth remained vital with no adverse effects.

The effect of Nd:YAG could be confirmed by Orchardson [845], but not the effect of HeNe. Only the HeNe aiming beam of the Nd:YAG laser was used and no dosage is indicated.

A study by Yamaguchi [705] was conducted to evaluate the results of treating hypersensitive dentine with 30 mW, 790 nm, using a double blind technique. For this purpose, 66 teeth were examined. 30 of the teeth were treated with laser irradiation (active group), while the other 36 were not (dummy group). The following results were obtained: Two hours after laser irradiation, 40% of the active group and 13.9% of the dummy group showed effective results. After one day these values were 36.9% and 13.9%, and after 5 days 43.3% and 19.4%, respectively. An overall evaluation indicated these values to be 60.0% and 22.2% respectively.

Groth [644] treated 25 hypersensitive teeth with 790 nm, 30 mW, 7 J per treatment. The irradiation was repeated after 72 hours. Evaluation was performed during a period of 2-4 weeks and the results proved to be significant as compared to control teeth.

In a study by Brugnera [910] 300 human teeth were treated for hypersensitivity. Pulpal vitality was verified using thermal tests, and only reversible processes were treated. HeNe and GaAlAs lasers were used. All teeth received 4 J/session for up to 5 sessions. 79% of the patients were treated in 3 sessions with success; 8.6% were cured in 4 sessions; and 4.3% were successfully treated in 5 sessions, obtaining 92% success in total. In a more recent article [1127] Brugnera reports on the outcome of treating 1102 teeth and 338 patients. 40 mW GaAlAs was mainly used, 25 seconds per point, *four points per tooth, total energy per tooth 4 J, dose 50 J/cm². A maximum of five treatments were given, but the therapy was always finished when the symptoms were gone. 36.7% of the patients required only one session, 23.14% needed two sessions, 16.1% three sessions, 9.7% four sessions and 5.35% five sessions. 8.71% did not respond.*

In the study by Marsilio [1509] 25 patients, with a total number of 106 cases of dentinal hypersensitivity (DH), were treated with GaAlAs LPT. 65% of the teeth were premolars; 14% were incisors and molars; 6.6% were canines. The teeth were irradiated with 3 and 5 J/cm² for up to six sessions, with an interval of 72 h between each application, and they were evaluated initially, after each application, and at 15 and 60 days follow-up post-treatment. The treatment was effective in 86 and 88% of the irradiated teeth, respectively, with the minimum and maximum energy recommended by the manufacturer. There was a statistically significant difference between DH and after a follow-up of 60 days for both groups. The difference between the energy maximum and minimum was not significant.

660 nm was found to be more effective than 830 nm in the study by Ladalardo [1295].

The aim of the study by Corona [1536] was to evaluate in vivo the use of GaAlAs laser and sodium fluoride varnish (Duraphat) in the treatment of cervical dentine hypersensitivity. Twelve patients, with at least two sensitive teeth were selected. A total of 60 teeth were included in the trial. Prior to desensitising treatment, dentine hypersensitivity was assessed by a thermal stimulus and patients' response to the examination was considered to be a control. The GaAlAs laser (15 mW, 4 J/cm²) was irradiated on contact mode and fluoride varnish was applied at cervical region. The efficiency of the treatments was assessed at three examination periods: immediately after first application, 15 and 30 days after the first application. The degree of sensitivity was determined following predefined criteria. Data were submitted to analysis and no statistically significant difference was observed between fluoride varnish and laser. Considering the treatments separately, there was no significant difference for the fluoride varnish at the three examination periods, and for LPT, significant difference was found solely between the values obtained before the treatment and 30 days after the first application. It may be concluded that both treatments may be effective in decreasing cervical dentinal hypersensitivity. Moreover, the low-level GaAlAs laser showed improved results for treating teeth with higher degree of sensitivity.

Rodrigues de Santana [1467] points out that LPT is a good indication for hypersensitivity in patients with amelogenesis imperfecta.

The survey by Mahdavi [1632] was undertaken in a randomised clinical trial. 34 vital teeth scheduled for posterior fixed prosthesis abutment were chosen for the survey. In all stages (temporary, framework, porcelain, primary and permanent cementation laser was used. In the control group the laser was used in the switched off mode. The applied GaAs laser had the following properties: 5 W, 80 Hz, 100 ns, 2 minutes per point. Irradiating over *teeth which were sensitive after preparation showed that after the framework stage and onwards, pain decreased and the differences between laser and control group were significant.*

The aim of study by Pesevska [2070] was to compare the effectiveness of laser irradiation to traditional topical fluoride treatment for treatment choices of dentinal hypersensitivity following scaling and root planing. The experimental group (15 patients) was treated with low-energy-level diode laser at each site of dentinal hypersensitivity following scaling and root planning. The control group (15 patients) received topical fluoride treatment (protective varnish for desensitisation). All the patients were treated at baseline visit, and then at day 2 and 4 after the initial treatment; the pain was subjectively assessed by the patients as strong, medium, medium low, low, or no pain. Total absence of the dental hypersensitivity was reported in 26.66% of the examined group even after the second visit, compared to the control group where complete resolution of the hypersensitivity was not present after the second visit in any of the treated cases. Complete absence of pain was achieved in 86.6% of patients treated with laser and only in 26.6% in the fluoride treated group, after the third visit.

The study by Vieira [2107] evaluated the immediate and 3 month clinical effects of a GaAlAs laser and a 3% potassium oxalate gel for the treatment of dentinal hypersensitivity. A total of 164 teeth from 30 patients with clinical diagnoses of dentinal hypersensitivity were selected for this randomised, placebo-controlled, double-blind clinical study. The teeth were randomised to three groups: GaAlAs laser, oxalate gel, and placebo gel. The treatment sessions were performed at 7 d intervals for four consecutive weeks. The degree of sensitivity in response to an air blast and tactile stimuli was assessed according to a Visual Analogue Scale at baseline, immediately after the fourth application, and then 3 months after the fourth application. The reductions in dentinal hypersensitivity from baseline at the two follow-up assessments were evaluated as the main outcome. In both the active and control groups, there were statistically significant reductions in dentinal hypersensitivity immediately after and 3 months after the treatments, when compared with the hypersensitivity at baseline. No significant differences among the three groups could be detected in their efficacy at either the immediate or 3 month evaluations irrespective of the stimulus.

Forty-eight patients with 244 teeth affected by dentinal hypersensitivity were included in a trial by Yilmaz [2139]. To be included in the study, the subjects had to have 4 or more hypersensitive teeth at different quadrants. Selected teeth were randomly assigned to a GaAlAs laser group, placebo laser group, NaF varnish group, or a placebo NaF varnish group. LPT was performed at 8.5 J/cm^2. In the placebo laser group, the same laser without laser emission was used. In the NaF varnish group, the varnish was painted at the cervical region of the teeth. In the placebo NaF varnish group, the same treatment procedures were performed with a saline solution. DH was assessed with a Visual Analogue Scale (VAS); immediately, at 1 week, and at

1, 3, and 6 months after treatments. GaAlAs laser and NaF varnish treatments resulted in a significant reduction in the VAS scores immediately after treatments that were maintained throughout the study when compared to the baseline and placebo treatments. In the NaF group, there was a significant increase in the VAS scores at 3 and 6 months compared to at 1 week and 1 month. The placebo treatments showed no significant changes in VAS scores throughout the study period.

The aim of the study by Orhan [2385] was to evaluate LPT in cervical dentin hypersensitivity. A randomised controlled clinical trial was conducted with a total of 64 teeth. Dentin desensitiser and diode laser were applied on the cervical dentin surfaces. Distilled water and placebo laser was used as the placebo groups. The irradiance used was 4 J/cm^2 per treatment site. The baseline measurement of hypersensitivity was made by using Visual Analogue Scale. Twenty-four hours and 7 days after the application of desensitiser, diode laser and placebo groups, a new VAS analysis was conducted for the patients' sensitivity level. The mean pain scores of placebo groups were significantly higher than the desensitiser's and diode laser's mean scores The VAS analysis revealed a significant decrease in dentin hypersensitivity in 7 days with the use of the desensitiser and LPT and no statistically significant difference was observed between these two treatments Although LPT and glutaraldehyde containing desensitiser present distinct modes of action, experimental agents caused a significant reduction of dentin hypersensitivity without showing secondary effects, not irritating the pulp or causing pain, not discolouring or staining the teeth, and not irritating the soft tissues at least for a period of 1 week with no drawbacks regarding handling and/or ease of application. LPT and desensitiser application had displayed similar effectiveness in reducing moderate dentin hypersensitivity.

The study by Flecha [2386] includes 434 sensitive teeth from 62 patients. A total of 216 teeth were treated with laser and 218 with cyanoacrylate. A numeric rating scale was used to record the parameters of pain related to the stimuli at baseline and after the treatment at intervals of 24 hours and 30, 90, and 180 days. Both groups had significant reductions in DH. However, there was no significant difference between the two groups at 6 months. Intragroup analysis showed that the effect of cyanoacrylate obtained at 24 hours remained for 90 days in response to air-jet test and 30 days for cold-spray test. There was a statistically significant difference between all other intragroups. It was concluded that cyanoacrylate is as effective as LPT in reducing DH.

The study by Lund [2478] aimed to evaluate and compare the effectiveness of two treatments for dentin hypersensitivity in vivo during 90 days of follow-up. The sample consisted of 117 teeth (13 patients) that were divided into three groups: control with carbomer gel (n = 32) (placebo treatment), 2% sodium fluoride gel (n = 31) and LPT (n = 54). Prior to the desensitizing treatment, the dentin hypersensitivity status of each tooth was assessed. Re-evaluations of the treatments occurred after 5 min, 7, 15, 30 *and 90 days. No significant differences were observed among the low-level laser, 2% topical fluoride and carbomer gel applications. When the methods of evaluation (VAS and ETAB) were compared, there was no difference among the groups with respect to the values for every period of evaluation verifying that the scores obtained with the VAS decreased at the same proportion as the remaining time of ETAB increased. This study showed that both tested therapies were efficacious in controlling painful symptoms associated with dentin hypersensitivity over the entire 90-day follow-up period. The treatments were able to reduce the painful symptoms caused by dentin hypersensitivity, including placebo.*

The aim of the study by Lopes [2477] was to evaluate different protocols for dentin hypersensitivity treatment with LPT at different dosages, desensitizing agent, and associations, for a period of 6 months. After analysis of the inclusion and exclusion criteria of volunteer participants, those who present pain resulting from non-carious cervical lesions were selected. Twenty-seven patients participated in the study, and 55 lesions were recorded. The lesions were divided into five groups (n = 11), treated, and evaluated: G1: Gluma desensitiser, G2: LPT at low dose (three vestibular points and one apical point of irradiation: 30 mW, 10 J/cm^2, 9 s per point, 810 nm), three sessions were performed with an interval of 72 h between them; G3: LPT at high dose (application at one cervical and one apical point: 100 mW, 90 J/cm^2, 11 s per point, 810 nm), three sessions were performed with an interval of 72 h between irradiations; G4: LPT at low dose + Gluma Desensitiser; and G5: LPT at high dose + Gluma desensitiser. The level of sensitivity of each volunteer was evaluated with a Visual Analogue Scale of pain (VAS) with the use of air from a triple syringe and exploration with a probe after time intervals of 5 min, 1 week, and 1, 3, and 6 months after treatment. From the difference in pain, it was observed that for both stimuli, the protocol with the Gluma desensitizing agent presented immediate effects of pain reduction. For lasers, it was observed that there were distinct effects for the different doses. However, both were efficient in reducing pain up to the 6 months of clinical follow-up. Therefore, it could be concluded that all the desensitizing protocols were effective in reducing dentin hypersensitivity, but with different effects. The combination of protocols is an interesting alternative in the treatment of cervical dentin hypersensitivity.

Tooth bleaching often results in temporary hypersensitivity and LPT has therefore been suggested as a suitable treatment after performing whitening. The aim of the study by Lima [2361] was to evaluate the effect of LPT on odontoblast-like cells exposed to a bleaching agent. MDPC-23 cells were seeded in wells of 24-well plates. Eight groups were established according to the exposure to the bleaching agent and LPT (0, 4, 10, and 15 J/cm^2). Enamel-dentin discs were adapted to artificial pulp chambers, which were individually placed in wells containing DMEM. A bleaching agent (35% hydrogen peroxide-BA35%HP) was applied on enamel (15 min) to obtain the extracts (DMEM + BA35%HP components diffused through enamel/dentin *discs). The extracts were applied (1 h) to the cells, and then subjected to LLLT. Cell viability (MTT assay), alkaline phosphatase (ALP) activity, as well as gene expression of ALP, fibronectin (FN), and collagen type I, were evaluated. The bleaching procedures reduced the cell viability, ALP activity, and gene expression of dentin proteins. Laser irradiation did not modulate the cell response; except for FN, since LPT decreased the gene expression of this protein by the cells exposed to the BA35%HP. It can be concluded that BA35%HP decreased the odontoblasts activities that were not recovered by the irradiation of the damaged cells with the laser parameters tested.*

In the review by Blatz [2291] 8 trials reporting on a total of 234 patients were included based on the specified criteria and 20 articles were excluded. Sample size in each of the included studies varied from 20 to 70 patients with differing follow-up intervals of up to 6 months. Most studies used Visual Analogue Scale scores or other subjective tools to assess sensitivity. All 8 studies compared one kind of laser versus one kind of topical desensitising agent. However, types of lasers as well as types of desensitising agents differed among the reviewed studies. Half of the studies compared GaAlAs lasers with various topical desensitising agents; however, findings were conflicting. Two moderate-quality trials indicated that GaAlAs laser and the control desensitising agents preformed similarly. Another moderate-quality trial demonstrated that the application of a bonding agent was significantly better than a GaAlAs laser in the reduction of hypersensitivity. The only reviewed study that was classified as an A-level study revealed a significantly greater immediate and long-term desensitising effect than the control. The remaining studies involved Nd:YAG, Er:YAG, and CO_2 *lasers, all of them reporting a slightly greater decrease in sensitivity as compared with topical desensitising agents. Five of 8 studies reported on the safety of laser application and did not find any detrimental pulpal effects, allergic reactions, or clinically detectable complications during follow-up. The authors concluded that the results obtained from the 8 studies included in this systematic review were conflicting but indicated a slight clinical advantage of laser therapy over topical medicaments in the treatment of dentin hypersensitivity. It was further concluded that application of lasers under controlled parameters for this indication may not lead to adverse effects.*

An innovative method of treating dentinal hypersensitivity is presented by Ko [2521], using a toothbrush with integrated LEDs. Unfortunately the paper keeps calling the LEDs "lasers".

A systematic review and meta-analysis by Sgolastra [2225] assessed the efficacy of lasers in reducing dentin hypersensitivity (DH) as compared with placebo or no treatment. Seven electronic databases and a manual search resulted in 2,538 unique publications. After selection, 13 studies were included in the meta-analysis. A CONSORT-based quality assessment revealed that 3 and 10 studies were at low and high risk of bias, respectively. A random-effects model with the generic inverse variance standardised mean difference (SMD) was used because of expected heterogeneity. Meta-analy-

ses of the baseline-end of follow-up changes in pain revealed no differences for Er,Cr:YSSG vs. placebo but did reveal differences in favour of lasers for Er:YAG vs. placebo, Nd:YAG vs. placebo, and GaAlAs vs. placebo. High and significant heterogeneity was found for all comparisons. In conclusion, Er:YAG, Nd:YAG, and GaAlAs lasers appear to be efficacious in reducing DH. However, given the high heterogeneity of the included studies, future randomised controlled clinical trials are needed to confirm these results.

Further literature: [66, 68, 80, 451, 1332]

5.3.13 Implantology

LPT can achieve good results on postoperative swelling and pain and shorten the healing period of an oral surgical wound [1151], as in implant work. There are also studies indicating that the integration of titanium implants is accelerated. "Early loading" of dental implants has been a trend in implantology and preliminary studies indicate the potential of LPT here. (See chapter 4.1.9 “Bone regeneration” on page 202)

In a literature review Tang [2494] writes: "The use of dental implants has become a mainstay of rehabilitative and restorative dentistry. With an impressive clinical success rate, there remain a few minor clinical issues with the use of implants such as peri-implant mucositis and peri-implantitis. The use of laser technology with implants has a fascinating breadth of applications, beginning from their precision manufacturing to clinical uses for surgical site preparation, reducing pain and inflammation, and promoting osseointegration and tissue regeneration. This latter aspect is the focus of this review, which outlines various studies of implants and laser therapy in animal models. The use of low level light therapy or photobiomodulation has demonstrated its efficacy in these studies. Besides more research studies to understand its molecular mechanisms, significant efforts are needed to standardise the clinical dosing and delivery protocols for laser therapy to ensure the maximal efficacy and safety of this potent clinical tool for photobiomodulation."

Literature:

In vitro studies

The aim of the study by Dortbudak [1440] was to determine the effect of continuous wave irradiation on osteoblasts derived mesenchymal cells. Three groups of 10 cultures each were irradiated 3 times (days 3, 5, 7) with a pulsed diode soft laser with a wavelength of 690 nm for 60 s. Another 3 groups of 10 cultures each were used as control groups. A newly developed method employing the fluorescent antibiotic tetracycline was used to compare bone growth on these culture substrates after a period of 8, 12 and 16 days, respectively. It was found that all lased cultures demonstrated significantly more fluorescent bone deposits than the non-lased cultures. The difference was significant in the cultures, examined after 16 days. Hence it is concluded that irradiation with a pulsed diode soft laser has a biostimulating *effect on osteoblasts in vitro, which might be used in osseointegration of dental implants.*

In a study by Khadra [1439] the effect of LPT on attachment and proliferation of human gingival fibroblasts (HGF) cultured on titanium implant material. HGF were exposed to 830 nm at dosages of 1.5 or 3 J/cm and then cultured on commercially pure titanium discs. Cell profile areas were measured after 1, 3 and 24 h, using scanning electron microscopy and an automatic image analyser. The results were expressed as percentage of attachment. In order to investigate the effect of LPT on cellular growth after 8 and 10 days, HGF were cultured on titanium discs for 24 h and then exposed to laser irradiation on 3 consecutive days. Colony-forming efficiency (CFE) and clonal growth rates (CGR) were measured. Cell viability was determined by Hoechst and prodidium iodide staining. Non-lased cultures served as controls. Morphologically, the cells spread well on all titanium surfaces, indicating good attachment by both irradiated and non-irradiated cells. Fibroblasts exposed to laser irradiation had significantly higher percentages of cell attachment than the non-exposed cells. CFE and CGR were also enhanced for the irradiated cells. Cell viability was high in the irradiated and control groups, without significant differences.

Animal studies

Asanami [91] placed hydroxyapatite implants in the lower jaws of rabbits. The laser group was treated with a HeNe laser (6 mW, 10 minutes). After three weeks, both groups were studied histologically. A macroscopically visible extrusion had arisen in the control group, while no such extrusion could be observed in the experimental group. Very little granulation tissue was observed in the experimental group. There was evidence of direct contact between the implant and bone with strong osteoblast activity and new formation of bone. A comparison of the calcium content of the bone around the implant showed a considerable difference between the experimental and control groups.

Guzardella [1305] placed cylindrical hydroxyapatite implants in both distal femurs of 12 rabbits. From postoperative day 1 and for 5 consecutive days, the left femurs of all rabbits were submitted to LPT of the following parameters: 830 nm, 1000 mW, 300 J/cm^2, 300 Hz, 10 minutes. The right femurs were sham irradiated. 3 and 6 weeks after implantation, histomorphometric and microhardness measurements were taken. A higher affinity index was observed at the HA-bone interface in the laser group at 3 and 6 weeks; a significant difference in bone microhardness was seen in the laser group as compared to the sham group.

Kusakari [121] studied the effects of GaAlAs 30 mW on implants in the lower jaws of dogs. The following are some of the findings: the collagen and RNA content of the gum reached its peak on the fifth day; no change in DNA content was observed; and the number of cell elements in the bone marrow had risen by day 3. By day 7, the amount of new-formed bone around the *operation defect was greater on the side treated with laser than on the control side. LPT increased DNA synthesis in the osteoblasts without affecting morphology. LPT also increased the alkaline phosphate activity.*

In an adult dog experiment by Monteiro Martins [970], 830 nm, 4.8 J/cm² was given around the implants three times a week for two weeks. SEM analysis 45 and 60 days after surgery showed better osseointegration with more compact and organised cancellous bone, with increased vascularisation in the irradiated group. These characteristics were more pronounced in the superior and median third of the implants.

Pinheiro [1128] made implants in five dogs with another five serving as control. The animals were sacrificed after 45 and 60 days. Transcutaneous irradiation was performed with a 40 mW, 830 nm laser, 4.8 J/cm², total energy 1.2 J per point. The specimens were analysed through SEM. The irradiated specimens showed better bone healing.

The effects of 680 and 830 nm lasers on osseointegration were studied by Blay [1220]. 30 adult rats were divided into three groups; two laser groups and one control. The rats in the two laser groups had pure titanium Frialit-2 implants implanted into each proximal metaphysis of their respective tibias, inserted with a 40 Ncm torque. The initial stability was monitored by means of a resonance frequency analyser. Ten irradiations were performed, 48 hours apart, 4 J/cm² on two points, starting immediately after surgery. Resonance frequency analysis indicated a significant difference between frequency values at 3 and 6 weeks, as compared to control. At 6 weeks the removal torque in the laser groups was much higher than in the control group.

Through near-infrared Raman spectroscopy (NIRS), Lopes [1444] studied the incorporation of hydroxyapatite of calcium (CHA) on the healing bone around dental implants submitted or not to low-level LPT. Fourteen rabbits received a titanium implant on the tibia; eight of them were irradiated with 830 nm laser (seven sessions at 48-h intervals, 21.5 J/cm² per session, 10 mW, 85 J/cm² treatment dose), and six acted as control. The animals were sacrificed at 15, 30, and 45 days after surgery. Specimens were routinely prepared for Raman spectroscopy. Twelve readings were taken on the bone around the implant. The results showed significant differences in the concentration of CHA on irradiated and control specimens at both 30 and 45 days after surgery.

The aim of the study by Khadra [1438] was to investigate the effect of LPT with GaAlAs on titanium implant healing and attachment in bone. This study was performed as an animal trial of 8 weeks duration with a blinded, placebo-controlled design. Two coin-shaped titanium implants with a diameter of 6.25 mm and a height of 1.95 mm were implanted into cortical bone in each proximal tibia of twelve New Zealand white female rabbits (n=48). The animals were randomly divided into irradiated and control groups. The LPT was used immediately after surgery and carried out daily for 10 consecutive *days. The animals were killed after 8 weeks of healing. The mechanical strength of the attachment between the bone and 44 titanium implants was evaluated using a tensile pullout test. Histomorphometrical analysis of the four implants left in place from four rabbits was then performed. Energy-dispersive X-ray microanalysis was applied for analyses of calcium and phosphorus on the implant test surface after the tensile test. The mean tensile forces, measured in Newton, of the irradiated implants and controls were 14.35 and 10.27, respectively, suggesting a gain in functional attachment at 8 weeks following. The histomorphometrical evaluation suggested that the irradiated group had more bone-to-implant contact than the controls. The weight percentages of calcium and phosphorus were significantly higher in the irradiated group when compared to the controls, suggesting that bone maturation processed faster in irradiated bone.*

The aim of another study by Khadra [1610] was to investigate the effect of LPT with GaAlAs on titanium implant healing and attachment in bone. This study was performed as an animal trial of 8 weeks duration with a blinded, placebo-controlled design. Two coin-shaped titanium implants with a diameter of 6.25 mm and a height of 1.95 mm were implanted into cortical bone in each proximal tibia of twelve New Zealand rabbits (n=48). The animals were randomly divided into irradiated and control groups. The laser was used immediately after surgery and carried out daily for 10 consecutive days. The animals were killed after 8 weeks of healing. The mechanical strength of the attachment between the bone and 44 titanium implants was evaluated using a tensile pullout test. Histomorphometrical analysis of the four implants left in place from four rabbits was then performed. Energy-dispersive X-ray microanalysis was applied for analyses of calcium and phosphorus on the implant test surface after the tensile test. The mean tensile forces, measured in Newton, of the irradiated implants and controls were 14.35 (SD+/-4.98) and 10.27 (SD+/-4.38), respectively, suggesting a gain in functional attachment at 8 weeks following laser. The histomorphometrical evaluation suggested that the irradiated group had more bone-to-implant contact than the controls. The weight percentages of calcium and phosphorus were significantly higher in the irradiated group when compared to the controls, suggesting that bone maturation processed faster in irradiated bone.

In the paper by Kim [1844] the author concludes: "From the above results, the expression of OPG, RANKL, and RANK during the osseointegration of the dental titanium implant was observed within bone tissue. The application of the LPT influenced the expression of OPG, RANKL, and RANK, and resulted in the expansion of metabolic bone activity and increased the activity of bone tissue cells."

A study by Pereira [2074] aimed to histometrically evaluate the influence of LPT treatment on bone healing around titanium implants placed in rabbit tibiae. Each tibia of 12 adult rabbits received a 3.3 x 6-mm titanium implant. The implants placed in the right tibiae were irradiated with a

GaAlAs laser every 48 hours for 14 days postoperatively, and the left tibiae were not irradiated. After 3 or 6 weeks, the animals were sacrificed (six animals per period), and non-decalcified sections were obtained and analysed for bone-to-implant contact (BIC) and bone area within the implant threads. BIC was significantly increased in the laser-treated group at both 3 weeks and 6 weeks. BIC did not increase significantly with time (3 weeks versus 6 weeks). Conversely, bone area within the threads was significantly increased with time (3 weeks versus 6 weeks), regardless of whether the laser was used. Considering bone area within the threads, no significant difference was found for treatment, e.g., with or without laser. In conclusion, LPT did not affect the area of bone formed within the threads, but it may improve BIC in rabbit tibiae.

Coelho [2304] evaluated the systemic effects of LPT on the early stages of bone repair after implantation of poly-L-lactic/polyglycolic acid (PLLA-PGA) screws 24 rabbits were randomly allocated to one of two groups, experiment or control. Each animal underwent implantation of one 5×1.5 mm PLLA-PGA screw in each tibia (right and left). The experiment group received infrared laser irradiation (830 nm, 4 J, 100 mW, 10.1 s) over the right paw immediately after implantation and every 48 h thereafter, for a maximum of seven sessions. The control group was not irradiated. Both groups were divided into three subgroups according to the observation period (5, 15, or 30 days), after which animals were euthanised. The results observed in the left paw of experimental animals were compared with the left paws of control animals. We also compared the right and left paws of experimental animals so as to compare local and potential systemic effects. Bone specimens were analysed to assess the extent of peri-implant bone formation, quantitative analysis revealed greater bone formation in the left tibia of experimental animals as compared to controls on 5-day follow-up. Descriptive analysis revealed slightly larger and thicker trabeculae in the irradiated animals at 5 days post-procedure. There were no significant differences at any other point in time. As used in this study, LPT had a positive systemic effect on the early stages of bone formation.

100 mW x 10.1 s is actually 1.1 J, not 4.

A study by Primo [2141] measured removal torque and bone-implant interface resistance of machined implants, acid etched implants, or machined implants irradiated around the implant area with infrared low-level laser therapy (830 nm) immediately after surgery. There were statistically significant differences between Groups A (control) and B (rough surface). Implants with a rough surface seem to add resistance to the bone-implant interface when compared with smooth titanium implants or implants treated with LPT.

Omasa [2220] placed seventy-eight titanium mini-implants into both tibiae of 6-week-old male rats. The mini-implants in the right tibia were subjected to LPT (830 nm) once a day during 7 days, and the mini-implants in the left tibia served as non-irradiated controls. At 7 and 35 days after *implantation, the stability of the mini-implants was investigated using the diagnostic tool (Periotest). New bone volume around the mini-implants was measured on days 3, 5, and 7 by in vivo microfocus CT. The gene expression of bone morphogenetic protein (BMP)-2 in bone around the mini-implants was also analysed using real-time reverse-transcription polymerase chain reaction assays. The data were statistically analysed using Student's t test. Periotest values were significantly lower and the volume of newly formed bone was significantly higher in the LPT group. LPT also stimulated significant BMP-2 gene expression in peri-implant bone.*

The review by Vasconcellos [2265] investigates the influence of LPT on bone healing in the femur of osteopenic and normal rats with titanium implants. Ovariectomy and control group were randomly submitted to LPT, which was applied by GaAlAs laser at the surgical site before and after placing the implant, for seven times. Histomorphometric and statistical analysis were performed. Most irradiated groups showed higher values than the non-irradiated groups. The infrared diode laser may improve the osseointegration process in osteopenic and normal bone, particularly based on its effects in the initial phase of bone formation.

The work by Maluf [2334] evaluated mechanically the bone-implant attachment submitted or not to LPT, 795 nm, CW, 120 mW. The implant was placed in one of the shinbones of 24 mice, randomly distributed into two groups. The experimental group was submitted to six laser applications, divided into four points previously established, two lateral and two longitudinal, six times 8 J/cm^2 with an interval of 2 days, totalling the dose of 48 J/cm^2. The control group did not receive laser therapy. The interval between applications was 48 h and the irradiations began immediately after the end of the implant surgeries. The two groups were killed on the 14th day and a bone block of the area was removed where the implant was inserted. A torque machine was used to measure the torque needed for loosening the implants. A statistically significant difference was observed between the two groups. The experimental group presented larger difficulty for breaking up the implant interface with the bone block than the control group.

A study by Teixeira [2347] aimed to evaluate the influence of LPT on the early stages of osseointegration. Ninety-six external hex implants (3.75 mm X 5.0 mm) were placed in 24 rabbits, being one machined and one sand-blasted acid-etched per tibia, and later divided in laser group, which received a total dose of 24 J/cm^2 of GaAlAs laser over 15 days; and control group. At 16 and 30 days after surgery, removal torque and histomorphometric analyses were performed. No statistical differences in removal torque or histomorphometric analyses were verified between laser and control groups regardless of implant surface. Time was the only variable presenting significant differences between measurements. LPT had no significant short-term effect on bone-to-implant contact and removal torque values regardless of implant surface characteristics.

The study by Boldrini [2396] aimed to evaluate the removal torque of titanium implants irradiated with LPT during surgical preparation of implant bed, in comparison to non-irradiation. Sixty-four rats were used. Half of the animals were included in LPT group, while the other half remained as control. All animals had the tibia prepared with a 2 mm drill, and a titanium implant (2.2 × 4 mm) was inserted. Animals from LPT group were irradiated with 808 nm, 50 mW, to emit radiation in collimated beams (0.4 cm^2), for 1 min and 23 s, and an energy density of 11 J/cm^2. Two applications (22 J/cm^2) were performed immediately after bed preparation for implant installation. Flaps were sutured, and animals from both groups were sacrificed 7, 15, 30, and 45 days after implant installation, when load necessary for removing implant from bone was evaluated by using a torquimeter. In both groups, torque values tended to increase overtime; and at 30 and 45 days periods, values were statistically higher for LPT group in comparison to control.

The work by Soares [2403] assessed the influence of LPT on bone volume (BV) and bone implant contact (BIC) interface around implants inserted in blocks of bovine or autologous bone grafts (autografts), irradiated or not, in rabbit femurs. Twenty-four adult rabbits were divided in 8 groups: AG: autograft; XG: xenograft; AG/L: autograft + laser; XG/L: xenograft + laser; AG/I: autograft + titanium (Ti) implant; XG/I: xenograft + Ti implant; AG/I/L: autograft + Ti implant + laser; and XG/I/L: xenograft + Ti implant + laser. The animals received the Ti implant after incorporation of the grafts. The laser parameters in the groups AG/L and XG/L were 780 nm, 70 mW, CW, 21.5 J/cm^2, while in the groups AG/I/L and XG/I/L the following parameters were used: 780 nm, 70 mW, 0.5 cm^2 (spot), 4 J/cm^2 per point (4), 16 J/cm^2 per session, 48 h interval x 12 sessions, CW, contact mode. LPT was repeated every other day during 2 weeks. To avoid systemic effect, only one limb of each rabbit was double grafted. All animals were sacrificed 9 weeks after implantation. Specimens were routinely stained and histomorphometry carried out. Comparison of non-irradiated and irradiated grafts (AG/L versus AG and XG/L versus XG) showed that irradiation increased significantly BV on both grafts. Comparison between irradiated and non-irradiated grafts (AG/I/L versus AG/I and XG/I/L versus XG/I) showed a significant increase of the BIC in autografts. The same was seen when xenografts were used, without significant difference. The results of this investigation suggest that the use of LPT is effective for enhancing new bone formation with consequent increase of bone-implant interface in both autologous grafts and xenografts.

Clinical studies

The aim of a randomised clinical study by García-Morales [2140] was to assess the LPT effect on implants stability by means of resonance frequency analysis (RFA). Thirty implants were distributed bilaterally in the posterior mandible of eight patients. At the experimental side, the implants *were submitted to LPT (830 nm, 86 mW, 92.1 J/cm², 0.25 J, 3 s/point, at 20 points), and on the control side, the irradiation was simulated (placebo). The first irradiation was performed in the immediate postoperative period, and it was repeated every 48 h in the first 14 days. The initial implant stability quotient (ISQ) of the implants was measured by means of RFA. New ISQ measurements were made after 10 days, 3, 6, 9, and 12 weeks. The initial ISQ values ranged from 65-84, with a mean of 76, undergoing a significant drop in stability from the 10th day to the 6th week in the irradiated group, and presenting a gradual increase from the 6th to the 12th week. The highest ISQ values were observed on the 10th day in the irradiated group, and the lowest in the 6th week in both groups. Under the conditions of this study, no evidence was found of any effect of LPT on the stability of the implants when measured by RFA. Since high primary stability and good bone quality are of major relevancy for a rigid bone-implant interface, additional LPT may have little impact macroscopically.*

Further literature: [91, 121, 213, 583, 931, 1218, 1219, 1607, 1608]

5.3.14 Leukoplakia

Leukoplakia is a condition where areas of keratosis appear as adherent white patches on the mucous membranes of the oral cavity. Oral leukoplakia is defined as a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion. This condition does not always produce subjective symptoms. If the patient does have leukoplakia symptoms, they can be alleviated with LPT. Whether LPT can actually cure the condition has not been reported, but a stimulation of the immune system in the area affected is worth trying.

Literature:

After removal of oral leukoplakia by cryotherapy, LPT is suggested by Ribeiro [2146]. Ten patients with oral leukoplakia were submitted to cryosurgical treatment (Non-LPT group) and eight were submitted to cryosurgical treatment associated with LPT (LPT group). Laser irradiation of patients within the LPT group was performed using a 50 mW, 660 nm continuous wave laser with a spot size at the tissue surface of 0.0286 cm², irradiance 1.75 W/cm². Three points within an area of 1cm² around the cryosurgical site were irradiated in contact mode for 28s per point (1.4 J at 49 J/cm² per point). Irradiation was carried out immediately following cryosurgical treatment and at 48 and 72h post-cryosurgical treatment. A numerical rating scale was used to assess the pain. Treated OL sites appeared to be clinically normal and with no evidence of recurrence during the average 9-month follow-up period. The LPT group reported less pain than did the non-LPT group.

Further literature: [209]

5.3.15 Lingua geographica (glossitis)

Geographic tongue is an inflammatory condition of the mucous membrane of the tongue, usually on the dorsal surface. It is a common condition, affecting approximately 2-3% of the general population. It is characterised by areas of smooth, red depapillation (loss of lingual papillae) which migrate over time. The name comes from the map-like appearance of the tongue, with the patches resembling the islands of an archipelago. The cause is unknown, but the condition is entirely benign (importantly, it does not represent oral cancer), and there is no curative treatment. Uncommonly, geographic tongue may cause a burning sensation on the tongue, for which various treatments have been described with little formal evidence of efficacy.
In symptomatic cases, 3-4 J LPT over 5-6 points relieves the symptoms. Its effect on long-term healing is not clear, but there is no effective treatment of any other kind that can heal this condition.

Literature:

Mezawa [114] studied the effects of GaAlAs laser light on nociceptors in cat tongues. A decrease in nociceptor activity could be demonstrated after one minute's irradiation. No further change was noted in the 5-10 minute interval, and the authors drew the conclusion that a plateau was reached after five minutes.

Hubacek [1036] reports successful treatment of glossodynia using GaAlAs laser, 4-6 J/cm², 4-10 sessions.

See also: Burning mouth syndrome

5.3.16 Lip wounds

Angular cheilitis caused by a low vertical dimension can be successfully treated with LPT but will reappear if the fundamental cause is not dealt with. Wounds on lips usually heal quickly with LPT in cases of trauma and mechanical/chemical irritation. Lip fissures are well worth treating. A typical symptom is that they begin to bleed after having been very dry - this is the beginning of the healing process. HeNe or low doses of GaAlAs laser are recommended.

Literature: [1201]

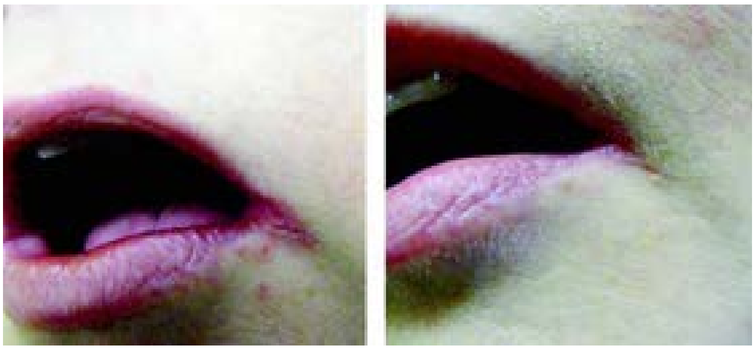


Figure 5.8 Non-healing angular chielitis after one week of daily red laser therapy

5.3.17 Nausea

A common complication in dentistry is nausea and gagging. Some patients are very sensitive to operations behind the premolars and taking impressions may be very difficult. In these cases, the laser can be applied to the sulcus mento-labialis in the contact mode. 2-3 J will reduce nausea in a great number of cases. If not successful, the acupuncture point P6 on the wrist can be used. The effect will arise a couple of minutes post irradiation.

Literature: [892]

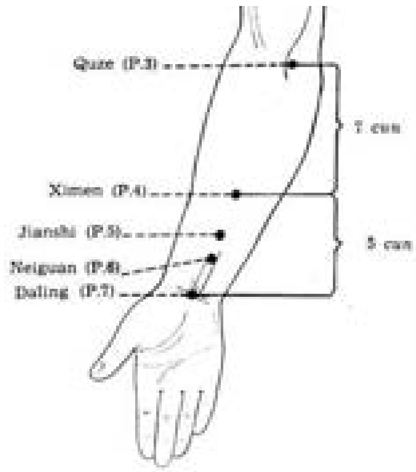


Figure 5.9 Location of the P6 point

5.3.18 Nerve injury

Damaged nerves heal slowly. Feared complications in odontology are damage to n. alveolaris inferior and n. lingualis. It is not uncommon for a patient to be afflicted by lengthy or permanent paraesthesia as a result of oral surgery. General practice dentists can also cause paraesthesia through trauma from hypodermic needles, the use of elevator of the lingual side of the lower jaw, and other causes. LPT is the only available treatment in these cases. An indication of the effects of LPT is the patient's unspecified sense of emerging anxiety in the area treated with laser. Dentists have carried out a great deal of successful research in this field.

(See chapter 4.1.40 “Nerve regeneration and function” on page 333)

5.3.19 Orthodontics

After the insertion of any orthodontic apparatus, a few days of noticeable pain follow in the areas subjected to stress. LPT used directly after treatment delays the onset of pain and reduces its intensity. LPT also appears to be able to increase the speed of tooth movement and the bony remodeling. Some studies indicate a faster process of tooth movement but since one paper has come to the opposite conclusion, the effect of laser here is, as always, dose dependent. In a literature review on increased movement through LPT, a total of 109 articles were identified by Torri [2249], of which 14 were selected for detailed analysis. Diode laser was used in all studies with different energies, frequencies, and doses. In animal studies, the most common and effective energy input was 54 J per session daily; in humans, it was 2 J per ooth and session on the first days, with 72-96 h intervals. Orthodontic force also influenced orthodontic movement. A force of 10 g/force seems to be indicated for moving molars in rats, versus 150 g for canines in humans. Most authors report positive effects of the use of LPT on speed increase of orthodontic tooth movement when compared with control or placebo groups.

Literature:

In vitro studies

Shimizu [370, 1012] studied the effect of GaAlAs laser light on prostaglandin E_2 and interleukin-1ß production in stretched human periodontal ligament (PDL) cells in vitro at varying intervals and doses. The PDL cells showed a marked elevation of prostaglandin and interleukin in response to mechanical stretching. PGE_2 production was significantly inhibited by LPT in a dose-dependent manner. IL-1ß production was also reduced, but only partially under these conditions. It is therefore possible to propose a mechanism whereby pain relief and bone resorption activity could be modulated through LPT.

Ozawa [522] suggests that LPT may reduce collagen breakdown around the PDL, associated with traumatic occlusion. Stretched healthy human PDL cells were irradiated with GaAlAs laser light. Plasminogen activator (PA) activity was elevated in cells subjected to stretching. LPT reduced this activity in a dose-dependent manner, between 55% and 86%.

A study by Xu [1915] aimed to investigate the effect of 650 nm, 2 mW irradiation on mRNA expression of receptor activator of NF-kappaB ligand (RANKL) and osteoprotegerin (OPG) in rat calvarial cells. Cultured cells were treated with LPT irradiation of 1.14 J/cm^2 (group A) or 2.28 J/cm^2 (group B), and non-irradiated cells (group C) were used as controls. The changes in cell numbers, alkaline phosphatase (ALP) activity, RANKL, and OPG mRNA expression in the three study groups was determined using MTT, UV/VIS spectrophotometry, and RT-PCR analyses. The cell numbers in groups A and B increased significantly (7.52% and 8.80%, respectively), as did ALP activity (71.95% and 88.20%, respectively), compared with group C. RANKL and OPG mRNA expression in group A were 51.06% lower and

3.35 times higher, respectively, than those seen in the controls and the RANKL:OPG mRNA ratio in group A was 81.82% lower than that in group C. In conclusion, the irradiation may directly promote osteoblast proliferation and differentiation, and indirectly inhibit osteoclast differentiation, by downregulating the RANKL:OPG mRNA ratio in osteoblasts.

The purpose of a study by Huang [2138] was to analyse proliferation, inflammation, and osteogenic effects on periodontal ligament (PDL) cells after LPT under simulated orthodontic tension conditions. A human PDL cell line was cultured in an incubator. The PDL cells were treated with a 670 nm laser, output 500 mW (CW) for 2.5 or 5 sec, spot area 0.25 cm^2, corresponding to 1.25 and 2.5 J at an energy density of 5 or 10 J/cm^2, respectively. PDL cell viability was assayed by detecting the ability of the cells to cleave tetrazolium salt to formazan dye. Inflammation and osteogenic markers were analysed by Western blot analysis. PDL cell viability increased in the experimental group, based on the ability of the cells to cleave tetrazolium salt at day 7. The experimental group showed no difference in PDL cellular morphology compared with the control group. The inflammation markers inducible NO synthase (iNOS), cyclooxygenase (COX)-2 and interleukin (IL)-1 showed stronger expression in 5 and 10 J/cm^2 therapy at days 1 and 5, but decreased in expression at day 7. The osteogenic marker osteocalcin (OC) expression level was significantly higher at day 7 than in the control cells. LPT significantly increased PDL cell proliferation, decreased PDL cell inflammation, and increased PDL OC activity under the tension conditions used in this study.

Animal studies

Saito [569] expanded the midpalatal suture in rats. A 100 mW GaAlAs laser was used to influence bone regeneration. Irradiation during the two first postoperative days was effective, showing acceleration at 1.2 to 1.4-fold as compared to the control group. Irradiation in the late period (days 4 to 6) was not effective, nor one single irradiation.

Kawasaki [917] applied 10 g of orthodontic force to rat molars to cause experimental tooth movement. Irradiation was performed daily for ten days, 54 J per session. Increased osteoclast activity was observed on the pressure side in the laser group as well as increased rate of cellular proliferation on the tension side. Tooth movement was increased 1.3-fold.

Sudoh [695] applied a load of 100 g to maxillary canines in 15 cats. GaAlAs laser irradiation was performed daily over the area for two weeks. At day 7 and 14 the moving distance was measured and the animals sacrificed for histological examination. At two weeks the moving distance was larger in the laser group than in the control group. In the laser group a prominent new bone deposition with marked osteoblastic activity was seen on the alveolar bone on the tension side. On the compressed side, bone resorption with an increased number of tartrate resistant acid phosphatase-positive osteoclasts took place at the inner aspect of the alveolar bone adja-

cent to the hyalinised zone. Morphometric analysis demonstrated that the area of both newly formed bone and bone cavity and the number of TRAcP-positive osteoclasts were significantly larger in the irradiated area as compared to control.

The aim of a study by Sun [1779] was to investigate effects of LPT on experimental tooth movement and the remodeling of alveolar bone in rabbits. A total of 42 white rabbits were chosen and randomised into one control group and six experimental groups, with 6 rabbits in each group. After anaesthesia orthodontic appliances consisting of a coil spring connected bilaterally the upper first molar with the upper incisor by using a ligature wire. The force exerted at the time of insertion was approximately 80 g. The left side served as the control side, and the right side was the experimental side treated by receiving irradiation of laser. The treatment periods of different groups lasted separately for 1, 3, 5, 7, 14, 21 days respectively. The displacement extent of teeth was measured by employing the computer image analysing system. The results were analysed statistically. Through HE staining, the histomorphological character of tissue around first molar was also investigated, and numbers of osteoclasts were counted. The displacement extent of teeth on the experimental side, which was irradiated by laser, was more obvious than that of the normal control side. The difference was statistically significant 1, 3, 14, 21 days after the beginning of the treatment. Through histological observation under a light microscope, the osteoclasts and osteoblasts on the experimental side remained more active than those of the control side. There is significant difference in amount of osteoclasts between the experimental and the control sides, 3, 5 or 7 days after the treatment.

The purpose of yet another study by Sun [1780] was to investigate the effect of HeNe irradiation on the expression of transforming growth factor ß1 (TGF-ß1) during experimental tooth movement in rabbits. Thirty-five rabbits were used. The animals were randomly divided into 7 groups equally: normal group and experimental (1, 3, 5, 7, 14, 21 days) groups, 5 rabbits in each group. An orthodontic appliance, consisting of a coil spring was ligated to the bilateral first maxillary molar and connected to an orthodontic wire ligated onto the incisors, and exerting a force of approximately 80 g. The left side was used as control, and the right side was designed as irradiated side. The animals from each group were sacrificed at the time discontinued. The histological sections were proceeded with immunohistochemical staining of TGF-ß1. Then it was analysed by Computer Image Analyzing System and statistically processed. The expression of TGF-ß1 was demonstrated in the area of tension and pressure of periodontium tissue in both of the irradiated and control sides. The TGF-ß1 staining in the pressure area of the irradiated side decreased significantly at 1 day compared with the control side. TGF-ß1 staining increased significantly at 3 to 5 days in the pressure area. But in the tension area of the irradiated side, TGF-ß1 staining was significantly increased at 3 to 7 days. The peak value of the area of tension and pressure both appeared at the same time of the 5th day.

The purpose of the study by Zhu [1661] was to investigate the effects of LPT on basic fibroblast growth factors (bFGF) expression in periodontal tissue during tooth movement. 18 white rabbits were randomly divided into 6 groups with 3 rabbits in each group, including groups of 1, 3, 5, 7, 14 and 21 days. Under an anaesthesia condition by 2% pentobarbital sodium, stainless coil springs were fixed between the first maxillary molar and the incisor producing the force of 80 g. The right side of maxilla was considered as the experimental group under the irradiation of laser, with the left side as the control groups. The expression of bFGF was investigated half-quantitatively through immunohistochemical analysis. The expression of bFGF in periodontal tissue with irradiation of laser was higher than the control side. There were significant differences among the 5, 7, and 14 day groups. In the tension area of the experimental side, the expression of bFGF in the osteoblastic surface of alveolar bone was characteristically greater than that of the control side. Thus, LPT promotes the expression of bFGF in the periodontal tissue and alveolar bone remodelling.

The aim of a study by Goulart [1689] was to evaluate, through a double-blind study, the effect of GaAlAs laser irradiation on the speed of orthodontic movement in canine premolars. Eighteen dogs were divided into two groups, and their third molars were extracted. An orthodontic device was placed between the first molar and the second premolar for stabilisation purpose. Group I was irradiated with a dosage of 5.25 J/cm² on the right side, whereas the left side was used as the control group. Group II was submitted to the same procedure, but was irradiated with a dosage of 35.0 J/cm². Irradiations were done every 7 days, for a total of nine irradiations. The orthodontic space was measured every 21 days. The 5.25 J/cm² dosage accelerated orthodontic movement during the first observation period, from 0 to 21 days, whereas the 35.0 J/cm² dosage retarded the orthodontic movement in the treated group when compared with the control group, during both the first and second observation periods, from 0 to 42 days. The results suggest that LPT may accelerate orthodontic movement at a dosage of 5.25 J/cm², whereas a higher dosage, 35.0 J/cm², may retard it.

However, the experimental study by Seifi [1671] has come to the opposite conclusion. The study was conducted on 18 male albino rabbits divided into three equal groups: Laser 1 (5 mW peak power, 850 nm wavelength, 3 minutes per session, pulsed, pulse repetition rate of 3000 Hz, duration of pulse 100 nsec, total energy in experiment 2.43 J) and Laser 2 (10 mW, continuous, wavelength 630 nm, 5 minutes per session, total energy in experiment 27 J), and a non-irradiated group. The first mandibular molars, in all groups were under a four ounce tension using NiTi-Closed coil springs. The control group was not irradiated but the laser groups were irradiated for nine days. After sixteen days, following the termination of therapeutic regime; samples were sacrificed. The distance between the distal surface of the first molar and the mesial surface of the second molar was measured with 0.05 mm accuracy. The mean orthodontic tooth movements of the first man-

dibular molars were 1.7±0.16 mm in control group, 0.69±0.16 mm in Laser 1 group and 0.86±0.13 mm in Laser 2 group. These results indicate that the orthodontic movement velocity can be modulated with the energy density or the total energy applied.

In another experimental animal trial by Seifi [2512], 16 male albino rabbits were selected with similar characteristics and randomly divided in two groups. Under general anesthesia, an artificial socket, 8 mm in height, was created in the mesial aspect of the first premolars of the rabbits and filled with demineralised freeze dried bone allograft (DFDBA). The first premolars were connected to the incisors using nickel titanium coil springs. In experimental group, 808 nm laser was irritated mesial to first premolar where artificial socket was created continuously. The cycle was 10 days irritation, 14 days rest, 10 days irritation, 14 days rest. Control group was not laser irradiated. All animals were sacrificed after 48 days and the distance between the distal aspect of the first premolars, and the mesial surface of the second premolars was measured with leaf gauge. The specimens underwent histological assessments. Integrity of root and its resorption was observed under microscope calibration. The size of resorption lacunae was calculated in mm2. Normality of data was proved according to, Kolmogorov-Smirnov analysis, and Student's t-test was done. The mean OTM were 5.68 ± 1.21 mm in the control group and 6.0 ± 0.99 mm in the laser irradiated teeth with no statistically significant differences. The mean root resorption was 1.61 ± 0.43 mm and 0.18 ± 0.07 mm2 in the control and experimental groups respectively being significantly lower in the laser irradiated teeth. The findings of the present study show that LPT together with the application of DFDBA led to limited amount of the stimulated OTM. The LPT in combination with alloplastic materials used for socket preservation could reduce the degree of root resorption significantly.

The receptor activator of the nuclear factor-kB (RANK) / RANK ligand (RANKL)/osteoprotegerin (OPG) system is essential and sufficient for osteoclastogenesis. A study by Fujita [1917] was designed to examine the effects of LPT on expressions of RANK, RANKL, and OPG during experimental tooth movement. To induce experimental tooth movement in rats, 10 g of orthodontic force was applied to the molars. Next, a GaAlAs laser was used to irradiate the area around the moved tooth and the amount of tooth movement was measured for 7 days. Immunohistochemical staining with RANK, RANKL, and OPG were performed. Real time PCR was also performed to elucidate the expression of RANK in irradiated rat osteoclast precursor cells in vitro. In the irradiation group, the amount of tooth movement was significantly greater than in the non-irradiation group by the end of the experimental period. Cells that showed positive immunoreactions to the primary antibodies of RANKL and RANK were significantly increased in the irradiation group on day 2 and 3, compared with the non-irradiation group. In contrast, the expression of OPG was not changed. Further, RANK expression in osteoclast precursor cells was detected at an early stage (day 2 and 3) in the *irradiation group. In conclusion, these findings suggest that LPT stimulates the velocity of tooth movement via induction of RANK and RANKL.*

The objective of the study by Kim [2099] was to investigate the combined effects of Corticision and LPT on the tooth movement rate and paradental remodeling in beagles. The maxillary second premolars (n=24) of 12 beagles were randomly divided into four groups (n=6 per group) based on the treatment modality: group A, only orthodontic force (control); group B, orthodontic force plus Corticision; group C, orthodontic force plus LPT; group D, orthodontic force plus Corticision and LPT. Ratios of second premolar-to-canine movement were greater by 2.23-fold in group B and 2.08-fold in group C, but 0.52-fold lesser in group D than in group A. The peak velocity was observed at an earlier stage of tooth movement in group B but at a later stage in group C during the 8-week treatment period. At week 8, both tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts on the compression side and proliferating cell nuclear antigen (PCNA)-positive osteoblasts on the tension side increased significantly in group C but decreased in group D. Histomorphometric analysis revealed that the mean apposition length of newly formed mineralised bone during the 8 weeks of treatment significantly increased in both group B (2.8-fold) and group C (2.2-fold). In group D, the labeling lines on lamina dura were thin and discontinuous, but intratrabecular remodeling and lamellation were found to be active.

The aim of a study by Cossetin [2234] was to analyse the effect of LPT on bone remodelling during induced tooth movement in rats. A diode laser (808 nm, 100 mW, 54 J on an area of 0.0028 cm^2) was used. The application was continuous, punctual, and with contact. Forty-two 70-day-old Wistar rats had the maxillary left first molar moved using a force level of 25 g. In two experimental subgroups the movement was performed over 7 days and in three subgroups the movement occurred over 14 days. In the 7-day movement subgroups, one subgroup received laser irradiation on day 1 only; the other subgroup received laser irradiation on days 1, 3, and 5. In the 14-day movement subgroups, one subgroup received laser irradiation on day 1 only; the second on days 1, 3, and 5; and the third on days 1, 3, 5, 7, 9, 11, and 13. The control group was also divided into two subgroups, and movement occurred over two different periods of treatment (7 days and 14 days) without laser application; these were used as controls for the respective experimental subgroups. The subgroup with three laser applications showed significantly greater osteoclastic activity and bone resorption than the other subgroups in the 7-day movement subgroups. LPT application significantly increased the osteoclastic but not the osteoblastic activity during the initial phases of tooth movement. In addition, the osteoclastic activity was dose-dependent.

The aim of a study by Habib [2395] was to assess by light microscopy changes in alveolar bone during orthodontic movement in rats. Thirty rats were divided into two groups (n=15) and subdivided according to animal death (7, 13, and 19 days). Half of the animals in each group were treated *with LPT during orthodontic movement. After animal death, specimens were processed and underwent histological and semi-quantitative analyses (HE and Sirius red). LPT-irradiated specimens showed significantly higher numbers of osteoclasts when compared with controls at 7 and 19 days, as well as significant increases in the number of os-teoblasts between days 7 and 13. The amount of collagen matrix was significantly reduced between days 7 and 13 at both pressure and tension sites in controls but not in LPT-treated animals. LPT-treated subjects showed significantly greater deposition of collagen matrix at the pressure site at both the thirteenth and nineteenth days. At the tension site, a significant increase in the amount of collagen matrix was observed in non-irradiated specimens between days 7 and 19. LPT caused significant histological changes in the alveolar bone during in-duced tooth movement, including alterations in the number of both osteoclasts and osteoblasts and in collagen deposition in both pressure and tension areas.*

In the animal study by Rodrigues Pinto [2235], LPT was capable of increasing stability of self-threading orthodontic mini-implants.

Clinical studies

a. Increased tooth movement

Eleven patients were recruited for a 2-month study by Cruz [1432]. One half of the upper arcade was considered control group (CG) and received mechanical activation of the canine teeth every 30 days. The opposite half received the same mechanical activation and was also irradiated with a diode laser emitting light at 780 nm, during 5 x 10 seconds at 20 mW, 5 J/cm^2, on 4 days of each month. Data of the biometrical progress of both groups were statistically compared. All patients showed significant higher acceleration of the retraction of canines on the side treated with LPT when compared to the control. These findings suggest that LPT accelerates human teeth movement and could therefore considerably shorten the whole treatment duration.

A study by Rattanayatikul [1662] was a double blind, randomised placebo/control matched pairs clinical trial to test the efficacy of GaAlAs LPT on 12 young adult patients who required retraction of maxillary canines into first premolar extraction spaces using tension coil springs with fixed edgewise appliance. Laser was applied on the mucosa buccally, distally and palatally to the canine on the test side and using a sham laser on the placebo side. The laser was a 100 mW GaAlAs laser and the energy per point was 2.3 J, 5 points in total, 25 J/cm^2. Laser was applied immediately after placing the retraction and for the two following days. Dental impressions and casts were made at the commencement of the trial and at the end of the first, second and third months after starting the trial. Measurement of tooth movements was made on each stage model using a stereo microscope. There was no significant difference of means of the canine distal movement between the laser side and the sham side for any time periods.

The purpose of the study by Meguro [1660] was to investigate the inhibitory effect of LPT on an incidence of open gingival embrasure space after orthodontic treatment. The patient was a 20-year, 7-month-old Japanese female with an Angle Class I malocclusion and crowding in the mandible. Treatment consisted of extraction of maxillary and mandibular first premolars and use of the Edgewise technique. A GaAlAs laser was used to irradiate an area of 0.5 cm^2 at the labial and lingual gingival papilla between the canines. The time of exposure was 6 minutes for 3 days, carried out between the relevelling and en masse stages of movement. The total energy corresponding to 6 minutes of exposure varied from 1.90 J/cm^2. There was no further evidence of open gingival embrasure space, except at the mandibular central incisor. Further: an improvement in the gingival inflammation caused by a periodontal disease was observed, and periodontal pocket depth was maintained. These results suggest that laser irradiation may inhibit the incidence of open gingival embrasure space after orthodontic treatment.

In a literature review Jawad [2168] questions the interpretation of the reports on acceleration of tooth movements by LPT.

The conclusion of the Meta analysis by Long [2440] found that weak evidence suggests that LPT at the wavelength of 780 nm, at the fluence of 5 J/cm^2 and/or the output power of 20 mW could accelerate orthodontic tooth movement within 2 months and 3 months. However, the authors could not determine its effectiveness within 1 month due to potential measurement errors.

b. Pain reduction

The effect of LPT on reduction of pain while undergoing orthodontic treatment was examined by Harazaki [81]. The patients were randomly separated into 3 groups: non-treated control group (CG), blind irradiation group (BG), and GaAlAs laser irradiated group (LG). The effect of laser irradiation on reduction in pain was analysed by a questionnaire given to patients who had been wired with an edgewise appliance of a multi-bracket system for orthodontic therapy. Just after application of the initial wire, LG patients were irradiated with the laser from the labial and lingual sites for a total of one minute. A delay in the pain appearance was noted as compared to the other two control groups.

In a study by Lim [464], 39 patients had elastomeric separators placed at the proximal contacts of one premolar in each quadrant to induce orthodontic pain. 830 nm, 30 mW laser light was applied for 15, 30 and 60 seconds and one placebo treatment of 60 seconds with each patient for a period of 5 days. Patients were asked about pain levels after each session. Analysis of the VAS scores showed that pain was less after laser treatment but not statistically significant.

The objective a study by Turhania [1729] was to analyse the effect of a single laser irradiation on pain perception in patients having fixed appli-

ance treatment. 76 patients enrolled in this single-blind study were assigned to 2 groups. The patients in group 1 received a single course of 670 nm, 75 mW for 30 seconds per banded tooth. The patients in group 2 received placebo laser. Pain perception was evaluated at 6, 30, and 54 hours after LPT by self-rating with a standardised questionnaire. Major differences in pain perception were found between the 2 groups. The number of patients reporting pain at 6 hours was significantly lower in G1 (n = 14) than in G2 (n = 29), and the differences persisted at 30 hours (G1, n = 22; G2, n = 33). At 54 hours, no significant differences were seen between the number of patients reporting pain, although the women had a different prevalence between G1 and G2.

The aim of a study by Youssef [1806] was to evaluate the effect of 809 nm, 100 mW on the canine retraction during an orthodontic movement and to assess pain level during this treatment. A group of 15 adult patients with age ranging from 14 to 23 years was included. The treatment plan for these patients included extraction of the upper and lower first premolars because there was not enough space for a complete alignment or presence of biprotrusion. The orthodontic treatment was initiated 14 days after the premolar extraction with a standard 18 slot edgewise brackets. The canine retraction was accomplished by using prefabricated Ricketts springs, in both upper and lower jaws. The right side of the upper and lower jaw was chosen to be irradiated with the laser, whereas the left side was considered the control without laser irradiation. The laser was applied with 0-, 3-, 7-, and 14-day intervals. The retraction spring was reactivated on day 21 for all sides. The amount of canine retraction was measured at this stage with a digital electronic caliper and compared each side of the relative jaw (i.e., upper left canine with upper right canine and lower left canine with lower right canine). The pain level was prompted by a patient questionnaire. The velocity of canine movement was significantly greater in the lased group than in the control group. The pain intensity was also at lower level in the lased group than in the control group throughout the retraction period.

The purpose of a study by Tortamano [2117] was to clinically evaluate the effect of LPT as a method of reducing pain reported by patients after placement of their first orthodontic archwires. The sample comprised 60 orthodontic patients (ages, 12-18 years; mean, 15.9 years). All patients had fixed orthodontic appliances placed in 1 dental arch (maxillary or mandibular), received the first archwire, and were then randomly assigned to the experimental (laser), placebo, or control group. This was a double-blind study. LPT was started in the experimental group immediately after placement of the first archwire. Each tooth received a dose of 2.5 J/cm^2 on each side (buccal and lingual). The placebo group had the laser probe positioned into the mouth at the same areas overlying the dental root and could hear a sound every 10 seconds. The control group had no laser intervention. All patients received a survey to be filled out at home describing their pain during the next 7 days. The patients in the LPT group had lower mean scores for *oral pain and intensity of pain on the most painful day. Also, their pain ended sooner. LPT did not affect the start of pain perception or alter the most painful day. There was no significant difference in pain symptomatology in the maxillary or mandibular arches.*

The aim of a study by Artés-Ribas [2156] was to evaluate the pain sensation that orthodontic patients experience when elastic separators are placed between molars and premolars and to determine the degree of analgesic efficacy of LPT compared to a placebo treatment. The study was conducted with 20 volunteers who were fitted with elastic separators between the maxillary molars and premolars. One quadrant was randomly chosen to be irradiated with an 830 nm laser, 100 mW, beam diameter of 7 mm, 250 mW/cm^2 applied for 20 s per point 5 J/cm^2. Three points were irradiated in the buccal face and three were irradiated in the palate. The same procedure was applied in the contralateral quadrant with a placebo light. A Visual Analogue Scale was used to assess pain 5 min, 6 h, 24 h, 48 h, and 72 h after placement of the separators. Maximum pain occurred 6-24 h after placement of the elastic separators. Pain intensity was significantly lower in the laser-treated quadrant (mean 7.7 mm) than in the placebo-treated quadrant.

The purpose of a study by Eslamian [2237] was to assess the effect of 810 nm LPT on the pain caused by orthodontic elastomeric separators. Thirty-seven orthodontic patients participated. Four elastomeric separators were placed for the first permanent molars (distal and mesial), either for maxillary (22 patients) or mandibular (15 patients) arches; one quadrant was randomly selected and used as a placebo group (received no laser irradiation). After separator placement for each quadrant, patients received 10 doses (2 J/cm^2, 100 mW, 20 s) of laser irradiation on the buccal side (at the cervical third of the roots), for distal and mesial of the second premolars and first permanent molars, as well as distal of second permanent molars (five doses). The same procedure was repeated for the lingual or palatal side (five doses). After 24 h, patients returned to the clinic and received another 10 doses of laser irradiation on the same quadrant. Post-separation pain level recorded on a 10 cm Visual Analogue Scale for both jaws immediately (hour 0), and after 6, 24, 30 h, as well as on days 3, 4, 5, 6, and 7. Significant differences in the pain perception (PP) were found between the laser and placebo groups at 6, 24, 30 h, and day3 of the experiment In both groups, pain was highest at 6 and 30 h after placing elastomeric separators. No gender differences were observed in both groups. More pain was recorded in the mandible at 24 (laser group) and 30 h (both groups) after starting the experiment. The PP was significantly higher for the group aged 18 years or more, only at days 3 [both groups] and 4 [laser group only] of the experiment. The 810 nm CW LPT significantly reduced the PP in the first 3 days after orthodontic separation. However, the mean post-separation PP in both groups was low and wide ranges of PP scores were observed.

The objective of a study by Nóbrega [2157] was to evaluate the effectiveness of the use of irradiation with LPT, 830 nm, for treating pain inherent *to tooth movement caused by orthodontic devices, simulated by positioning interdental elastomeric separators. Sixty orthodontic patients were randomly assigned to two groups: GA (ages 12-25 years; mean 17.1 years) was the control, and GB (ages 12-26 years; mean 17.9 years) the intervention group. All patients received elastomeric separators on the mesial and distal surfaces of one of the lower first molars, and immediately after insertion of the separators received irradiation as randomly indicated. The intervention group (GB) received irradiation with LPT by a single spot in the region of the radicular apex at a dose of 2J/cm^2 and application along the radicular axis of the buccal surface with three spots of 1J/cm^2 wavelength 830 nm. Control group (GA) received irradiation with a placebo light in the same way. This was a double-blind study. All the patients received a questionnaire to be filled out at home describing their levels of pain 2, 6, and 24 h and 3 and 5 days after orthodontic separator placement, in situations of relaxed and occluded mouth. The patients in the intervention group had lower mean pain scores in all the measures. The incidence of complete absence of pain was significantly higher the intervention group.*

In a study by Domínguez [2158], the sample was 60 orthodontic patients from a private practice, treated by straight wire technique; 30 of them with mini brackets and 30 with self-ligation slot 0.022 inch brackets. The archwires used in the final stage of orthodontic treatment were stainless steel in both groups. In a design of divided mouth, the dental arches were randomly assigned to receive one dental arch irradiation with 830 nm, 100 mW LPT for 22 sec (2.2 J, 80 J/cm^2) along the vestibular surface and 22 sec (2.2 J, 80 J/cm^2) along the palatal surface of the root in the randomly selected arch. The opposite dental arch received placebo treatment, with the laser light off. Pain was evaluated using a Visual Analogue Scale (VAS) after 2, 6, and 24 h, and 2, 3, and 7 days of application. The time course of pain showed the same tendency in both groups, reaching a peak 24 h after the archwire activation. The application of LPT reduced pain for any period of time up to 7 days and for any kind of bracket.

The aim of a study by Bicakci [2159] was to investigate the effect of LPT on reducing post-adjustment orthodontic pain via evaluation of gingival crevicular fluid (GCF) composition changes at the level of prostaglandin-E2 and Visual Analogue Scale. Nineteen patients were included in this study. Maxillary first molars were banded and then a randomly selected first molar at one side was irradiated (820 nm; 50 mW; focal spot 0.0314 cm^2; exposure duration 5 sec; power density 1.59 W/cm^2; energy 0.25 J; energy density 7.96 J/cm^2 for each shot), while the molar at the other side was served as placebo control. The GCF was collected from the gingival crevice of each molar to evaluate PGE_2 levels, before band placement, 1 and 24 h after laser irradiation. Pain intensity was analysed at 5 min, 1 h, and 24 h after band placement by using VAS. Although no difference was found in pain perception at 5 min and 1 h, significant reduction was observed with laser treatment 24 h after application. The mean PGE_2 levels were significantly elevated in con-

trol group, whereas a gradual decrease occurred in laser group. The difference in PGE2 levels at both 1 and 24 h were statistically significant between two groups .

The purpose of a study by Abtahi [2444] was to determine the effect LPT on dental pain induced by forces from separators in orthodontic treatment. Twenty-nine patients were recruited for the experiment. GaAs, 200 mW average output, 30 seconds, 6 J per day for five days was applied on one half of the maxillary and mandibular arches for 5 days. The opposite half of the arches was considered the control group. Laser irradiation was applied in the alveolar bone between the second premolars, first molars, and second molars. Pain perception was evaluated with a standardised questionnaire that was answered by patients before and after laser irradiation. The highest pain level was reported at day 1 following separator placement and decreased gradually until day 5. At day 4 and 5, the pain intensity was lower in the laser group than in the control group; however, this finding was not statistically significant. At day 1 and 3, the pain intensity was higher in the laser group than in the control group; however, it was not statistically significant. At day 2, the pain intensity was lower in the laser group than in the control group and was statistically significant. These findings suggested that there is no statistically significant difference in pain by using LPT at these parameters.

This review by He [2160] aimed to identify the efficacy of LPT in the management of orthodontic pain. Risk of bias assessment was performed via referring to the Cochrane tool for risk of bias assessment. As a result, four RCTs, two quasi-RCTs, and two CCTs were selected from 152 relevant studies, including 641 patients from six countries. The meta-analysis demonstrated that 24 % risk of incidence of pain was reduced by LPT. In addition, compared to the control group, brought forward "the most painful day". Furthermore, the LPT group also implied a trend of earlier end of pain compared with the control group and the pseudo-laser group However, because of the methodological shortcomings and risk of bias of included trials, LPT was proved with limited evidence in delaying pain onset and reducing pain intensity. In the future, larger and better-designed RCTs will be required to provide clearer recommendations.

c. Root resorption

The results of a clinical study by Nimeri [2521] showed that LPT did not cause root resorption greater than the normal range that is commonly detected in orthodontic treatments. Furthermore, no correlation between Little's Irregularity Index and root resorption was detected.

d. Laser and/or LED

LEDs have also been used to reduce pain related to orthodontic therapies. The aim of a study by Kim [2237] was to analyse the effect of LPT on perception of pain after separator placement and compare it with percep-

tions of control and placebo groups using a frequent irradiation protocol. Eighty-eight patients were randomly allocated to a laser group, a light-emitting diode (LED) placebo group, or a control group. Elastomeric separators were placed on the first molars. In the laser and LED groups, first molars were irradiated for 30 seconds every 12 hours for 1 week using a portable device. Pain was marked on a Visual Analogue Scale at predetermined intervals. Repeated measure analysis of variance was performed for statistical analysis. The pain scores of the laser group were significantly lower than those of the control group up to 1 day. The pain scores in the LED group were not significantly different from those of the laser group during the first 6 hours. After that point, the pain scores of the LED group were not significantly different from those of the control. Thus, frequent LPT decreased the perception of pain to a non-significant level throughout the week after separator placement, compared with pain perception in the placebo and control groups.

Esper [2365] reports a pain relieving effect when an LED is used to reduce pain after applying elastic separators during orthodontic therapy. The positive outcome is of interest, since up till now only lasers have been used for this kind of treatment. ***The authors have compared the effect of an LED to that of a laser and found that the LED was superior. Fortunately, the authors give a good account of the parameters used and this gives a clue to the poor effect of the laser. In order to compare two phototherapies, the parameters need to be as equal as possible. In this case, they are far from equal. The dose is correctly indicated as 4 J/cm² in both groups, but using the J/cm² parameter can lead to several pitfalls. A dose (energy density) is calculated by dividing the applied energy by the size of the irradiated area. If the probe has a size of 1 cm² and the energy is 1 joule, the dose becomes 1 J/cm². If the size of the probe is 0.25 cm², the same energy results in 4 J/cm². In the paper by Esper, the size of the LED is almost 10 times as wide as that of the laser. In order to reach the 4 J/cm² the laser needs 25 seconds and the LED 70 seconds. The energy used for the laser is 0.7 J and 7 J for the LED. Thus, all parameters except the local energy density at the irradiated spots vary considerably.***

Pain reduction with phototherapy stems partly from a reduction of the inflammatory process and partly from an inhibition of neural signalling. The inflammatory process is best reduced by low power output and longer time, whereas acute pain reduction requires higher energies. The time for the 300 mW laser was almost 1/3 of the 100 mW LED. The energies used in the quoted papers by Turhani and Youseff [1729, 1806] were 2.25 and 8 J, respectively, and the best effect reported comes from the latter. In the Esper study, 0.7 J was applied with the laser.

The importance of coherence is still controversial, but referring to the work by Karu is misleading. The investigations by Karu are based upon irradiation of monolayers of cells. Here coherence is of no importance. For bulk tissue, it is quite different. Coherence is not lost, but the length of

coherence is split up into coherent laser speckles throughout the entire illuminated area.

In conclusion, the Esper paper is valuable in that it suggests and alternative light source for pain reduction, but the conclusion that an LED should be better than a laser is not verified.

d. Other applications

The study by Caccianiga [2351] was designed to examine the effects of LPT on alveolar bone remodelling during orthodontic tooth movement and finally on formation of new keratinised gingiva. 22 patients and 27 teeth in vestibular mucosal without keratinised gingiva were selected. Every patient was treated with self-ligating appliances. In every orthodontic session the patient was treated with LPT. At the moment of debonding, 27 teeth involved in the research were evaluated in terms of quality and quantity of attached gingiva. BOP and CAL loss were investigated. Results: every tooth considered at the end of orthodontic treatment showed an attached gingiva around the crown: The average of keratinised gingiva at the end of the study was 3.10 mm and the mean increasing at each month was 0.49 mm. The combination between self-ligating appliances and LPT could improve the differentiation of periodontal ligaments stem cells in fibroblasts, able to promote attached gingiva around the crown of the teeth erupted in oral vestibular mucosa.

From the above studies it can be concluded that dosage is essential. Low dosage seems to stimulate orthodontic movement whereas high doses inhibit the speed of movement. As suggested by Goulart, low doses can be used during the orthodontic movement period and higher doses when the movement is finished. The higher bone density stimulated by higher doses would assist the moved tooth to remain in place. Infrared is recommended since it has a greater penetration and often higher power densities but the Chinese studies above indicate that even HeNe can be used. The review by He [2160] serves well as an example of the difference between established clinical experience and strict scientific evidence. The systematic review by Subraian [2462] suggests that LPT improves orthodontic treatment in reducing treatment time and pain. However, the quality of the studies was limited and further research is required to achieve a higher level of evidence.

A review by Carvalho-Lobato [2505] attempts to organise the existing published literature regarding tooth movement in orthodontic treatment when LPT is applied. Studies in humans and animals in which LPT was applied to increase the dental movement were reviewed. The resulting studies were analyzed according to the parameters used in the application of laser and existing changes clinically and histopathologically. Out of 84 studies, 5 human studies were selected in which canine traction had been performed after removing a premolar, and 11 studies in rats were selected in which first premolar traction was realised. There were statistically significant changes in four human studies and eight animal studies. Varying the wavelength with a reasonable dose in the target zone leads to obtaining the desired biological effect and achieving a reduction of the orthodontic treatment time, although there are studies that do not demonstrate any benefit according to their values.

Further literature: [411, 412, 615, 1223, 1693, 1695, 1713, 2532]

5.3.20 Mild dental pain

It is a part of the dentist's everyday work to cause patients mild forms of pain, which we dentists tend to think of as a trifling matter. It may be caused by wedging, depuration, intraligamental anaesthesia, proximal polishing, etc. This type of "petty pain" is so common and so undramatic that dentists (and patients to a certain extent) take it for granted as nothing to worry about. However, we believe this to be an erroneous point of view, stemming from the time when we did not have the facilities to prevent pain that we have today. Dentistry has moved from amalgam to ceramic laminates, so we should be able to improve quality to the same extent when it comes to dealing with pain. Patients may have resigned themselves to accepting these milder forms of pain, but don't imagine that they can't do without it! Rounding off routine treatment with 2-3 J of LPT can reduce or eliminate mild post-operative pain. The patient will experience this as improved quality of treatment, and the dentist will certainly receive many good references. Assisting staff can perform the treatment.

5.3.21 Paediatric dental treatment

Treating children with a therapeutic laser is no different from treating adults. However, a non-traumatic introduction to dentistry is very important, and will save future chair time and patient anxiety. To a child, a laser is not a threat; it's "cool", an attractive tool. Some suggested therapeutic uses are listed below:

1. The eruption of deciduous as well as permanent teeth is sometimes painful. A few joules over the painful area will alleviate the problem and avoid analgesics. Irradiating the lymph nodes in the area is recommended [915].
2. 2 J at the injection site has a brief anaesthetic effect in the mucosa, permitting an injection without pain if injected slowly with a 30g needle. 2-3 J over the anaesthetised area before dismissing the patient will shorten the duration of anaesthesia, thus reducing the risk of bite wounds in the lip, tongue, and cheek.
3. Before drilling takes place, 4-6 J at the tooth neck and the same amount of energy over the projection of the apex of a decidious tooth will in many cases produce complete or partial anaesthesia.

4 Trauma to the lips and front teeth is common in children. 3-4 J over a bleeding and swollen lip will reduce swelling and pain and allow dental treatment on the following day. 1-2 J around mobile teeth will improve healing and facilitate normal chewing.

0.5-2 J as an additional treatment in pulp capping will improve the outcome of the treatment. Irradiate the exposed pulpal area before applying the capping agent. The same dose is given for pulpectomies [109, 2517].

7 years old female falling off a horse. Left upper permanent incisor exfoliated, left incisor partially vertically evulsed. After repositioning and splinting of the two teeth, 2 x 4 J, 808 nm was given to the lip and 2 J over each of the apices. At 24 hrs additional 4 J was given to the lip and 2 J over each of the apices. This protocol was used at days 3, 7 and 9. On day 14 the splint was removed and LPT performed again and on day 17. Follow-up one month, 3 and 6 reveals intact normal mobility, white colouration, healing gingiva and root formation is continuing.
Courtesy: Martin A Kaplan

Literature:

The aim of study by Toomarian [2161] was to investigate the stimulatory effect of 808 nm laser irradiation on root development of rat molars and also to evaluate the histological reaction of pulp and periapical tissues. Twenty-four 30-day-old Wistar male rats were randomly assigned to three-time and five-time laser therapy groups. After initial x-ray, using mammography equipment, laser energy was applied at a wavelength of 808 nm (2 J/cm², 100 mW, 20 s) to the midroot area of the lower molars of one side of *mouth at repeated intervals of the 48 h. The animals were killed 1 day after the final treatment, and root length development of the experimental samples was compared to contra-lateral non-irradiated molars using mammography. The histological reaction of the pulp and periapical tissue was evaluated under light microscopy. Root development was more advanced in irradiated groups than in the non-irradiated controls. No significant differences, however, could be found between the root development changes in the three-time and five-time laser therapy groups. Histological findings showed that the occurrence of secondary cement formation was significantly higher in the irradiation groups compared to the controls. However, there were no statistically significant differences for the frequencies of pulp hyperemia, periodontal ligament fiber organisation, or lamina dura remodelling between the groups. Under the conditions used in this study, 808 nm low-level laser accelerates the rat molar root development in the presence of favourable histological reactions.*

The aim of a study by Viela [2163] was to perform histological evaluation of dental and periodontal ligament of rats central upper-left incisor teeth re-implanted and irradiated with 685 nm, 50 J/cm^2, 15, 30, and 60 days after re-implantation. Seventy-two male rats had the central upper left incisor removed and kept for 15 min on dry gauze before replantation. Laser was irradiated over the root surface and empty alveolus prior replantation and over surrounding mucosa after the re-implantation. After histological procedures, all slices were analysed regarding external resorption area and histological aspects. We observed an increase of root resorption in the control group compared to the laser group at 15, 30, and 60 days. These results showed that the laser groups developed less root resorption areas than the control group in all experimental periods. Additionally, histological analysis revealed less inflammatory cells and necrotic areas in laser groups.

The study by Tanboga [2397] was carried out on 10 children aged 6 to 9 years old for a total of 20 primary molar teeth. For laser preparation an Er:YAG laser was used. Half of the preparations were treated by LPT before laser preparation and the remaining half without LPT (non-LPT) before laser preparation. All cavities were prepared by ER:YAG laser, restored with light-cured composite resin following the application of acid etching and bonding agent. Children were instructed to rate their pain on the Visual Analogue Scale from 0 to 5 points. VAS Median (min-max) scores were 1 (0-2) for LPT and 3 (1-4) for the non-LLT treated children. Between LPT and non-LPT groups results were statistically significant. The use of LPT before cavity preparation with laser decreased pain in paediatric dental patients.

Traumatic injuries and dental caries can be a big challenge to immature teeth. In these cases, the main purpose of treatment is to maintain the pulp vitality. The purpose of a study by Fekrazad [2528] was to investigate the effect of LPT on accelerating the rate of dentinogenesis in pulpotomy of immature permanent teeth (apexogenesis). Three dogs, 4-6 months old, were used in this study. One jaw in each dog was randomly assigned to laser irra-

diation group. All selected teeth were pulpotomized with mineral trioxide aggregate (MTA) and restored with amalgam. In the laser group, 810 nm, 0.3 W, 4 J/cm2, 9 s) was used on buccal and lingual gingiva of each tooth in 48 h intervals for 2 weeks. In order to observe the newly formed dentine, tetracycline was injected on the 1st, 3rd, 7th, and 14th day after the operation. Then, ground sections of teeth were observed under a fluorescence microscope. The mean distance between the lines of tetracycline formed on the 1st and 14th day was significantly higher in the laser group.

5.3.22 Periodontics

A reduction of the inflammatory process has been demonstrated in many studies and makes LPT an excellent adjuvant treatment modality to conventional periodontal therapy. Good oral hygien after SRP is mandatory for good results, but the addition of the laser will not only reduce the inflammatory process but also lead to less postoperative pain and oedema.

According to some reports [202, 203], it is possible to reduce epithelial down-growth after flap operations. Laser treatment administered only at the time of the operation relieves postoperative discomfort and improves tensile strength after suturing. To achieve positive effects, repeated treatment is required. In addition to treatment of the operation area, each tooth neck can be treated with 2-3 J. This reduces postoperative sensitivity in the root surfaces. When the periodontal dressing is removed, the patient's root surfaces will be less sensitive (supplementary treatment can be administered after a check-up), and the patient will be able to heed the advice given regarding dental hygiene.

Another important aspect in periodontology is the regeneration of bone, also in combination with GTR and bone grafts.

HSV viruses are not uncommon findings in periodontal pockets [1942, 1943] and the well-established effect of LPT on HSV1 and 2 may have an influence in this field.

The combination of dyes like TBO and LPT can have dramatic bactericidal effect [827] and this PDT-like therapy has a great potential in periodontics. Dortbudak [1709], Haas [1710] and Shibli [1711] have demonstrated the usefulness of this concept for peri-implantitis.

Literature:

In vitro studies

The aim of the study by Saygun [1842] was to determine whether laser irradiation can enhance the release of basic fibroblast growth factor (bFGF), insulin-like growth factor-1 (IGF-1), and receptor of IGF-1 (IGFBP3) from human gingival fibroblasts (HGF). The number of all samples in the study were 30, and the samples were randomly divided into three equal groups; In the first group (single dose group), HGF were irradiated with laser energy of 685 nm, for 140 s, 2 J/cm² once, and in the second group, energy at the same dose was applied for two consecutive days (double *dose group). The third group served as non-irradiated control group. Proliferation, viability, and bFGF, IGF-1, IGFBP3 analysis of control and irradiated cultures were compared with each other. Both of the irradiated groups revealed higher proliferation and viability in comparison to the control group. Comparison of the single-dose group with the control group revealed statistically significant increases in bFGF and IGF-1 but IGFBP3 increased insignificantly. When the double dose group was compared with the control group, significant increases were determined in all of the parameters. In the comparison of the differences between the two irradiated groups (one dose and two doses), none of the parameters displayed any statistically significant difference. In both of the laser groups, LPT increased the cell proliferation and cell viability. The results of this study showed that LPT increased the proliferation of HGF cells and release of bFGF, IGF-1, and IGFBP3 from these cells. LPT may play an important role in periodontal wound healing and regeneration by enhancing the production of the growth factors.*

Porreau-Schneider [37] carried out an in vitro study of the effect of HeNe laser light on human fibroblasts, and found that the laser energy caused the fibroblasts to turn into myofibroblasts. Biopsies of gingiva were taken in conjunction with the removal of wisdom teeth in order to examine the clinical effect. After 48 hours, myofibroblasts could be found in the laser-treated biopsies, while the contralateral biopsies showed active or dormant fibroblasts. These findings have been confirmed by Rigau [415].

Smoking is a considerable risk factor in periodontal disease. The aim of the study by Fujimaki [1543] was to examine the effects of LPT on the production of reactive oxygen (ROS) species by human neutrophils. The laser device used was the infrared diode laser of 830 nm continuous wave (150 mW/cm^2). After irradiation, ROS production by neutrophils was measured using luminol-dependent chemiluminescence (LmCL) and expression of CD11b and CD16 on neutrophil surface was measured by flow cytometry. The LmCL response of neutrophils was reduced by laser irradiation at 60 min prior to the stimulation with opsonised zymosan and calcium ionophore. The attenuating effect of LPT was larger in neutrophils of smokers than non-smokers, while the amount of produced ROS was larger in neutrophils of smokers. Expression of CD11b and CD16 on neutrophil surface was not affected by LPT. Attenuation of ROS production by neutrophils may play a role in the effects of LPT in the treatment of inflammatory tissues. There is a possible usage of LPT to improve wound healing in smokers.

In periodontal tissue, mast cells may influence either the destructive events or the defense mechanism against periodontal disease via secretion of cytokines and through cellular migration to improve the healing process. Mast cells play an important role in the inflammatory process. In a study by Silveira [1907] twenty patients with gingival enlargement indicated for gingivectomy were selected. Gingival fragments were obtained from each patient and divided into three different groups before surgery. One fragment was removed without any irradiation. The two others were submitted to *punctual irradiation with an energy density of 8 J/cm^2 at an output power of 50 mW at 36 Hz for 36 sec before gingivectomy. Non-degranulated and degranulated mast cells were counted in five areas of the gingival fragment connective tissue. Both red and infrared radiation promoted a significant increase in mast cell degranulation compared to controls; however, no statistically significant differences were observed between the irradiated groups.*

Retaining or improving periodontal ligament (PDL) function is crucial for restoring periodontal defects. The aim of the study by Wu [2314] was to evaluate the physiological effects of LPT on the proliferation and osteogenic differentiation of human PDL (hPDL) cells. Cultured hPDL cells were irradiated (660 nm) daily with doses of 0, 1, 2 or 4 J/cm^2 . Cell proliferation was evaluated by the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay, and the effect of LPLI on osteogenic differentiation was assessed by Alizarin Red S staining and alkaline phosphatase (ALP) activity. Additionally, osteogenic marker gene expression was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR). The data showed that LPT at a dose of 2 J/cm^2 significantly promoted hPDL cell proliferation at days 3 and 5. In addition, LPT at energy doses of 2 and 4 J/cm^2 showed potential osteogenic capacity, as it stimulated ALP activity, calcium deposition, and osteogenic gene expression. The investigators also showed that cyclic adenosine monophosphate (cAMP) is a critical regulator of the LPT-mediated effects on hPDL cells. This study shows that LPT can promote the proliferation and osteogenic differentiation of hPDL cells. These results suggest the potential use of LPT in clinical applications for periodontal tissue regeneration.

Animal studies

Kami [67] has studied how GaAlAs laser light affects flaps, and observed that the frequency of success, measured in area, was greater in the LPT group than in the control group. Microvascular flow was greater in the LPT group. Hypovascularised zones, with reactive surrounding vasodilatation, could be seen in the laser probe's contact zones, observed one hour after the irradiation. This effect disappeared after 48 hours, although a greater occurrence of blood vessels could be seen in the irradiated flaps.

Kubota [14] performed a similar experiment in which he treated a group of animals with LED light of the same dosage and wavelength as the LPT group. The LPT group exhibited 45% better vascularisation of the flap than the LED and control groups when measured with fluorescent angiography. More flaps survived in the LPT group than in the other two groups. The failure of LED may be dose-dependent. The use of LED, by the way, is controversial, but LEDs are not totally ineffective

. *Yoo [288] reports effects on musculoskeletal pain using polarised LED light at 1800 mW. Such high power led to first and second degree burns, however.*

Kami's and Kubota's experiments were performed with a GaAlAs laser. Kubota also used GaAlAs laser in a clinical study together with Yasuda [287] and Ohshiro involving patients where musculo-cutaneous flaps were indicated following surgery related to circulatory disorders. There was a significant rise in blood flow and volume following LPT.

Kubota [479] has also checked flap survival and microcirculation using the laser speckle method. 4 J was given at the centre of the flap. After five days, the survival area of the laser diode-irradiated flaps was greater than in the control group. A noticeable improvement in microcirculation was observed following LPT.

Amir [480] used HeNe laser for the same kind of study on rats. The treated animals healed faster and the flaps showed tremendous capillary and fibroblast proliferation.

In a study by Kubota [1116], a 1000 mW, 830 nm laser was used to treat skin ulcers. The power density was 669 mW/cm^2 and the dose 6.3 J/cm^2. Less postoperative pain, better coagulation, better bone regeneration, increased tensile strength and enhanced angiogenesis can be expected.

Zhang [94] carried out an experiment similar to Kubota's, but using a defocused CO_2 laser at a power density of 300 mW/cm^2, in a rat model. Mean survival length of the flap was 5.83 cm in the LPT group and 3.60 cm in the control group.

The “surgical” lasers can, at advantage, be defocused and used as biostimulators, as demonstrated by Pourzarandian [1606].

Schenk [78] studied the effects of a HeNe laser on gingiva and sublingual mucous membrane in dogs. The preparation was produced with 60 and 120 seconds' exposure, and sub-cellular changes were studied. An increased number of vesicles, vacuoles, enlarged mitochondria and dilation of the endoplasmic reticulum were observed. The investigators consider that the morphological changes confirm the hypothesis about the stimulating effect of HeNe laser on various cell systems.

Kawamura [202] studied the effects of Nd:YAG and GaAlAs lasers on epithelium downgrowth in the pocket after a flap operation. Flaps with root scaling and iatrogenic bone defects were given to 54 hamsters. One group received irradiation (as much as 80 J/cm^2) once, immediately after the operation. Another group was given laser treatment once a week. Unacceptable necrosis could be seen in the Nd:YAG group. Of the GaAlAs groups, the group that received a single dose of laser showed a reduced downgrowth of pocket epithelium when inspected during week 1. This difference had disappeared by week 3. The group that underwent three laser treatments was no different from the control group when inspected in week 3, but by week 5 exhibited better bone regeneration and reduced downgrowth of epithelium in the pocket. Some stimulation of fibroblasts could be established.

Kim [203] studied the effects of GaAs laser treatment on experimentally produced parodontitis in dogs. The experiment consisted of four groups: 1. An experimental parodontitis group treated with a laser; 2. A con-

trol group with experimentally produced parodontitis, not treated with a laser; 3. An experimental parodontitis group on which a flap operation was performed and laser treatment was administered; and 4, as 3, but without laser treatment. Laser groups 1 and 3 received laser treatment on five consecutive days. The histopathological findings were: reduced pseudoepitheliomatous proliferation and a reduced degree of inflammation could be observed in group 1. This group also exhibited increased formation of periodontal ligaments, and the infiltration of newly formed collagen could be observed. Group 3 exhibited a reduced degree of inflammation and osteoclast activity, further capillary proliferation, and reduced pseudoepitheliomatous proliferation. By MT coloration, newly formed collagen in periodontal ligaments and alveolar bone was also observed in group 3.

The aim of an investigation by Gerbi [1471] was to assess histologically the effect of LPT (830 nm, 40 mW, CW, area diameter approximately 0.6 mm, 16 J/cm^2 per session) on the repair of surgical defects created in the femur of the Wistar Albinus rat. The defects were filled to lyophilised bovine bone associated or not to GTR. Surgical bone defects were created in 42 animals divided into five groups: Group I (control, 6 animals); Group II (Gen-ox, 9 animals); Group III (Gen-ox + Laser, 9 animals); Group IV (Gen-ox + Gen-derm, 9 animals); Group V (Gen-ox + Gen-derm + Laser, 9 animals). The animals on the irradiated group received 16 J/cm^2 per session divided into four points around the defect (4 J/cm^2) being the first irradiation immediately after surgery and repeated seven times at every 48 h. The animals were humanly killed after 15, 21, and 30 days. The results of the present investigation showed histological evidence of improved amount of collagen fibers at early stages of the bone healing (15 days) and increased amount of well organised bone trabeculae at the end of the experimental period (30 days) on irradiated animals compared to non-irradiated ones.

The aim of the investigation by Torres [1905] was to histologically assess the effect of laser photobiomodulation (LBPM) on the repair of autologous bone grafts in a rodent model. A major problem in modern dentistry is the recovery of bone defects caused by trauma, surgical procedures, or pathologies. Several types of biomaterials have been used to improve the repair of these defects. These materials are often associated with procedures of guided bone regeneration (GBR). In the present study twenty four animals were divided into four groups: group I (control); group II (LPBM of the bone graft); group III (bone morphogenetic proteins [BMPs] + bone graft); and group IV (LPBM of the bed and the bone graft + BMPs). When appropriate, the bed was filled with lyophilised bovine bone and BMPs used with or without GBR. The animals in the irradiated groups received 10 J/cm^2 per session, divided over four points around the defect (4 J/cm^2), with the first irradiation immediately after surgery, and then repeated seven times every other day. The animals were humanely killed after 40 d. The results showed that in all treatment groups, new bone formation was greater and qualitatively better than the untreated subjects. Control specimens showed a less advanced *repair after 40 d, and this was characterised by the presence of medullary tissue, a small amount of bone trabeculi, and some cortical repair. It is conclude that LPBM has a positive biomodulatory effect on the healing of bone defects, and that this effect was more evident when LPBM was performed on the surgical bed intraoperatively, prior to the placement of the autologous bone graft.*

Fekrazad [1551] performed an experimental clinical trial in 5 healthy dogs. A square lesion was made in the exposed periodontal bone. The lesions were divided into three groups: (1) Control group, where the flap was closed an sutured. (2) Flap was closed and sutured with a resorbable membrane inserted in the bony defect. (3) As with group 2 but followed by 890 nm daily irradiation during two weeks, 0.01 J/cm^2. After two months the specimens were observed clinically and histomorphologically. The amount of regeneration was highest in group 3 but the difference between group 2 and 3 was not statistically significant. The height of the regenerated bone was higher in groups 2 and 3 as compared to control, but the difference was just in the limit of significance.

The aims of the study by Silveira [1907] were to investigate the effect of laser irradiation on the total number of mast cells as well as the percentage of degranulation in human gingiva. Blood vessel dilation was also evaluated. In periodontal tissue, mast cells may influence either the destructive events or the defense mechanism against periodontal disease via secretion of cytokines and through cellular migration to improve the healing process. Mast cells play an important role in the inflammatory process. Twenty patients with gingival enlargement indicated for gingivectomy were selected. Gingival fragments were obtained from each patient and divided into three different groups before surgery. One fragment was removed without any irradiation. The two others were submitted to punctual irradiation with either 688 or 785 nm, with an energy density of 8 J/cm^2 at an output power of 50 mW at 36 Hz for 36 sec before gingivectomy. Non-degranulated and degranulated mast cells were counted in five areas of the gingival fragment connective tissue. Major and minor diameters of the blood vessels were also measured. Both red and infrared radiation promoted a significant increase in mast cell degranulation compared to controls; however, no statistically significant differences were observed between the irradiated groups. No significant differences among the groups were observed regarding blood vessel size.

The aim of a study by Garcia [2079] was to compare LPT as adjuvant treatment for induced periodontitis with scaling and root planing (SRP) in dexamethasone-treated rats. One-hundred twenty rats were divided into groups: D group (n = 60), treated with dexamethasone; ND group (n = 60) treated with saline solution. In both groups, periodontal disease was induced by ligature at the left first mandibular molar. After 7 days, the ligature was removed and all animals were subjected to SRP and were divided according to the following treatments: SRP, irrigation with saline solution (SS); SRP +

LPT, SS and laser irradiation, 660 nm; 24 J; 0.428 W/cm². Ten animals in each treatment were killed after 7 days, 15 days and 30 days. The radiographic and histometric values were statistically analysed. In all groups radiographic and histometric analysis showed less bone loss in animals treated with SRP + LPT in all experimental periods. ***The dose used in this study is much higher than expected for stimulation.***

Clinical studies

Sokolova [364] studied 60 patients with periodontitis (ages 25-55), divided into two equal groups. Conventional treatment was given in both groups, but one group also received therapeutic laser treatment. Healing was studied using periodontal index, hygiene index, bacterioscopy of the gingival pockets, SIgA-level in saliva, and R-protein level in gingival blood. LPT shortened healing time considerably.

Mamedova [365] used ultraviolet and HeNe lasers in combination in the treatment of a group of 90 persons suffering from periodontitis. The optimal doses for the antimicrobic effect on the pocket microorganisms were assessed.

Mousques [73] carried out simultaneous periodontal operations in two quadrants, treated on one side with HeNe laser, and compared the results in terms of healing. Several parameters were studied using a double-blind technique, and all showed better results in the laser group.

Masse [461] reports no effect on periodontal flap surgery using a combined HeNe/GaAs laser. However, independent measurement of the output, initiated by the researchers, showed 0.27 mW for the HeNe from the fibre (4 mW stated) and 80 mW peak power for the GaAs (2 watts stated). The dosage is not reported but is calculated to be 0.04 J/cm², which predisposes the study to fail.

Conlan [735] has performed a literature study and come to the conclusion that LPT has no place in dentistry. Interestingly enough, not one dental study is listed among the references.This paper is from 1996 and an updated review would come to different conclusions.

An investigation by Efanov [1721] was made of applying pulsed 890 nm laser radiation in the treatment for early diagnosed periodontitis. The investigation was made on 65 patients (47 patients constituted the experimental group and 18 patients constituted a control group affected by periodontitis). Clinical and functional tests revealed that LPT produced a strong effect on the course of the illness. It reduced bleeding, inflammation, and pruritus. Biomicroscopic examinations and periodontium rheography revealed that the gingival blood flow became normal after the course of LPT. The capillary permeability and venous congestion decreased, which was confirmed by the increased time of vacuum tests, raised gingival temperature, reduced tissue clearance, and increased oxygen tension. Apart from that, LPT subsided fibrinolysis, proteolytic tissue activity, and decreased the exudative inflammation of the periodontium.

The effect of LPT in periodontal surgery has been reported by Silveira [1241]. 20 patients with periodontal disease were subjected to gingivectomies. Gingival biopsies were taken from a non-mineralised wall of a suprabony periodontal pocket. The first sample was taken before laser irradiation, the second after 785 nm laser irradiation and the third after 688 nm laser irradiation (50 mW, 8 J/cm²). After biopsy the samples were fixed, cut and stained. Both laser wavelengths promoted mast cell degranulation as compared to control and there was no statistical difference between the two wavelengths.

In the study by Qadri [1185] a combination of 635 nm diode laser and GaAlAs laser were used to treat gingivitis and periodontal disease. 17 patients received laser on one side of the upper arch and placebo laser on the other side, after the teeth having been debrided. 635 nm diode laser 0.9 J was applied at the base of the interdental papilla and GaAlAs 3.5 J at the projection of the alveolar bone margin. The results were as follows (laser side/placebo side): gingival index 0.54/1.4, plaque index 0.26/0.68, pocket reduction 0.92/0.16. The gingival exsudate was reduced on the laser side, 0,04 µl vs. 0.14 µl. The metalloproteinase-8 (MMP-8) was slightly reduced on the laser side and elevated on the placebo side. There was no difference in elastase activity or of the amount of IL-1β, nor any significant changes in microbiology.

The aim of another study by Qadri [1634] was to study whether or not the length of coherence is of importance in phototherapy. Laser light is coherent but the length of coherence of gas lasers such as a HeNe laser is much greater than that of a diode laser of the same wavelength. The biological significance of the length of coherence has hitherto not been investigated. 20 patients with light to moderate periodontitis were selected. After instruction about oral hygiene, scaling and root planing (SRP), one side of the upper jaw of each patient was randomly selected for HeNe (632.8 nm, 3 mW) or InGaAlP (650 nm, 3 mW) laser irradiation, using the same power and dose, irradiating once of week during six weeks. One week after the SRP the following parameters were measured: pocket depth, gingival index, plaque index, GCF volume, MMP-8, IL-8 and microbiology in the pocket. The irradiation (180 seconds per point, 0.54 J/cm²) was then performed by a dental hygienist and the selection of side was blinded to the evaluators. After six weeks renewed measurements revealed that all clinical parameters had improved significantly better on the HeNe side. MMP-8 was more reduced on the HeNe side while there was no difference for IL-8 or pathogens. Coherence is an important factor in phototherapy but even the length of the coherence appears to be of importance.

The aim of the work of Kiernicka [1629] was to evaluate the influence of LPT on the periodontal pocket depth after routine conservative periodontal treatment with or without additional use of LPT; in two groups of pockets: above and below 5 mm. The laser was an 830 nm probe of 200 mW. 4 Joules were applied on the papilla every day or every two days for seven days. In six *patients having periodontitis 613 sites were submitted to statistical analysis (290 treated conservatively only, including 251 with the depth 2-5 mm and 39 above 5 mm as well as 323 with the use of LPT including 297 shallow pockets and 26 deep pockets). The initial values of Proximal Plaque Index, Plaque Index, Sulcus Bleeding Index, Periodontal Pocket Depth (PPD) and their changes in the course of the treatment were registered. During each control appointment the patients subjectively estimated periodontal pain occurrence. In both groups a statistically essential decrease of the evaluated parameters was obtained. Reinforcing the conventional treatment with LPT shortened the healing time and led to elimination of pain faster than with the use of conservative treatment only. The changes of the PPD index were statistically higher in the laser group, especially in relation to deep pockets.*

Damante [1443], however, could not find that 670 nm accelerated the healing of the oral mucosa after gingivoplasty. 4 J/cm² was applied to each point in one single session.

In the study by Mârtu [2398] 38 patients were selected, without any systemic diseases, presenting with gingival hypertrophy developed exclusively within the clinical context of gingivitis and/or periodontitis. All patients required several surgical interventions at the level of the superficial periodontium. Subgroup 1 (17 patients) was treated only through gingivectomy procedures. For subgroup 2 (21 patients), the gingivectomy was associated with LPT, applied every day for seven days. Gingival mucosa fragments were taken on day 1 (curative gingivectomy) and on day 21 (clinical control and corrective gingivectomy), and routinely processed for the microscopic exam. The comparison between the morphological pictures characterizing the healing process associated or not with LPT, allowed the identification of some features supporting the benefits of laser therapy. It is believed that the decrease in the inflammatory infiltrate located in the lamina propria is the critical morphological trait for the control of a healing process as near to restitutio ad integrum as possible. The diminished number of lymphocytes and macrophages will implicitly determine a lower production of chemical mediators interfering with the sequences of the healing process. The morphological differences identified at the gingival epithelium level and subjacent lamina propria support the value of LPT, stimulating an improved healing of the damaged tissues.

The aim of a study by Calderín [2399] was to evaluate the clinical, anti-inflammatory, and osteoimmunological benefits of the single (PT) and repeated laser phototherapy (rPT) as an adjunctive treatment of inflamed periodontal tissue. Twenty-seven patients with chronic peri-odontitis were randomly divided into three groups of nine patients each in order to undergo scaling and root planing (SRP), SRP followed by one session of adjunctive PT (Day 1; SRP + PT), or SRP followed by adjunctive repeated PT five times in 2 weeks (Days 1, 2, 4, 7, and 11; SRP + rPT). For phototherapy session, 670 nm, 200 mW, 60 s/tooth was applied into the sulcus. Clinical parameters, including full-mouth plaque score, full-mouth bleeding score, probing pocket *depth, and clinical attachment levels were recorded. Samples of gingival crevicular fluid (GCF) were taken at baseline, 4, and 8 weeks after treatment. Interleukin 1-ß, tumor necrosis factor alpha (TNF-alpha), receptor activator of nuclear factor kB ligand (RANKL), and osteoprotegerin (OPG) levels in the collected GCF were measured. PT used in a single or repeated doses, does not produce a significant reduction in the clinical pa-rameters essayed. Levels of IL-1ß in GCF were significantly reduced in SRP + PT and SRP + rPT groups compared with the SRP group. However, the SRP + rPT group showed a significant reduction of pro-inflammatory cytokine TNF-alpha and RANKL/OPG ratio at 4 weeks post-treatment compared with the SRP + PT and SRP groups. SRP + PT group also showed a sig-nificant reduction in TNF-alpha and RANKL/OPG ratio at 8 weeks post-treatment compared with the SRP group. PT exerts a biostimulative effect on the periodontal tissue. Multiple sessions of PT showed a faster and greater tendency to reduce proinflammatory mediators and RANKL/OPG ratio.*

In the study by Ribeiro [1906] ten patients were selected and submitted to measurement of six sites per tooth, four teeth per hemiarch (960 sites in all). All patients then received subgingival scaling and root planing. Besides periodontal treatment, the test side was also submitted to laser application. The analysis comprised measurement of probing depth, clinical attachment level, and gingival index. Laser energy was applied at a wavelength of 780 nm (35 J/cm², 70 mW, 20 sec per site) for preoperative analgesia, and scaling and root planing were performed with application of laser energy at a wavelength of 780 nm (35 J/cm², 70 mW, 20 sec) for analgesia, and at a wavelength of 630 nm (8.8 J/cm², 35 mW, 10 sec) for healing. The patients filled out a Visual Analogue Scale to assess the pain they felt during the procedure. After 24 and 48 h, the laser was again applied at the wavelength of 630 nm, and the patients were re-evaluated after 3 days. There was a reduction in gingival inflammation, yet without a statistically significant difference between the study and control sides, both in clinical aspects and evaluation of pain during the procedure. ***While the therepeutic dose (fluence) was well within the therapeutic window, the presumed energy of 1.4 J per point is below the pain relieving energy.***

The study by Aboelsaad [1913] aimed to investigate the influence of 830 nm, CW, 40 mW and 4 J/cm² on the healing of surgically created bone defects in rats treated with bioactive glass graft material. Surgical bone defects were created in the mandibles of 36 Wistar rats divided into two groups, each consisting of 18 rats. Group I was treated with bioactive glass plus laser irradiation. Group II was treated with graft material only. The animals were killed at 4 weeks, 8 weeks and 12 weeks postoperatively for histological examination. Laser irradiation had significantly accelerated bone healing at 4 weeks and 8 weeks in comparison with that at the sites not irradiated. However at 12 weeks, complete healing of the defects had occurred with no difference detected.

In a following clinical study [1914] Aboelsaad aimed to investigate the same procedure in a clinical setting, with total energy density of 16 J/cm^2 on the healing of human infra-bony defects treated with bioactive glass graft material. Twenty patients with chronic periodontitis and bilateral infra-bony defects were included. Using a split mouth design, the group treated 20 defects with bioactive glass plus laser irradiation during surgical procedures and on days 3, 5, 7 postoperatively; 20 contra-lateral defects were treated with bioactive glass only. Clinical probing pocket depths, clinical attachment levels and standardised periapical radiographs were recorded at baseline and at 3 months and 6 months postoperatively. At 3 months there was a statistically significant difference between the laser and non-laser sites in the parameters investigated. However, at 6 months, no difference was observed.

The purpose of the study by Emrem Dogan [2510] was to evaluate the clinical results of guided tissue regeneration (GTR) after the application of equine bone and membrane alone or combined with low-level laser therapy (LPT) for the treatment of periodontal defects. This study was an intra-individual longitudinal study of 6 months' duration conducted using a split-mouth and randomised design. In 13 periodontitis patients with bilateral intrabony periodontal defects, while one defect site was treated with GTR plus LPT (1064 nm, 100 mW, 4 J/cm^2), the contralateral defect site was treated with guided GTR alone. GTR was performed with a combination of equine bone and membrane. LPT was used both intra- and postoperatively. Clinical probing depth (PPD), clinical attachment level (CAL), clinical gingival recession level (REC), plaque index (PI) score, and sulcus blooding index (SBI) score were recorded at the time of surgery, and at the 3rd and 6th months after operation. The treatment of periodontal intrabony defects with equine bone and membrane in the operation of GTR alone or GTR plus LPT in combination led to statistically significant PPD reduction, CAL gain, and lower SBI score at the end of the study. In addition, between the two groups, GTR plus LPT resulted in statistically significant lower REC, lower SBI score, more reduction of PPD and CAL gain compared with GTR alone at 6th months control.

Lai [1916] evaluated the adjunctive effect of a HeNe laser in the non-surgical periodontal treatment of patients with moderate to advanced chronic periodontitis. Sixteen patients with probing pocket depth (PPD) >/=5 mm and comparable bone defects on both sides of the mouth were recruited. Supragingival plaque (PL), bleeding on probing (BOP), PPD, and probing attachment level (PAL) were recorded at baseline and at 3, 6, 9, and 12 mo, while gingival crevicular fluid (GCF) samples and standardised intra-oral radiographs for digital subtraction radiography were taken at baseline and at 1, 3, 6, 9, and 12 mo. After non-surgical mechanical periodontal treatment, the test sites were selected randomly and irradiated with a HeNe laser (output power 0.2 mW) for 10 min for a total of eight times in the first 3-mo period, while the control sites received no additional treatment. PL percentage (83-16%) and BOP percentage (95-34%) decreased significantly *after 12 mo. Statistically significant changes in reductions of PPD and GCF volume, gain in PAL, and increase in recession were seen in both test and control sites when compared to baseline. No statistically significant differences in any clinical parameters or radiographic findings were found between the test and control sites. Changes in GCF volume were significant only at 3 mo in the test sites.* ***The energy delivered by a 0.2 mW laser during 10 minutes is 0.12 J and the total energy applied during eight sessions was less than 1 J. The negative outcome of this study is therefore to be anticipated.***

Twenty patients with inflammatory gingival hyperplasias on their symmetrical teeth were included in a study by Ozcelik [1822]. After gingivectomy and gingivoplasty, a diode laser (588 nm, 120 mW) was randomly applied to one side of the operation area for 7 days. The overall energy density per irradiation of 5 min was stated to be 4 J/cm^2. During irradiation, the tip of the laser probe was placed on both the buccal and the lingual side of the periodontal defect area (5 min. for each). The flaps were then replaced and sutured with modified internal mattress sutures. LPT was again applied for 10 min. from the outer buccal and lingual surfaces (again for 5 min. for each) of the flaps immediately after suturing for the test sites. The surgical areas were disclosed by a solution to visualise the areas in which the epithelium is absent. Comparison of the surface areas on the LPT-applied sites and controls were made with an image-analysing software. Despite the prolonged time needed for application, patients tolerated LPT well. While there were no statistically significant differences between the stained surface areas of the LPT applied and the control sites immediately after the surgery, LPT-applied sites had significantly lower stained areas compared with the controls on the post-operative third, seventh and 15th day. Within the limitations of this study, the results indicated that LPT may enhance epithelisation and improve wound healing after gingivectomy and gingivoplasty operations.

The aim of another study by Ozcelik [1921] was to evaluate the immediate post-operative pain, wound healing and clinical results after the application of an enamel matrix protein derivative (EMD) alone or combined with a LPT for the treatment of deep intra-bony defects. This study was an intra-individual longitudinal test of 12 months' duration conducted using a blinded, split-mouth, placebo-controlled and randomised design, and the same type of laser as above. In 22 periodontitis patients, one intra-bony defect was randomly treated with EMD+LPT, while EMD alone was applied to the contra-lateral defect site. LPT was used both intra- and post-operatively. Clinical measurements were performed by a blinded periodontist at the time of surgery, in the first week and in the first, second, sixth and 12th month. Visual analogue scale (VAS) scores were recorded for pain assessment. The results showed that the treatment of intra-bony defects with EMD alone or EMD+LPT leads to probing depth reduction and attachment-level gain. In addition, EMD+LPT had resulted in less gingival recession less swelling and less VAS scores compared with EMD alone.

The aim of a split-mouth, double blinded, short-term, controlled clinical trial by Makhlouf [2147] was to study the effect of LPT as an adjunct to scaling and root planing (SRP) for treatment of chronic periodontitis. Sixteen patients with a probing pocket depth (PPD) of 4-6mm involving at least three teeth in each quadrant were recruited for the study. Afterwards, SRP quadrants were randomly assigned for 10 sessions of LPT. Results showed that when compared to sites treated with SRP alone, those treated with SRP+LPT (10 sessions, 830 nm, 100 mW, 3 J per point, 3 J/cm^2 exhibited greater reductions in PPD at 5 weeks and 3 months but not at 6 months. Further, SRP+LPT-treated sites had a statistically significant increase in mean radiographic bone density when comparing 6- and 12-month data and overall from baseline to 12 months. There was a trend to reduce interleukin (IL)-1 but the difference between control and laser sites was not statistically significant. SRP combined with LPT improved radiographic bone density and short-term PPD reduction in patients with chronic periodontitis, but did not significantly affect either the gingival crevicular fluid of IL-1ß or the gingival or plaque index.

Obradovic [2162] divided 300 patients in three equal groups: Group 1 consisted of patients with periodontitis and type 1 DM (diabetes mellitus), Group 2 of patients with periodontitis and type 2 DM, and Group 3 of patients with periodontitis (control group). After oral examination, smears were taken from gingival tissue, and afterward all of the patients received oral hygiene instructions, removal of dental plaque, and full-mouth scaling and root planing. A split-mouth design was applied; on the right side of jaws LPT (670 nm, 5 mW, 14 min/day) was applied for five consecutive days. After the therapy was completed, smears from both sides of jaws were taken. Investigated parameters were significantly lower after therapy compared with values before therapy. After therapy on the side subjected to LPT, there was no significantly difference between patients with DM and the control group. It could be concluded that LPT as an adjunct in periodontal therapy reduces gingival inflammation in patients with DM and periodontitis.

Further literature: [1106, 1225, 1307, 1314, 1320]

5.3.23 Prosthetics

Opening the gingival pocket with retraction cord in conjunction with the taking of impressions can cause postoperative discomfort. Electrosurgery can cause even greater distress, especially if the electrocoagulator comes in contact with bone. 2-3 J in each proximal space eases pain and should be given prophylactically before the anaesthetic has worn off.

When trying in a crown on a vital tooth, the patient is often reluctant to anaesthetise again, particularly in the front of the upper jaw. 2-3 J on the exposed dentine raises the pain threshold enough to test the crown. The same applies to cementing, in which cleaning, drying and exposure to the cement can cause postoperative discomfort. If you have not administered treatment prophylactically, postoperative problems can be dealt with after cementing by irradiating over the apex. The dosage depends on the position of the root apex. If vital dentine is irradiated directly, a brief pain reaction can arise. This passes quickly, so pause for a while before continuing the laser treatment.

The preparation of vital teeth is traumatic for the pulp, although this is a trauma that most teeth can cope with. 1-2 J to stimulate the pulp and reduce any postoperative difficulty is recommended.

Transient pain reactions in the pulp can be the result of vigorous occlusal adjustment. The laser here presents an excellent source of immediate help for the patient. 3-4 J over the apex of each involved root is the normal dosage.

If a dental prosthesis chafes, superfluous acrylic must be ground away. Because the decubital wound is sensitive and swollen, an overadjustment of the surface of the prosthesis is required in order to relieve all symptoms. Recommended treatment for the dentist equipped with a laser is as follows: adjust only until the patient is free from symptoms when lightly biting. Treat the wound with a laser and polish the adjusted area. It should now be possible to bite hard. The laser has stopped the wound from being painful and keeps the patient free from symptoms during the time it takes for the oedema to disappear. The healing process is also shortened.

Figure 5.10 Upper denture once worn by George Washington

Literature:

A study by Ferreira [1882] investigated the biomodulatory effect of the 670 nm laser in pulp cells on reactional dentinogenesis, and on the expression of collagen type III (Col III), tenascin (TN), and fibronectin (FN) in irradiated dental tissues and controls (not irradiated). Sixteen human premolar teeth were selected (after extraction due to orthodontal reasons) and divided into irradiated and control groups. Black class V cavity preparations were accomplished in both groups. For the irradiated group, laser (670 nm, 50 mW) with an energy density of 4 J/cm² was used. Soon after, the cavities *were restored with a glass ionomer and the extractions made after 14 and 42 days. Histological changes were observed by light microscopy; less intense inflammatory reaction in the irradiated group was found when compared to the controls. Only the irradiated group of 42 days exhibited an area associated with reactional dentinogenesis. After immunohistochemical analysis, the expression of Col III, TN, and FN was greater in the irradiated groups. : These results suggest that a laser with energy density of 4 J/cm^2 and wavelength of 670 nm causes biomodulation in pulp cells and expression of collagen, but not collagen of the extracellular matrix, after preparation of a cavity.*

Marei [515] divided 18 male denture wearers with mucosal lesions into three groups of six according to the treatment applied: denture removal, relining dentures with temporary tissue, or application of laser while continuing to wear the dentures. Clinically and histologically, the laser group healed best. Furthermore, the bone underlying the lesions showed an increase in optical density.

The aim of a study by Simunovic-Soskic [2116] was to monitor therapeutic response by determining the level of proinflammatory cytokines TNF-alpha and IL-6 in whole unstimulated saliva in patients with denture stomatitis (DS), before and after laser phototherapy (LPT). A sample consisting of 40 consecutive subjects was selected on a voluntary basis from patients who presented for the diagnosis and treatment of DS. A clinical examination was performed according to the standard clinical criteria. Lesions described as palatal inflammation were diagnosed as Newton type II denture stomatitis. The patients were randomly assigned to either an experimental group (20 patients receiving real LPT) or a control group (20 patients receiving inactive/placebo laser treatment). Following treatment with LPT for 4 wk, the levels of TNF-alpha and IL-6 decreased and were significantly different from controls.

The purpose of the report by Maver-Biscanin [2400] is to present the effect of LPT on Candida albicans growth and palatal inflammation in two patients with denture stomatitis. The most common oral mucosal disorder in denture wearers is denture stomatitis, a condition that is usually associated with the presence of the yeast Candida albicans. Two denture-wearing patients, both with palatal inflammation diagnosed as Newton type II denture stomatitis were treated with different wavelengths (685 and 830 nm) for 5 d consecutively. In both patients, palatal mucosa and acrylic denture base were irradiated in noncontact mode (probe distance of 0.5 cm from irradiated area) with different exposure times-5 min (830 nm, 3.0 J/cm^2, 60 mW) and 10 min (685 nm, 3.0 J/cm^2, 30 mW). The effect of laser light on fungal growth in vivo was evaluated after the final treatment using the swab method and semiquantitative estimation of Candida albicans colonies growth on agar plates. The severity of inflammation was evaluated using clinical criteria. After laser treatment, the reduction of yeast colonies on the agar plates *was observed and palatal inflammation was diminished. LPT is effective in the treatment of denture stomatitis.*

Further literature: [79, 80, 66, 363]

5.3.24 Root fractures

Vertical root fracture (VRF) has been a great challenge in dentistry; most fractures often result in tooth extraction. Inflammation of tissues around the fractured root is the main reason for tooth extraction. Based on the strategic importance of some fractured teeth, treatment may be necessary and often complicated. However, performing a proper repair or even splinting the fractured segments may result in tooth preservation. Accordingly, in a case Leal da Silva [2167] reports a new method for fractured tooth preservation. The surgical exposition of the fracture tooth was carried out through the radicular portion of the element via ultrasonic preparation, filling with composed resin and a synthetic hydroxyapatite graft. All these were performed around the tooth which received five sections of LPT. The patient was followed for two years with no signs or symptoms of inflammation and gingival recession. In conclusion, the used treatment protocol could be considered as a promising approach for VRF treatment, especially in cases where there is advanced or moderate bone loss in the surrounding sites of the fractured tooth.

5.3.25 Secondary dentine formation

Being able to stimulate secondary dentine formation with LPT would be of great benefit to the dental practitioner eager to preserve as much as possible. There are signs that this may be possible, but we do not yet know the optimum wavelengths and dosages.

Literature:

Nagasawa [106, 107] reported strong secondary dentine formation when rat teeth received Nd:YAG laser treatment at dosages within the biostimulating range. These results have recently been confirmed on human teeth.

In a pig experiment Prezotto [1466] found that 12,8 J/cm² (10 mW during 10 secs) stimulated secondary dentine formation when checked at 7 days post irradiation, while 89.7 J/cm² (70 mW during 10 secs) delayed formation as compared to control. At 45 days after irradiation there was no difference between low dose/high dose or control group.

Arany [2517] showed that LPT can be used as a minimally invasive tool to activate an endogenous latent growth factor complex, transforming growth factor-beta1 (TGF-beta1) that subsequently differentiates host stem cells to promote tissue regeneration. LPL treatment induced reactive oxygen species (ROS) in a dose-dependent manner, which, in turn, activated latent TGF-beta1 (LTGF-beta1) via a specific methionine residue (at position 253 on LAP). Laser-activated TGF-beta1 was capable of differentiating human dental stem cells in vitro. Further, an in vivo pulp capping model in rat teeth *demonstrated significant increase in dentin regeneration after LPL treatment. These in vivo effects were abrogated in TGF-beta receptor II (TGF-betaRII) conditional knockout mice or when wild-type mice were given a TGF-betaRI inhibitor. These findings indicate a pivotal role for TGF-beta in mediating LPL-induced dental tissue regeneration.*

Further literature: [2357]

5.3.26 Temperature caveats

Low level lasers do not cause harmful levels of heating in tissues, but there are always caveats. The pulp is sensitive to heating and especially the pulp in young persons. Curing lights are sold at increasingly higher output and there seems to be no concerns for side effects. An average LED curing light at 1000 mW/cm^2 has a power of about 250 mW. There are curing lights with considerably higher outputs on the market, and the study below gives a caveat for high outputs, be it curing lights or lasers.

Literature:

The study by Alencar Mollo [2173] was an in vitro evaluation of temperature increases in the human tooth pulp chamber after 808 nm laser irradiation using different power densities. Twelve human teeth (three incisors, three canines, three premolars and three molars) were sectioned in the cervical third of the root and enlarged for the introduction of a thermocouple into the pulp chamber. The teeth were irradiated with 417 mW, 207 mW and 78 mW power outputs for 30 s on the vestibular surface approximately 2 mm from the cervical line of the crown. The highest average increase in temperature (5.6°C) was observed in incisors irradiated with 417 mW. None of the teeth (incisors, canines, premolars or molars) irradiated with 207 mW showed temperature increases higher than 5.5°C that could potentially be harmful to pulp tissue. Teeth irradiated with 78 mW showed lower temperature increases. The study showed that laser irradiation with a wavelength of 808 nm at 417 mW power output increased the pulp chamber temperature of certain groups of teeth, especially incisors and premolars, to critical threshold values for the dental pulp (5.5°C). Thus, this study serves as a warning to clinicians that "more" is not necessarily "better".

The study by Shigetani [2387] aimed to clarify pulpal responses to GaAlAs laser irradiation. Maxillary first molars of 8-week-old rats were irradiated at an output power of 0.5 or 1.5 W for 180 seconds, and the samples were collected at intervals of 0 to 14 days. The demineralised paraffin sections were processed for immunohistochemistry for heat-shock protein (HSP)-25 and nestin in addition to cell proliferation assay using bromodeoxyuridine (BrdU) labeling and apoptosis assay using deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling (TUNEL). Intense HSP-25 and nestin immunoreactivities in the odontoblast layer were weakened immediately after 0.5 W irradiation and recovered on day 1, resulting in slight tertiary dentin formation by day 14. On the contrary, 1.5 W irradiation *immediately induced the loss of HSP-25 and nestin-immunoreactivities in the odontoblast layer. On day 1, numerous TUNEL-positive cells appeared in a degenerative zone that was surrounded by intense HSP-25 immunoreactivity. BrdU-positive cells occurred within the intensely HSP-25-immunopositive areas during days 2 through 5, whereas TUNEL-positive cells gradually decreased in number by day 5. HSP-25- and nestin-positive odontoblast-like cells were arranged along the pulp-dentin border by day 7, resulting in remarkable tertiary dentin formation on day 14. The output energy determined pulpal healing patterns after GaAlAs laser irradiation; the higher energy induced the apoptosis in the affected dental pulp including odontoblasts followed by active cell proliferation in the intense HSP-25-immunoreactive areas surrounding. Thus, the optimal GaAlAs laser irradiation elicited intentional tertiary dentin formation in the dental pulp.*

***Comparing these two studies, it is obvious that there is a "conflict of interest" with regards to the temperature increase in the pulp. 270 J over a tooth is for the time being not recommended, not even 90 J. In spite of the following studies**:*

The study by Matsui [2388] was conducted to investigate the effects of GaAlAs laser irradia-tion on the mineralization ability of human dental pulp (HDP) cells. HDP cells in vitro were irradiated once at 0.5 W for 500 s and at 1.0 W for 500 s in order to investigate free radicals as one mechanism for transmission of laser photochemical energy to cells. Production of the hydroxyl radical (OH) was measured using the ESR spin-trapping method and was found to be increased by laser irradiation. The DMPO-OH was not detected in the presence of dimethyl sulfoxide (DMSO), a OH scavenger. The formation of calcification nodule was also investigated by von Kossa staining. The number of calcified nodules was increased by 1.0 W-laser irradiation. Alkaline phosphatase (ALP) activity was higher in the 1.0 W-laser irradiation group. Expression of mRNAs for heat shock protein 27, bone morphogenetic proteins (BMPs) and ALP were greater in the 1.0 W-laser irradiation group. Expression of BMPs in the condi-tioned medium was also higher in the 1.0 W-laser irradiation group. In particular, DMSO decreased the number of calcified nodule produced by 1.0 W-laser irradiation. These results supposed that the mineralisation of HDP cells is stimulated by laser irradiation, and that OH generated by laser irradiation is a trigger for promotion of HDP cell mineralization.

The study by Tate [2389] aimed to evaluate the effect of the GaAlAs laser on odontoblasts using immunohistochemistry for heat-shock protein (HSP)-25, which labels mature and newly differentiated odontoblasts. The mesial surface of the upper right first molar of 8-wk-old rats was lased at an output power of 0.5-1.5 W for 180 s. The animals were perfusion-fixed at intervals of 6 h to 30 d after irradiation. At 6 h to 7 d, the intensity of HSP-25-immunoreactivity was found to be disturbed in the coronal odontoblast-layer in an energy-dependent manner. At 30 d, tertiary dentin with/without bone-like tissue was formed abundantly in the dental pulp. Statistical analy-

sis revealed that the area occupied by the new hard tissues was significantly wider in 1.5 W-lased specimens than in 0.5 W-lased specimens. An intense HSP-25 immunoreactivity was seen in the odontoblasts underlying the tertiary dentin, whereas immunoreactivity was weak around the bone-like tissue. It was concluded that the GaAlAs laser may induce the formation of tertiary dentin by influencing the secretory activity of odontoblasts.

5.3.27 Temporo-mandibular disorders (TMD)

Evaluation of microcirculation in tender points in the m. masseter, using active and placebo laser.

Figure 5.11 Evaluation of microcirculation in tender points
Courtesy: Marie Tullberg

Lasers can be of benefit in various ways for problems relating to temporo-mandibular disorders. As with any treatment, a correct diagnosis is essential to obtain a satisfactory result. In a number of conditions, i.e. occlusal adjustment and taking impressions for a splint, the pain itself prevents conventional treatment. By irradiating the joint and tender points, pain relief can be achieved, musculature is relaxed, and treatment can begin. Recent clinical experience and clinical studies indicate that rather high doses are needed for myogenic conditions and that the energy density itself is of importance. The inconsistent success reported in older studies seems to be related to this fact.

In cases of trismus [293], tender points and muscle attachments are treated. 6-10 J per point is usually a good start, but higher energies are sometimes required. Make a note of the maximum jaw-opening ability before treatment starts, then measure it again afterwards. During subsequent treatment, even more peripheral muscle attachments (e.g. the sternocleidomastoid) are palpated and irradiated. The treatment in TMD patients should not be discontinued as soon as pain disappears, but should be continued at longer intervals. Two to three applications in the first week, then once a week, can be sufficient for myoses. Arthritis/arthrosis requires lower energies due to the superficial location; 4-6 J per session is suggested. LPT is almost as effective as intra-articular steroids for joint pain [435].

Additional irradiation of the stellate ganglion [691, 692, 685, 1053] in pain patients has been effective in several studies and can be recommended for TMD treatment as well.

TMD, or orofacial pain, is a multifactorial condition and individual adjustments of the energies and treatment zones have to be made. Therefore, preset parameters in clinical studies can make the therapy suboptimal.

Dentists should be aware of the potential connection between tinnitus/vertigo and TMD (somatosensory tinnitus). Occlusal adjustment and/or splints will be very helpful in this group of patients. LPT reduces palpation tenderness and improves microcirculation in the tense muscles, thus leading to more rapid success. Tinnitus patients are over-represented among TMD sufferers [1488, 1722, 1723, 1724]. There is also an overrepresentation of TMD problems in persons with sensorineural hearing loss [1633].

Typical findings in these patients are premature contacts in the lower incisives and crossbite. Apart from tender points in the masticatory muscles (dominated by m. pterygoidalis lateralis, always on the tinnitus side), the occipital muscles should be palpated since they are often involved. If tender, stretching of these muscles in combination with laser can temporarily lead to the reduction or even the elimination of tinnitus. This is an important diagnostic finding. The relation between muscular tension and tinnitus has been explained by Shore [1229] who found a connection between the sensory part of n. trigeminus and the ventral auditory nucleus in the brain stem. (See chapter 4.1.54 “Tinnitus, vertigo, Ménière´s disease” on page 419.)

Literature:

Animal studies

Eleven male New Zealand rabbits were included in study by Kucuk [2367]. Six randomly selected rabbits were imaged to provide normal joint images (normal group) before the initiation of the experiment. A 5% formalin solution was locally injected into both right and left TMJs of all rabbits. Subsequently, 815 nm; energy density: 12 J/cm^2; output power: 250 mW was applied for 48 seconds. The treatment was performed six times for 2 weeks to the left TMJ of all rabbits. The right TMJs of the rabbits were used as the control (nontreated) TMJ group, while left TMJs were used as the treated TMJ group. Static images of TMJ were taken at 24 hours, 7 days, and 14 days after the beginning of the treatment. The images of all TMJs were taken in the posteroanterior direction with the rabbit under sedation and its mouth open. Significant differences were found between normal and both the control and treated TMJ groups. A reduction of inflammation in both treated and a control TMJ group was obtained, but there was no statistically significant difference between the groups. Under the conditions used in this study, quantitative scintigraphic measurements of TMJ inflammation of the treated TMJ group decreased but did not differ significantly from those of the control TMJ group.

This paper is given a long comment here, since it contains a number of classical mistakes and serves an a didactic example:

The investigation of the anti-inflammatory effect of LPT on TMJ inflammation would suggest that the use of this therapeutic modality has little or no effect. In fact, this is a misinterpretation of the paper. To understand how LPT works, it is essential to be able to evaluate the involved parameters. The physical parameters required are: wavelength (nanome-

ter), output of the laser (milliwatt), size of the laser eye (cm²), applied energy (joule) and the dose (J/cm²). The numbers of irradiated points, number of sessions, intervals between sessions, contact or no contact with tissue are other important parameters. An independent measurement of the actual output of the laser is also needed if the researcher wants to be in control. Without an account of all these parameters, a future control study may very well become a completely different study. Too often the difference between the applied energy (J) and the dose (J/cm²) is confused. The energy is calculated by multiplying the output of the laser times the seconds of irradiation. Thus, 100 mW during 10 seconds becomes 1000 millijoule = 1 J. The dose (also called fluence), on the other hand, is the energy divided by the size of the irradiated area - often the size of the laser aperture in contact. Too often only one of these parameters is accounted for in scientific papers and in unfortunate cases other authors confuse the dose and energy. For example, in the study by Brosseau the dose is 3 J/cm² for finger arthritis. This may appear to be a reasonable dose. But since the laser fiber used was very thin, this dose was reached in a few seconds and the applied energy was only 0.12 J per finger joint. Energy and dose are two independent parameters which both have to reach an effective level.

In the paper by Kucuk, a laser of 250 mW was used for 48 seconds. This produces energy of 12 J. This parameter is not reported, only the dose of 12 J/cm². Since the laser aperture is reported to deliver a spot of approximately 10 mm, the dose and the energy in this case gets almost the same numeric value. So far so good. The problem is the understanding of the therapeutic window for biostimulation. The authors cite other researchers and here the complications start. For instance, Hansson used 904 nm, 0.3 mW, 3 minutes. 0.3 x 180 = 0.054 J for clinical use. Mazetto used 780 nm, 70 mW, 10 s, 89.7 J/cm² = 0.7 J for clinical use. Venanzio used 780 nm, 30 mW, 10 s, 6.3 J/cm² at three TMJ points. 0.3 x 3 = 0.9 J. The energies in these studies have had to be recalculated since they are not reported. The three examples above are for TMD arthritic pain. The myalgic studies discussed in the Kucuk paper have the same problem.

Now, looking at the energies used in the three studies above, these have been in the range 0.5 - 0.9 J per point. For an average human (keeping in mind that TMD appears to be more common in females) of 60 kg, this would mean approximately 0.2 J per kg. The mean weight of the rabbits was about 3 kg. The 12 joules applied brings 4 joules per kg. The Arndt-Schultz law stipulates that "For every substance, small doses stimulate, moderate doses inhibit, large doses kill." The exact optimum for biostimulation of inflammation in the TMJ is not known, but the World Association for Laser Therapy recommends 1-2 points and a total energy of 4 J for clinical use. The TMJ is quite superficial whereas muscles require considerable higher energies due to the poor penetration into these well vasculated tissues. The power density (mW/cm²) is also of importance

and low power and longer time are reported to be more effective for tissue repair than high power and short time, even using the same total energy.

It is suggested that the lack of effect in the Kucuk paper is due to gross over dosage and subsequent inhibition.

The aim of the study by Abtahi [2390] was to evaluate the effect of LPT on condylar growth during mandibular advancement in rabbits. Continuous forward mandibular advancement was performed in fourteen male Albino rabbits with the mean age of 8 weeks and the mean weight of 1.5 ± 0.5 kg, with acrylic inclined planes. The rabbits were randomly assigned into two groups after 4 weeks. LPT, 630 nm was performed at 3 points around the TMJ, through the skin in the first group. The exposure was performed for 3 minutes at each point (a total of 9 minutes) once a day for 3 weeks. The control group was not exposed to any irradiation. The rabbits in both groups were sacrificed after two months and the histological evaluation of TMJ was performed to compare fibrous tissue, cartilage, and new bone formation in condylar region in both groups. Disc displacement was also detected in both groups. The formation of fibrous tissue was significantly lower, while bone formation was significantly greater in lased group as compared with control group. The thickness of cartilage did not differ significantly between two groups.

The aim of the study by Barretto [2489] was to investigate the analgesic and anti-inflammatory activity of LPT on the nociceptive behavioral as well as histomorphological aspects induced by injection of formalin and carrageenan into the rat temporomandibular joint. The 2.5% formalin injection (FRG group) induced behavioral responses characterised by rubbing the orofacial region and flinching the head quickly, which were quantified for 45 min. The pretreatment with systemic administration of diclofenac sodium-DFN group (10 mg/kg i.p.) as well as the irradiation with LPT infrared (LST group, 780 nm, 70 mW, 30 s, 2.1 J, 52.5J/cm^2, significantly reduced the formalin-induced nociceptive responses. The 1% carrageenan injection (CRG group) induced inflammatory responses over the time-course of the study (24 h, and 3 and 7 days) characterised by the presence of intense inflammatory infiltrate rich in neutrophils, scanty areas of liquefactive necrosis and intense interstitial edema, extensive hemorrhagic areas, and enlargement of the joint space on the region. The DFN and LST groups showed an intensity of inflammatory response that was significantly lower than in CRG group over the time-course of the study, especially in the LST group, which showed exuberant granulation tissue with intense vascularization, and deposition of newly formed collagen fibers (3 and 7 days). It was concluded that the LPT presented an anti-nociceptive and anti-inflammatory response on the inflammation induced in the temporomandibular joint of rodents.

Figure 5.12 TMD frequently involves more muscles than the masticatory muscles.

Clinical studies

Bezuur [206] treated a group of 27 patients suffering from long-term problems related to TMJ (temporo-mandibular joint) disorders with a GaAs laser. The treatment was administered over the joint on five consecutive days. 80% of the 15 patients with arthrogenous pain experienced total pain relief. The maximum jaw-opening ability increased during the treatment period and continued to increase during the year that the group was monitored. The group suffering from myogenic problems also improved both in terms of pain and jaw-opening ability. The effect here was, however, much lower. As the muscles were not treated, it is assumed that this group also had undiagnosed arthritis. The reduction of joint sounds may possibly have been due to an increase of metabolism in articular cell structures, e.g. an activation of the synovial membrane, producing more synovial fluid.

Eckerdal [595] reports on the clinical experience of a 5-year non-controlled study of perioral neuropathias. The treated diagnoses were trigeminal neuralgia, atypical facial pain, paraesthesias and TMD pain. Of these diagnoses, the TMD pain group was the most successful one. At the end of treatment, 73% of the patients (N = 40) had a good response, at six months the number was still 73%, and at one year 70%. 10 J/cm^2 was applied to the joint over 4-8 sessions.

In a study comprising 75 cases, Bradley [435] found LPT effective as a monotherapy when treating acute joint pain (of less than eight weeks duration). In more chronic cases, without bone changes noticeable on X-ray, LPT *was used as an adjunct to splints and the like. In osteoarthritic cases, LPT can be almost as useful as intra-articular steroids.*

Bradley [117] used GaAs laser acupuncture when treating a small group of patients suffering from TMJ pain dysfunction syndrome who had not responded to treatment with a bite splint or psychotropic medicine. Needle acupuncture was used in a comparative group. Both types of acupuncture can be studied with thermography. Biostimulation was observed to yield vascular effects which locally resemble the vascular effects achieved with needle acupuncture, although it takes more time for laser stimulation to achieve an effect. Both forms of acupuncture were more effective on known acupuncture points than on randomly chosen points. St 6 was used throughout as a "known acupuncture point".

Kim [177] divided a group of 36 patients with maxillary joint problems into three therapy groups. The patients were treated either with bite splints, GaAlAs laser treatment or laser acupuncture. The treatment results were compared after two and four weeks with a check on status before treatment. The following conclusions were drawn. The patients' subjective discomfort was reduced in both the bite splint and laser treatment groups. The improvement in the laser group was much greater than in the bite splint group. Clinically noticeable symptoms showed a significant reduction in all groups, but the group treated with laser light responded faster to treatment than the other groups. EMG (electromyogram) activity gradually decreased in all groups, without any great difference between groups. Laser treatment had more beneficial effects than bite splints, while laser acupuncture produced the poorest results.

Kim [1119] found improvement in maximum mouth opening and increase in the pressure pain threshold after irradiating tender points in the masseter and trapezius. Laser was more effective than ultrasound.

Lopez [244] treated a group of 168 patients with problems related to TMJ disorders by using a combination of bite splints and HeNe laser light. An obvious improvement could be observed in 52 of the patients after a single application of treatment. After ten applications, 90% of the patients had improved. No further improvement was brought about in the other 10% by administering further treatment. The laser treatment was given directly over the maxillary joint - 6 mW for five minutes. The extent of healing was inspected using a tomographic X-ray before treatment and after six months. At that point, healing had advanced to a stage usually seen after 12 to 18 months when only a bite splint is used. In a group of 88 patients with pain in the jaw muscles, pain was alleviated for up to six hours, but without lasting results. The author concluded that HeNe lasers are effective as a complementary method to bite splints when treating arthrosis and arthritis, but that this wavelength is not optimal for myogenic pain.

Hatano [49] used a GaAlAs laser to study the effect on palpation pain in 15 patients with TMJ problems. A 30 mW laser was used for 3 minutes in the area of one temporo-mandibular joint. The other side served as control.

Palpation score was estimated directly after irradiation and 20, 40 and 60 minutes after irradiation. There was a significant decrease in palpation pain with better results after 20, 40 and 60 minutes than directly after irradiation.

Gray [1040] performed a clinical study where the effects of shortwave diathermy, megapulse, ultrasound and laser were compared in TMD therapy. There was no significant difference in success rate between the four therapies but all were better than placebo. The laser used was Space IRCEB-Up, 904 nm, and the reported dose was 4 J/cm², 3 minutes application, 3 times weekly for 4 weeks. There is no information in the text making a verification of this dose possible. This laser typically had 4 mW of power in contrast to pamphlet values and only at maximum pulsing. Nor is there any information on the therapeutic technique for either arthritis/arthrosis or myosis. This makes an evaluation of the laser part of the study difficult.

Bertolucci [532] compared two groups of patients (16+16) receiving physical therapy for mandibular dysfunction. One group received sham irradiation, the other GaAs laser over three weeks. The results were as follows (treatment group/placebo group): change in pain 40.25/1.56; change in vertical opening 1.35/-0.05; change in left and right deviation 3.78/0.62.

Cho [1183] performed a double blind study on the pressure pain threshold in patients with TMD. 19 dental students with TMD and 20 with no TMD were treated with LPT or placebo laser. There was a significant reduction in pain indexes in the laser group.

Conti [634] performed a double blind study on the effect of GaAlAs on two small groups of patients suffering from arthrogenous and myogenous problems respectively. Using a 100 mW laser, 4 J of energy was applied over the lateral joint surface in the arthrogenous group. In the myogenous group the same energy was applied to the most painful muscle point. The patients received three doses once a week. There was no statistical difference between placebo and laser groups. The lack of success in the study can probably be attributed to the low dose in the myogenic group, too few sessions, too long intervals between sessions and the fact that only a single myogenic pain point was irradiated. The arthrogenous group (5 + 5 patients) had very diverse diagnoses. 4 J for arthrogenous pain is a reasonable level, while for myogenous pain much higher doses are needed and more painful points must be irradiated, the lateral pterygoid not to be forgotten. The author himself also suggests the need for higher doses and more therapy sessions. The importance of higher doses and indeed higher energy densities is illustrated in the following studies.

The improved outcome of LPT, if higher doses are given, is documented in the study by Sanseverino [1224]. 10 patients with pain and limitation of movements of the jaw were treated by 785 nm, dose 45 J/cm². The joint and tender points in the masticatory and muscles otherwise involved were applied three times per week over three weeks. A control group of 10 patients was given sham LPT. The evaluation was performed through subjec-

tive pain assessment and measurement of the movements of the jaw. There was a significant improvement in the laser group only.

Sattayut [873] performed a double blind study on 30 patients. These patients had had their TMD problems for more than 6 months. One group received placebo laser, one was treated with a 60 mW GaAlAs laser (4 J per point) and the third with a 300 mW GaAlAs laser (20 J per point). Energy densities were 20 and 100 J/cm^2*, respectively. Assessment before and after the three treatment sessions was made by algometry of trigger points in masticatory muscles. Statistically significant increases in pressure point threshold and electromyographic amplitude recorded from voluntary triple clenching compared with placebo were seen in the high-energy group but not in the low-energy group, although a trend towards improvement was seen. A significantly greater number of patients recovered from myofascial pain and TMJ arthralgia as assessed clinically in the high-energy group compared to the placebo group.*

The inter-relation between TMD and tinnitus has been addressed by i.a. Myrhaug [711]. The influence of n. trigeminus and n. facialis in TMD is well recognised by dentists. These two nerves also govern m. tensor tympani and m. stapedius, respectively. Treating the TMD could therefore also influence these two muscles in the middle ear. Reducing the tonus of the masticatory muscles would also relax the two middle ear muscles.

The relation between Menière's disease and problems in the masticatory muscles (the lateral pterygoid in particular), the atlas and the axis has been discussed by Bjorne [874, 1227, 1228]. Laser treatment of these muscles has so far had a promising clinical result.

Wong [875] stresses the fact that the styloid process and its attachments are often overlooked in the treatment of oro-facial pain. No less than 11 pains and symptoms have been identified from this structure, among them tinnitus. A GaAlAs laser directed at this site could relieve the symptoms.

The purpose of this study by Farina [1468] was to analyse the effects of LPT associated or not to occlusal splints in patients with TMD. Pain, mouth opening, muscular functions and bite force were measured. Ten patients were selected and divided into three groups: laser (GL), laser + occlusal splint (GLO) and occlusal splint (GO). In the first visit, the patients answered a Mc.Gill's short form. In each visit, mouth opening ability was measured, and the patients filled a Visual Analogue Scale (VAS) form. Electromiography (EMG) in both sides of masseter and temporal muscles was performed in the first visit, and one week later. For EMG and the bite force measurements, an occlusal splint was positioned over the tooth in both arcades and then a transducer was positioned for the tasks. The EMG was measured with 0% (relaxed), 25%, 50%, 75% and 100% of maximum voluntary contraction (MVC). The LPT was performed during 4 sessions with an interval of 48 h. The laser used was continuous wave 780 nm. The dose was 25 J/cm^2*, in three points of TMJ, 15*J/cm^2*, in two points of masseter muscle as well as in three points of the temporal muscle and in one point of ptery-*

goid muscle. Patients from GLO showed a higher mouth opening ability and higher pain relief than other groups.

Lizarelli [1554] divided 60 patients with acute or chronic TMJ disorders into six groups: (1) Acute cases 5 J/cm², (2) Acute cases J/cm², (3) Acute cases placebo laser, (4) Chronic cases J/cm², (5) J/cm², and (6) Chronic cases placebo laser. Evaluation of the condition was performed before LPT, directly after LPT, one week and 30 days after LPT. Decrease in pain intensity and increase in average amplitude of all mandibular movements was found in all laser groups, as compared to the placeo groups.

de Medeiros [1618] examined the effects of LPT on the contraction force of the masseter muscle in patients with neuromuscular discomfort. Fifteen patients of both genders, ages 19-29, suffering from pain in the masseter muscle, were exposed to InGaAlP laser irradiation, applied from a 2-mm distance. Laser parameters were 670 nm, 15 mW, 2 J per each cm² irradiated, covering the whole projection of the masseter muscle. All patients showed improvement in muscle contraction strength of about 2.51-3.01 kgf on both sides.

The aim of the study by Makihara [1659] was to evaluate the facial thermographic changes before and after low-level laser irradiation applied to the temporomandibular joint in normal subjects. Nine healthy subjects underwent irradiation using the continuous wave setting of a CO_2 laser with a power output of 1.0 W. The laser tip was positioned 10 cm above the skin over the right TMJ area for 10 min. The actual fluence on the facial surface was 7.64 J/cm². Variation of the facial temperature was evaluated by using thermography. The facial temperature 10 min after stopping irradiation was higher than that after 10 min of irradiation applied to the opposite side. The warmer area was found not only over the TMJ area but also over the temporal area, forehead area, and eyelid area on both sides.

A study by Venancio [1737] aimed to evaluate the effectiveness of LPT in 30 patients presenting temporomandibular joint (TMJ) pain and mandibular dysfunction in a random and double-blind research design. The sample, divided into experimental group and placebo group, was submitted to the treatment with infrared laser (780 nm, 30 mW, 10 s, 6.3 J/cm², 0.3 J per point, total of 0.9 J per session) at three TMJ points. The treatment was evaluated throughout six sessions and 15, 30 and 60 days after the end of the therapy, through Visual Analogue Scale, range of mandibular movements and TMJ pressure pain threshold. The results showed a reduction in VAS but through the ANOVA with repeated measures it was observed that the groups did not present statistically significant differences. ***Negative result probably due to the low energy applied. WALT recommendation for TMJ is 4 J.***

In a study by Cetiner [1758] thirty-nine patients with myogenic TMD-associated orofacial pain, limited mandibular movements, chewing difficulties, and tender points were included. Twenty-four of them were treated with therapeutic laser (830 nm, 7 J/cm²) for 10 daily sessions, excluding weekends, as test group, and 15 patients with the same protocol received placebo *laser treatment as a control group. These parameters were assessed just before, just after, and 1 month after the treatment. Maximal mouth-opening improvement and reductions in pain and chewing difficulty were statistically significant in the test group when compared with the control group. Statistically significant improvements were also detected between the two groups regarding reduction in the number of tender points.*

The trial by Nuñez [1759] was performed in 10 patients, 18-56 years old, diagnosed with TMD of multiple causes. All patients received both methods of treatment in two consecutive weeks. Laser was delivered via a 670 nm diode laser, output power 50 mW, fluence 3 J per site/4 sites (masseter muscle, temporal muscle, mandibular condyle, and intrauricular). TENS therapy was applied with a two-electrode machine at 20 W, maximum pulse repetition rate of 60 Hz, adjusted by the patient according to their sensitivity. The amplitude of mouth opening was recorded before treatment and immediately after using a millimeter rule; the measurements were performed from the incisal of the upper incisors to the incisal of the lower incisors. A paired t-test was applied to verify the significance of the results. A significant improvement in the range of motion for both therapies was observed immediately after treatment. Comparing the two methods, the values obtained after laser were significantly higher than those obtained after TENS. Both methods are effective to improve mouth opening. Comparing the two methods, laser was more effective than TENS applications.

The objective of the study by Emshoff [1818] was to assess the effectiveness of LPT in the management of temporomandibular joint (TMJ) pain in a random and double-blind research design. TMJ pain patients, randomly assigned, received 2 to 3 treatments per week for 8 weeks of active LPT (632.8 nm, 30 mW) (n = 26) or sham LPT (n = 26). Measures of TMJ pain during function were evaluated at baseline and weeks 2, 4, and 8 after the first LPT session. At the 8-week point, within-group improvements were present for TMJ pain during function, for both the active and sham LPT groups. Between-group differences were not highly evident.

In a study by Fikackova [1870] the active group of 61 patients was treated with 10 J/cm^2 or 15 J/cm^2, and the control group of 19 patients was treated with 0.1 J/cm^2. LPT was performed by a 830 nm laser with output of 400 mW, in 10 sessions. The probe with an aperture of 0.2 cm^2 was placed over the painful muscle spots in the patients with myofascial pain. In patients with TMD arthralgia the probe was placed behind, in front of, and above the mandibular condyle, and into the meatus acusticus externus. Changes in pain were evaluated by self-administered questionnaire. Application of 10 J/cm^2 or 15 J/cm^2 was significantly more effective in reducing pain compared to placebo, but there were no significant differences between the energy densities used in the study group and between patients with myofascial pain and temporomandibular joint arthralgia. Results were most obvious in those with chronic pain.

Carrasco [1988] selected fourteen patients and divided them into two groups (active and placebo). Infrared laser (780 nm, 70 mw, 60s, 4.2 J/point, 105 J/cm^2) was applied precisely and continuously into five points of the temporomandibular joint (TMJ) area: lateral point (LP), superior point (SP), anterior point (AP), posterior point (PP), and posterior-inferior point (PIP) of the condylar position. This was performed twice per week, for a total of eight sessions. A Visual Analogue Scale and a colorimetric capsule method were employed. Data were obtained three times: before treatment (Ev1), shortly after the eighth session (Ev2), and 30 days after the first application (Ev3). Statistical tests revealed significant differences at one percent (1%) likelihood, which implies that superiority of the active group offered considerable TMJ pain improvement. Both groups presented similar masticatory behavior, and no statistical differences were found. With regard to the evaluation session, Ev2 presented the lowest symptoms and highest masticatory efficiency throughout therapy.

In a study by da Cunha [1989] the sample consisted of 40 patients, divided into an experimental group (G1) and a placebo group (G2). The treatment was done with an infrared laser (830 nm, 500 mW, 20 s, 4 J/point) at the painful points, once a week for four consecutive weeks. The patients were evaluated before and after the treatment through VAS and the Craniomandibular Index (CMI). The baseline and post therapy values of VAS and CMI were compared by the paired T-test, separately for the placebo and laser groups. A significant difference was observed between initial and final values in both groups. Baseline and post-therapy values of pain and CMI were compared in the therapy groups by the two-sample T-test, yet no significant differences were observed regarding VAS and CMI. After either placebo or laser therapy, pain and temporomandibular symptoms were significantly lower, although there was no significant difference between groups. ***The actual energy is 500 mW x 20 seconds = 10 J/point. The two studies above appear to be rather similar, but the one delivering positive results treated twice a week, the negative study once a week. The longer time used in the positive study may also be of importance, even though the energy per point was lower than in the negative study.***

Myofacial pain dysfunction syndrome (MPDS) is the most common reason for pain and limited function of the masticatory system. The aim of a study by Shirani [1995] was to evaluate the efficacy of a particular source producing 660 nm and 890 nm wavelengths that was recommended to reduce of the pain in the masticatory muscles. This was a double-blind and placebo-controlled trial. Sixteen MPDS patients were randomly divided into two groups. For the laser group, two diode laser probes (660 nm, 6.2 J/cm^2, 6 min, CW and 890 nm, 1 J/cm^2, 10 min, 1,500 Hz were used on the painful muscles. For the control group, the treatment was similar, but the patients were not irradiated. Treatment was given twice a week for 3 weeks. The amount of patient pain was recorded at four time periods (before and immediately after treatment, 1 week after, and on the day of complete pain relief).

A Visual Analogue Scale was selected as the method of pain measurement. In each group the reduction of pain before and after the treatment was meaningful, but, between the two groups LPT was more effective.

A study by de Moraes Maia [2164] investigated the effect of LPT on the masticatory performance (MP), pressure pain threshold (PPT), and pain intensity in patients with myofascial pain. 21 subjects, with myofascial pain were divided into laser group (n = 12) and placebo group (n = 9) to receive laser therapy (active or placebo) two times per week for 4 weeks. The measured variables were: (1) MP by analysis of the geometric mean diameter (GMD) of the chewed particles using Optocal test material, (2) PPT by a pressure algometer, and (3) pain intensity by the Visual Analogue Scale (VAS). Measurements of MP and PPT were obtained at three time points: baseline, at the end of treatment with low-level laser and 30 days after (follow-up). VAS was measured at the same times as above and weekly throughout the laser therapy. A reduction in the GMD of crushed particles and an increase in PPT were seen only in the laser group when comparing the baseline and end-of-treatment values. Both groups showed a decrease in pain intensity at the end of treatment.

The sample in the study by Rodrigues da Silva [2165] consisted of 45 subjects randomly divided into three groups (G) of 15 subjects each: G-I: 15 individuals with IA-TMD submitted to an e dose of 52.5 J/cm^2, G-II: dose of 105.0 J/cm^2; and G-III: placebo group (0 J/cm^2). In all groups, the applications were performed on condylar points on the masseter and anterior temporalis muscles. Two weekly sessions were held for five weeks, totalling 10 applications. The assessed variables were: mandibular movements and painful symptoms evoked by muscle palpation. These variables were measured before starting the study, then immediately after the first, fifth, and tenth laser application, and finally, 32 days after completing the applications. The results showed that there were statistically significant differences for G-I and G-II at the level of 1% between the doses, as well as between assessments.

*Kulekcioglu [1418] found a significant improvement in mandibular functional movements and reduction of tender points in myogenic and arthrogenic cases treated with the active laser probe, but not for the placebo treatment (Stated parameters : 904 nm, 17 mW, 1000 Hz, 180 seconds, 3 J, 3 J/cm^2. **The stated dose can only be correct provided that the laser aperture was one cm^2, which it most probably was not.***

The multifactorial background is underlined in the study by Carroll [2171]. 29 patients with TMD pain present for longer than 6 months were randomised to receive either active or placebo laser and LED treatments. A four-step treatment approach was used targeting lymph nodes, joint, nerve and trigger points. 44 points were treated using three different treatment probes. The clinical intent was to reduce inflammation in the TMJ with LED, deactivate myofascial trigger points with laser around the TMJ and neck, induce a neural blockade (analgesia) by treating over nerves with laser and stimulate lymph nodes with LED. The probe and treatment specifications *were: 810 nm, 200 mW laser, 30 seconds per point (5 W/cm², 6 Joules per point, 150 J/cm²), a laser cluster comprising 5 x 810 nm 200 mW laser (1 W aggregate, 5 W/cm² each laser) for 30 seconds per point (6 Joules per point, 150 J/cm²) and a cluster of 69 LEDs comprising 34 x 660 nm 10 mW each and 35 x 850 nm 30 mW (1.39 W aggregate) 60 seconds per point, (50 mW/cm² average power density, 1.2J per point, 3J/cm²). All subjects were treated 5 times within a 2-3 week period. Primary outcomes were measured by the change a Visual Analogue Scale (VAS) for pain. Secondary outcomes measured include the short-form 36 for quality of life analysis. Measurements were taken at baseline and 1-2 weeks following treatment. The mean VAS score for active treatment improved by 36.93 from a mean of 59.46. The sham placebo therapy improved by 10.23 from a mean of 55.7. Significant improvements were seen also in the active group compared to the control in SF-36-physical scores and SF-36 mental scores.*

Twenty patients diagnosed with myofascial pain according to the Research Diagnostic Criteria for Temporomandibular Disorder (RDC/TMD) participated in the study by Gokcen-Rohlig [2286]. Twenty healthy individuals, matched in age and gender, served as a control group. LPT was applied to the mastication muscles three times per week, for a total of 10 sessions. The mandibular mobility range was evaluated. The maximum bite force, occlusal contact area and occlusal pressure were measured bilaterally with a dental pre-scale before and after treatment. All variables were analysed descriptively. Changes in the masticatory muscle tenderness, mandibular movements, maximum bite force, occlusal contact area and occlusal pressure were compared by paired-sample Student's t-tests. There was a significant increase in the pressure pain threshold of the examined muscles. Mandibular movements were significantly improved in all patients. There was also a significant decrease in pain by palpation after laser exposure. However, no significant change was found in the maximum bite force, occlusal contact area or occlusal pressure after the treatment and also the values after the treatment were still significantly lower than those of the healthy individuals.

The aim of a study by Ahrari [2189] was to evaluate the efficacy of LPT in the management of patients with myogenic temporomandibular joint disorders. In this randomised, double-blind clinical trial, 20 patients with myogenic TMD were randomly divided into laser and placebo groups. In the laser group, a pulsed 810 nm laser (average power 50 mW, peak power 80 W, 1,500 Hz, 120 s, 6 J, and 3.4 J/cm² per point) was used on painful muscles three times a week for 4 weeks. In the placebo group, the treatment was the same as that in the laser group, but without energy output. The patients were evaluated before laser therapy (T1), after six sessions of laser application (T2), at the end of treatment (T3), and 1 month after the last application (T4), and the level of pain and the amount of mouth opening were measured. There was a significant increase in mouth opening and a significant reduction of pain symptoms in the laser group. A similar improvement was not observed in the placebo group. Between-group comparisons revealed no sig-

nificant difference in pain intensity and mouth opening measurement at any of the evaluation time points. LPT can produce a significant improvement in pain level and mouth opening in patients affected with myogenic TMD.

A study by de Carli [2187] aimed to evaluate the efficacy of piroxicam associated with low-level laser therapy compared with single therapies in 32 patients presenting temporomandibular joint arthralgia in a random and double-blind research design. The sample, divided into laser + piroxicam, laser + placebo piroxicam and placebo laser + piroxicam groups, was submitted to the treatment with infrared laser (830 nm, 100 mW, 28 s, 100 J cm^2) at 10 temporomandibular joint and muscle points on each side during four sessions concomitant to take one capsule a day of piroxicam 20 mg during 10 days. The treatment was evaluated throughout four sessions and 30 days follow-up through Visual Analogue Scale (VAS), maximum mouth opening and joint and muscle (temporal and masseter) pain on palpation. The results showed that all the study groups had a significant improvement in the VAS scores and there were no significant group differences. Piroxicam was effective in the reduction of joint and muscle pain on palpation and showed the lowest temporal pain at the 30-day follow-up. The combination of LPT and piroxicam was not more effective than single therapies in the treatment of temporomandibular joint arthralgia. The use of piroxicam was more effective in the following 30 days.

In this study the superficial and small TMJ was given 14 J, and the two masticatory muscles 14 J each. For the TMJ this is in the inhibitory range and for the muscles rather low energies.

The aim of a study by Uemoto [2352] was to evaluate different approaches to deactivating myofascial trigger points (MTPs). Twenty-one women with bilateral MTPs in the masseter muscle were randomly divided into three groups: laser therapy, needle treatment and control. Treatment effectiveness was evaluated after four sessions with intervals ranging between 48 and 72 h. Quantitative and qualitative methods were used to measure pain perception/sensation. The Wilcoxon test based on results expressed on a Visual Analogue Scale (VAS) demonstrated a significant decrease in pain only in the laser and needle treatments groups, although a significant increase in the pressure pain threshold was evident only for needling with anaesthetic injection and laser therapy at a dose of 4 J/cm^2. Based on these results, it was concluded that four sessions of needling with 2% lidocaine injection with intervals between 48 and 72 h without a vasoconstrictor, or LPT at a dose of 4 J/cm^2, are effective for deactivation of MTPs.

The study by Melchior [2353] included 12 female volunteers diagnosed with myofascial pain and ages ranging from 18 to 60 years old, with or without intra-articular TMD, according to axis I of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). Participants were assessed for pain on palpation, using a Visual Analogue Scale (VAS), before treatment (A1), immediately after 30 days of intervention, i.e, after eight sessions of LPT (A2), and 30 days after the end of the treatment with

LPT (A3) (follow-up). Comparing the three evaluation times, it was observed that there was a significant decrease in the values of subjective pain to palpation. The initial pain (A1) differed significantly from the A2, but did not differ significantly from A3.

The purpose of the study by Salmos-Brito [2391] was to address the following question: among patients with acute or chronic temporomandibular disorders (TMD), does LPT reduce pain intensity and improve maximal mouth opening? The sample comprised myogenic TMD patients (according Research Diagnostic Criteria for TMD). Inclusion criteria were: male/female, no age limit, orofacial pain, tender points, limited jaw movements and chewing difficulties. Patients with other TMD subtypes or associated musculoskeletal/rheumatologic disease, missing incisors teeth, LPT contra-indication, and previous TMD treatment were ex-cluded. According to disease duration, patients were allocated into two groups, acute (<6 months) and chronic TMD (6 months). For each patient, 12 LPT sessions were performed (830 nm, 40 mW, CW, 8 J/cm^2). Pain intensity was recorded using a 10 cm Visual Analogue Scale and maximal mouth opening using a digital ruler (both recorded before/after LPT). The investigators were previously calibrated and blinded to the groups (double-blind study) and level of significance was 5%. Fifty-eight patients met all criteria, 32 (acute TMD), and 26 (chronic TMD). Both groups had a significant pain intensity reduction and maximal mouth opening improvement after LPT. Between the groups, acute TMD patient had a more significant pain intensity reduction and a more significant maximal mouth opening improvement. LPT can be considered as an alternative physical modality or supplementary approach for management of acute and chronic myogenic temporomandibular disorder; however, patients with acute disease are likely to have a better outcome.

This study by Madani [2434] investigated the efficacy of LPT for the management of TMJ osteoarthritis. In a double-blind clinical trial, 20 patients with TMJ osteoarthritis were randomly divided into laser and placebo groups. The patients in the laser group received irradiation from an 810 nm laser (Peak power 80 W, average power 50 mW, 1500 Hz, 1 ms pulse width, 120 seconds, 6 J, 3.4 J/cm^2 per point), which was applied on four points around the TMJs and on painful muscles three times a week for 4 weeks. In the placebo group, the treatment was the same as that in the laser group, but with laser simulation. The patients were evaluated before laser therapy (T1), after 6 (T2) and 12 (T3) laser applications and 1 month after the last application (T4), and the amount of mouth opening and the pain intensity were recorded. No significant differences were found in mouth opening either between the study groups or between the different evaluation times in each group. There was no significant difference in pain symptoms of the masticatory muscles and TMJ between the laser and the placebo groups but some significant within-group improvements were present for Visual Analogue Scale (VAS) scores of the body of the masseter and TMJ in both *groups.* ***4 x 6 J around the TMJ is probably inhibitory, WALT recommendation is 4 J.***

The study by Demirkol [2499] was designed to evaluate the effects of low-level Nd:YAG therapy and occlusal splints in patients with signs and symptoms of temporomandibular disorders (TMD) characterised with myofascial pain (MP). A total of 30 patients were selected after being diagnosed with MP according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TDM). The patients were divided into three groups. The first group was occlusal splint (OS) group A (n=10), the second was LPT group B (n=10), and the last group C was placebo (n=10). LPT (1.064 nm, 8 J/cm2, 250 mW) was applied to the patients in the study group once a day for 10 days, for a total of ten sessions. The same parameters and application times were used for placebo group, but the patients were not irradiated. The application was on the trigger points. The patients in the OS group were instructed to wear occlusal splints 12 h/day for 3 weeks. Functional examination was based on RDC/TDM, and pressure pain values were obtained with the Visual Analogue Scale. The pain score values decreased significantly after both LPT and occlusal splint therapy compared to placebo group. There was no significant difference between LPT and OS groups after treatment. OS and LPT are effective for decreasing MP. In addition, this particular type of LPT was as effective as occlusal splint for pain relief.

The aim of the study by Pereira [2509] was to evaluate the efficacy of red and infrared laser therapy in patients with TMD, using a randomised parallel-group double-blind trial. Each hemiface of 19 subjects was randomised to receive intervention, in a total of 116 sensitive points. Pain was measured at baseline and time intervals of 24 hours, 30 days, 90 days, and 180 days after treatment. Irradiation of 4 J/cm2 in the temporomandibular joints and 8 J/cm2 in the muscles was used in three sessions. Both treatments had statistically significant results; there was statistical difference between them at 180 days in favour of the infrared laser. There was improvement in 24 hours, which extended up to 180 days in both groups.

The literature search by Herranz-Aparicio [2300] provided a bank of 35 articles, and 16 relevant articles were selected to this review. These articles were critically analysed and classified according to their level of scientific evidence. This analysis produced 3 literature review articles and 13 are clinical trials. The SORT criteria (Strength of Recommendation Taxonomy) was used to classify the articles. Only one article presented an evidence level 1, twelve presented an evidence level 2, and three presented an evidence level 3. According to the principle of evidence-based dentistry, currently there is a scientific evidence level B in favour of using LPT for treatment of TMDs. Discussion and conclusions: Publications on the use of LPT for treatment of TMDs are limited making difficult to compare the different studies due to the great variability of the studied variables and the selected laser parameters. The great majority of the studies concluded that the results should be taken with caution due to the methodological limitations.

Further literature: [83, 85, 100, 176, 206, 212, 218, 310, 370, 491, 514, 530, 618, 629, 635, 639, 751, 820, 932, 1108, 1329, 1886, 2370]

5.3.27.1 TMD and endodontics

In 2010 SBU - Swedish Council on Health Technology Assessment published an analysis of the available scientific support for performing endodontic therapy [2148]. The conclusion was that there was little, if any, scientific support for any endodontic method. The reasons were the technical variations in root canal debridement and widening, rinsing agents, diagnoses and types of fillers. Further to that, the groups were generally small and non-homogenous and follow up periods short. Now, we all know that endodontic methods are reasonably successful and widely used for decades. But when a strict scientific evaluation was performed, no method had a reasonable support in the scientific literature. This came as a total surprise to most dentists.

In 2011 Petrucci et al. [2149] published a literature review on the use of LPT for TMD. The correct conclusion was that there is no scientific support for the use of LPT for this indication. Yet, most users of LPT know that this is a very useful method. However, the available literature is quite non-homogenous. Even though many authors report good results, each author seems to have chosen his own wavelength, energy, dose, mode of application, patient selection, follow up period etc. So there are not two studies of any quality using the same concept. And just as in endodontics, the TMD background is multi-factorial. Consequently, from a strict scientific point of view, there is no support for the treatment modality. Not for LPT for TMD, nor for root fillings. Still, both work.

The above illustrates one of the obstacles for the acceptance of LPT. Not only is the collected scientific documentation distilled by being used for so many indications, the parameters vary a lot, even within a selected indication, as pointed out by Maia [2188]. And further to that, many authors do not seem to have control over their laser parameters.

Some indications for LPT (e.g. mucositis) have strong scientific evidence, but most have little or hardly any. So scientific work has to accelerate and also improve. In the meantime we sometimes have to rely on indirect evidence. For instance, there is general evidence of pain reduction, reduction of oedema and inflammation, all involved in TMD. With this, and the strong evidence for the lack of side effects, LPT for TMD appears to be a very promising method. Lack of Cochrane-style scientific evidence is no contraindication in itself - that would exclude many traditional medical methods.

It could be added that there is little consensus among TMD specialist about several treatment methods and that the evidence generally is poor [2301].

5.4 Other dental laser applications

5.4.1 Dental photo dynamic therapy

Laser light at LPT levels has been shown to activate the bactericidal effect of different dyes, such as toloudine blue (TBO) and methylene blue (630-660 nm) but also with a indocyanine green (808 nm). This combination therapy could have important advantages in the treatment of caries and periodontal disease. The commercial names are aPDT (antimicrobial Photo Dynamic Therapy) and PAD (Photo Activated Disinfection). And additional advantage of PAD is that it can be used prior to scaling and root planing in patients with a compromised health, thereby reducing the need for prophylactic use of antibiotics.

LED is likely to work just as well as laser in these superficial tissues . aPDT/PAD has been suggested as a suitable therapy for periodontal pockets, root canal disinfection, carious disinfection and periimplantitis [1709, 1710, 1711]. Apart from the antimicrobial effect, there is of course a stimulating effect from the laser itself. An interesting possibility is pointed out by Bisland [1685], suggesting that laser phototherapy can “prime” cancer cells to become more sensitive to PDT.

Literature:

The purpose of the study by Zanin [1571] was to evaluate the antimicrobial effect of toluidine blue O (TBO), in combination with either HeNe laser or a light-emitting diode on the viability and architecture of Streptococcus mutans biofilms. Biofilms were grown on hydroxyapatite discs in a constant depth film fermentor fed with artificial saliva that was supplemented with 2% sucrose four times a day, thus producing a typical 'Stephan pH curve'. Photodynamic therapy was subsequently carried out on biofilms of various ages with light from either the HeNe laser or LED using energy densities of between 49 and 294 J/cm^2. The LED system works with a spectrum ranging from 620 to 680 nm with a peak close to 633 nm. Significant decreases in the viability of S. mutans biofilms were only observed when biofilms were exposed to both TBO and light, when reductions in viability of up to 99.99% were observed with both light sources. Overall, the results showed that the bactericidal effect was light dose-dependent and that older biofilms were less susceptible to photodynamic therapy. Confocal laser scanning microscopy images suggested that lethal photosensitisation occurred predominantly in the outermost layers of the biofilms.

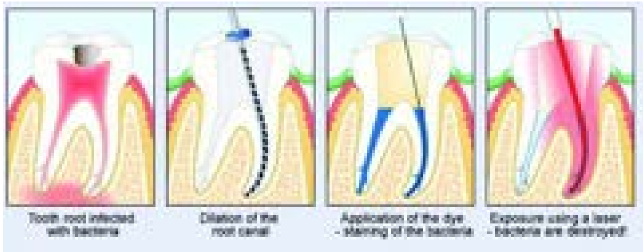


Figure 5.13 Photo Activated Disinfection. After scaling, the pocket is filled with the dye and irradiated with red laser light. Courtesy: HELBO

Literature:

Further literature: [708, 778, 827, 841, 842, 930, 1115, 1239, 1709, 1710, 1711]

5.4.2 Composite curing

A common wish among dentists is to be able to cure dental composite material quicker and more thoroughly. Experiments in curing have been conducted with argon lasers (488 nm), nitrogen lasers and HeCd lasers (443 nm). There were commercial systems based on argon lasers, but the high price was a disincentive to general use. The argon laser is capable of curing a layer of 2 mm within 10 seconds, compared to the recommended 20 seconds with traditional blue halogen curing light. Laser curing will improve the physical properties of the resins. It can, however, increase shrinkage and brittleness [455]. With the advent of plasma arch and LED-based curing lights, laser curing has lost its appeal.

The intense curing light is likely to have biological effects but this phenomenon has not been well studied. The LED curing lights are more narrow-banded than the halogen lights and even more likely to affect the irradiated cells. The bactericidal effect of the curing light could, for example, be used to support indirect pulpal capping.

Literature:

Soukos [1502] has shown that broadband light in the range 380-520 nm rapidly and selectively kills oral black-pigmented bacteria in pure cultures and in dental plaque samples obtained from human subjects with chronic periodontitis. Cultures of Prevotella intermedia and P. nigrescens were killed by 4.2 J/cm^2, whereas P. melaninogenica required 21 J/cm^2. Exposure to light with a fluence of 42 J/cm^2 produced 99% killing of P. gingivalis. In dental bleaching procedures the dosages of blue light are high.

Enwemeka [2108] has demonstrated that 470 nm light has a strong bactericidal effect on MRSA (Meticillinresistent Staphylococcus aureus). This wavelength happens to be near the peak wavelength in LED-based curing lights! The photos below shows a man of 80 years having had a therapy-resistant MRSA infection in his scalp for some 10 years. Two LED curing light were used for eight sessions. The photos show baseline, pus coming out at session 2 and final appearance.

An unexpected effect of the curing light is reported by Ishikawa [2178]. Some dental light-curving units can emit blue-violet wavelengths around 380-515 nm with two peaks (410 nm and 470 nm). These wavelengths can cover the maximum absorption spectra of hemoglobin (430 nm). Blue-violet LED 380-515 nm, 750 mW/cm², 10 sec (7.5 J/cm²) was used. Irradiation was performed for 10 sec or an additional 10 sec for 10 cases of tooth extraction at a distance of 1 cm from the socket. Bleeding was stopped by conventional roll pressure in another five cases as a control. Bleeding time for both procedures was measured. In vitro transmission electron microscope (TEM) studies were performed to clarify the mechanism of hemostasis by blue-violet LED irradiation. Irradiation with the blue-violet LED yielded immediate hemostasis of the socket. Five cases showed coagulation within the first 10 sec, and another five cases required an additional 10 sec to fully control the bleeding. In contrast, the conventional method required 2-5 min (median 180 sec) to obtain hemostasis. The difference between the time required to stop the bleeding in the two methods was found to be statistically significant. A week later, the LED-irradiated sockets were healed uneventfully with epithelial covering. TEM showed the formation of a thin amorphous layer and an adjacent agglutination of platelets and other cellular elements under the layer at the interface of the irradiated blood. In conclusion, blue-violet LED irradiation of bleeding sockets caused immediate clot formation and hemostasis. This procedure was safe and reliable and showed no adverse effects.

5.4.3 Demineralisation

A study by de Melo [2172] evaluated the effects of an 808 nm on the dentinal chemical composition and prevention of demineralisation. In addition, the study monitored temperature changes during the course of irradiation. Forty dentin specimens were randomly allocated into four groups (n = 10): G1 - No treatment (control), G2 - irradiated with 15 J/cm^2, G3 - irradiated with 30 J/cm^2, and G4 - irradiated with 60 J/cm^2. Each specimen was partially covered with nail varnish, treated according to the group irradiation levels, and exposed to an erosive challenge (1.0 M hydrochloric acid) for 5 min. Afterwards, dentin loss was profilometrically analysed and examined by scanning electron microscopy (SEM) combined with energy dispersive X-ray (EDX). Intrapulpal temperatures were measured during the dentin irradiation. For all irradiated groups, intrapulpal temperature changes were less than 3°C. The G2 group showed statistically significant differences when compared to the other groups, representing the lowest temperature increase. A quantitative element analysis via EDX did not significantly differ ($p < 0.05$) for Ca, P, F, O, or C between the four groups when measured after irradiation/erosion. The mean wear rates (± SD, m) were 35.66 ± 7.28; 40.70 ± 5.03; 38.17 ± 10.81 and 25.25 ± 6.87 for G1-G4, respectively. The G4 group statistically differed from all other groups representing the lowest wear rate. These results suggest that dentin irradiation, using a diode laser with levels set at 60 J/cm^2, may induce inhibitory effects on root dentin demineralisation without causing any harmful thermal effects. However, the exact mechanism of the action of the laser remains.

5.4.4 Tooth bleaching

Argon (488 nm), GaAlAs, Nd:YAG and CO_2 lasers as well as blue LED:s are used in combination with in-office tooth bleaching. The laser is marketed to make bleaching faster, but will not bleach teeth better than at-home bleaching or bleaching without laser [843]. The laser/LED is said to excite the hydrogen peroxide molecule in the bleaching gel. The short wavelength and the higher photon energy of the argon laser would then make it a first choice. Halogen lamps, plasma-arch lamps and other heat lamps emit short wavelengths as well as longer invisible infrared thermal wavelengths and are more likely to create unfavourable pulpal responses. Some manufacturers have added LPT diodes in the LED bleaching array to hopefully minimise the detrimental effects on the pulp.

Literature:

Tooth bleaching often results in temporary hypersensitivity and LPT has therefore been suggested as a suitable treatment after performing whitening. The aim of the study by Lima [2361] was to evaluate the effect of LPT on odontoblast-like cells exposed to a bleaching agent. MDPC-23 cells were seeded in wells of 24-well plates. Eight groups were established according to *the exposure to the bleaching agent and LPT (0, 4, 10, and 15 J/cm²). Enamel-dentin discs were adapted to artificial pulp chambers, which were individually placed in wells containing DMEM. A bleaching agent (35% hydrogen peroxide-BA35%HP) was applied on enamel (15 min) to obtain the extracts (DMEM + BA35%HP components diffused through enamel/dentin discs). The extracts were applied (1 h) to the cells, and then subjected to LPT. Cell viability (MTT assay), alkaline phosphatase (ALP) activity, as well as gene expression of ALP, fibronectin (FN), and collagen type I, were evaluated. The bleaching procedures reduced the cell viability, ALP activity, and gene expression of dentin proteins. Laser irradiation did not modulate the cell response; except for FN, since LPT decreased the gene expression of this protein by the cells exposed to the BA35%HP. It can be concluded that BA35%HP decreased the odontoblasts activities that were not recovered by the irradiation of the damaged cells with the laser parameters tested.*

5.4.5 Caries detection

Laser fluorescence can be used to detect occlusal caries. A diode of 655 nm has been successfully used to diagnose hidden occlusal caries.

5.4.6 Lasers as a diagnostic tool

Majlesi [2372] has shown that red laser light can be used as a diagnostic device. By irradiating through oral tissues, the change of the penetration properties of oedemas and pathological tissue will make them observable and their area determined.

5.5 Case reports

Case reports are of limited scientific value and are often referred to condescendingly as "anecdotal accounts". Of course, case reports should not be seen as anything other than treatment effects observed in particular cases, and perhaps by only a few therapists. They can, however, serve as useful guides for the clinician and as examples of what can be attempted. They are the kind of stories you might relate to a colleague during a coffee break between lectures but would not consider mentioning in the lecture itself. They are, in any event, the cases you sometimes remember most clearly, and are useful from a practical point of view. Below is a more readable rounding-off of this chapter - some case reports from the author's experience.

1 A.B. A 20-year-old woman with pain in the maxillary joint and who was grinding acutely. She could not open her mouth more than 17 mm with deviation. GaAs laser light was administered bilaterally (8 J) over the joint area and the immediately surrounding tissue, after which the patient could open her mouth 22 mm with greatly reduced pain and deviation. An imprint for a bite splint could be taken without any problems.

2. I.C. A 54-year-old man suffering from painful candida-infected leukoplakia bilaterally under the tongue. HeNe laser light had a good, but only temporary, pain relieving effect. After surgical removal of the leukoplakia, HeNe was administered on the side where the postoperative pain was greatest. This side healed more quickly. The patient later experienced pain in the area on occasion, but this could be eradicated after one or more laser treatments.

3 F.Å. A 56-year-old woman with few teeth remaining in the lower jaw, full upper jaw prosthesis, and partial prosthesis in the lower jaw. She was encouraged by a doctor to seek the help of a dentist for her long-standing headaches. The prostheses were highly abraded, and new prostheses with a larger vertical dimension and better occlusal stability were made. The patient returned five days after the new prostheses were fitted for the treatment of a small decubital wound. The headaches remained. By way of an experiment, a GaAs multi-probe (19 Hz) was placed against the right temple. The patient immediately said that it "felt good". After three minutes' irradiation (11 J), mainly on the most painful side, the patient said that most of the pain was gone. Out of scientific curiosity, the pulse repetition rate was increased to 5000 Hz, at which the patient experienced a sensation of pressure. At 6 Hz, the patient did not feel anything in particular. The changes in pulse repetition rate were made without the patient's knowledge, but she could tell immediately when it "felt good" and when it "tightened". At a new appointment the next day, the headache had disappeared completely. 8 J was administered, and the patient was still able to notice differences in pulse repetition rate. At a check-up after three months, the patient was still untroubled by headaches.

4 B.S. A 43-year-old woman with "fibromyalgia" as a preliminary diagnosis. The patient was in need of dental care, but lying in a dentist's chair even for as little as ten minutes increased her pain considerably. She could be treated in a sitting position, but this would make the planned treatment, involving porcelain inlays, more difficult. GaAs irradiation along the spine and on the trigger points of the back once a week and immediately before treatment made a 45-minute treatment session possible, and the patient experienced a much improved pain situation for one to three days after each laser treatment.

5 L.J. A 34-year-old man who needed emergency treatment for a fractured upper incisor. His usual dentist did not have the time to treat him. On the same day, the patient had injured his left hand and the tips of three fingers had been cut off. He arrived via the hospital's casualty department with bandaged fingers and in great pain, and would not take analgesics on principle. During the dental treatment, the patient held a GaAs multiprobe against the palm of his left hand and soon noticed a pleasant sensation. After four minutes (14 J) the pain had disappeared, leaving the patient both pleased and surprised.

6 T.D. A 23-year-old male football player. The patient noticed the LPT equipment in the dentist's surgery and wondered whether it might help his periostitis. He could play football for only 30 minutes or so without the pain in his legs becoming unbearable. Scanning laser treatment with HeNe once a week and immediately before a match increased the pain-free period by 100%.

7 M.D. A 49-year-old woman. At the age of 28, she had developed pains in the soles of her feet, which gradually spread to the palms of her hands. After a few years, the pain had spread throughout her skin. No certain diagnosis had been offered, despite many doctors' appointments. The patient had not taken the recommended pain-relief medication in order to avoid side effects. It was sometimes impossible for her to walk because of the pain. The problem came to the attention of the dentist when he touched the patient's cheek, at which she felt pain. 6 J of GaAs was administered over one side of the face. The patient experienced an obvious reduction in pain, and a new "itching" sensation in the cheek. When the patient came to the next appointment, she no longer had any pain in the side of her face treated with laser. The whole face was now treated, along with the palms of the hands and the soles of the feet, with a GaAs multiprobe. A total of 14 J was administered. At the next appointment, the patient reported a large, general reduction in pain. The arms and legs were also treated (20 J). At the following appointment, only mild pain in the part of the soles of the feet where the pain began remained. After six LPT applications, the patient no longer experienced pain and a few months later said she was enjoying her "best year in ages". After 7 years, there has been no recurrence.

8 J.S. A man in his 50s with shoulder pain since several years. Steroid injections had had a good but not long lasting, effect. Sleep was impaired, and he could not have his cameras hanging over his shoulder the way he was used to. After three treatments, he was able to sleep on the affected side, after six he was completely pain free. Full Range of Movement. A tennis elbow was cured in three sessions en passant.

9 A.M. This female patient had been suffering from pain in her neck and shoulders for about ten years. Due to the difficulties in moving her neck, GaAlAs laser treatment was administered prior to dental treatment, 10 J per point. This had a satisfactory effect. The patient said that the centre of her stiffness was in the right trapezius. As this part was treated the pain and stiffness were considerably reduced. At the following dental appointment the patient pointed out that her tinnitus on the right side had almost gone. This condition was not previously known by the therapist. Since there was some, although lighter, tinnitus on the left side as well, both sides of the body were treated, this time including the masticatory muscles. At the next appointment the tinnitus was almost gone in both ears, and the patient remarked: “my vertigo is much reduced!” This condition was also unknown to the therapist. Five follow up sessions were performed. The patient was almost free of problems at four months’ checkup. After five months the problems started to reappear since the patient had continued the kind of work that initially caused the problems.

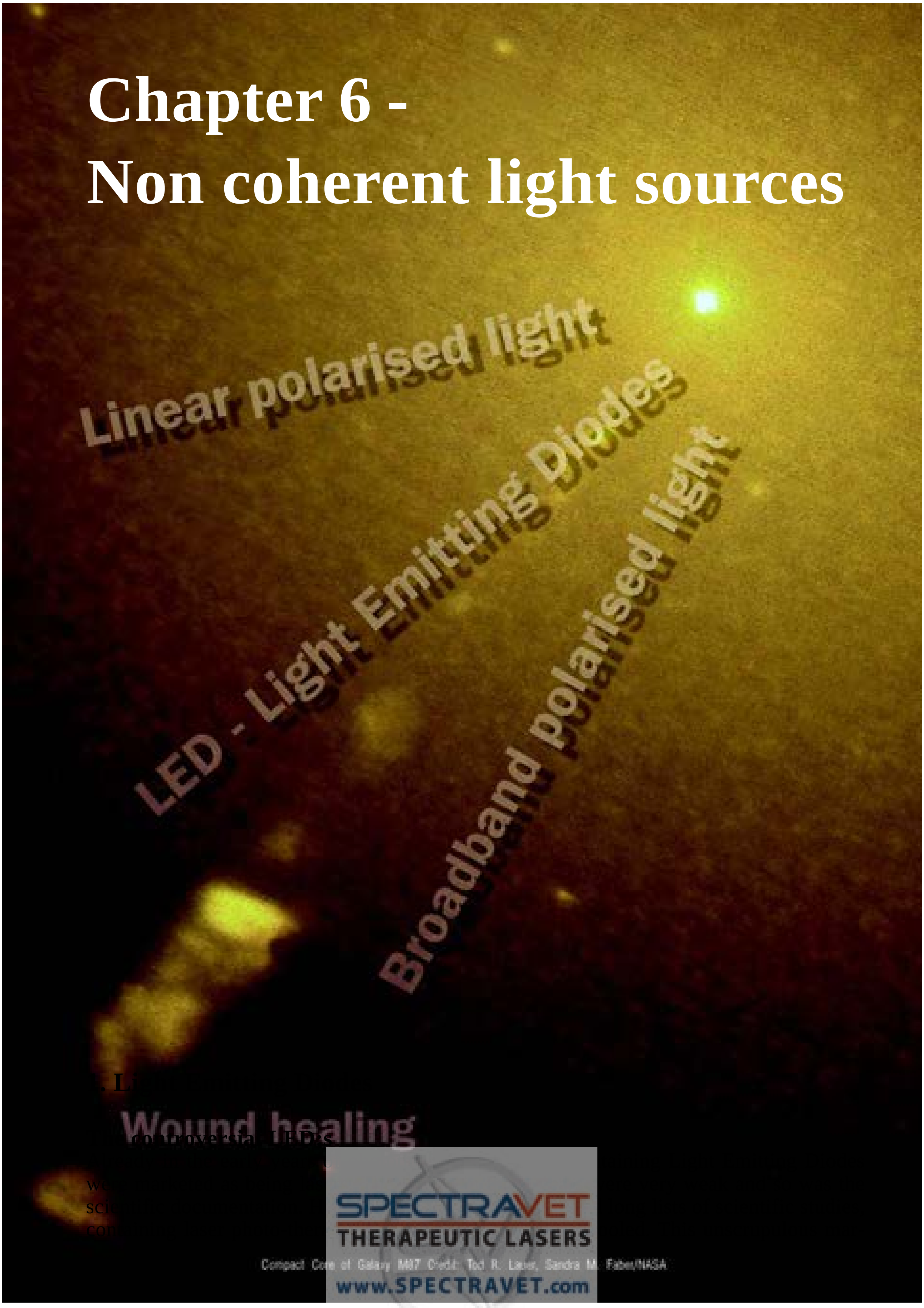
10 J.K. A 75 years old male has been skiing cross-country and now has two frozen and painful finger tips. No medical therapy had been offered, rather suggestions about the possibility of amputations. Indium over the finger tips removed the pain within an hour. Pain is back next day but is again removed with the laser. After 5 sessions pain is gone permanently and healing is taking place. The fingers were in the end completely healed.

11 G.M. A female patient had been suffering from her leg ulcer for about 10 year and "everything" had been tried. The "discovery" in the dental situation was just a coincidence, and she was offered LPT. One session was performed with 100 mW 660 nm, and then the patient had a home laser unit on loan (70 mW, 808 nm). After a few sessions, the pain was gone and within four months the wound caused no problems for the patient. She now only has a pigment change in the area.

12 M.E. Persistent wound during four months in spite of traditional therapy. Patient instructed to stop using dressings. One irradiation in the clinic, home care unit (808 nm, 100 mW) during ten days; full recovery.

The few examples above are cases in which laser treatment has helped when it has been difficult to find other forms of treatment which work, bearing in mind the circumstances. The latter cases, which do not really come under the "dental laser treatment" heading, do nevertheless give some indication of the various conditions in which a dentist can have the opportunity to use the laser.

Chapter 6 -
Non coherent light sources



keting harmed not only LED light therapy but laser therapy as well. Later on cluster arrays appeared, containing LED:s and lasers together. The advantage of this set up is not obvious. No certain knowledge exists about the interaction between different wavelengths of coherent and incoherent light sources. A further disadvantage is that any positive documentation of such therapy can only be reproduced using an array of the very same configuration. And there are not two manufacturers producing identical arrays. These combination arrays are the opposite to what is looked for in medicine - to identify the active ingredient.

Confusion between lasers and LED

It has not been unusual for manufacturers of LED equipment to use references to laser studies, pretending LED and laser are the same. This confusion has also spread among investigators and it is not uncommon for LED studies to be misinterpreted as laser studies when referred to in other articles. A few examples are the studies by Gupta [720] and Iusim [1063]. Sometimes the title of a study or the abstract is inconclusive in this respect and in lists of references LED studies can be found “disguised” as laser studies, even in Meta analyses. One example is the study by Iusim . The title of the paper is “Evaluation of the degree of effectiveness of Biobeam low level narrow band light on the treatment of skin ulcers and delayed postoperative wound healing”. The “low level narrow band light” is actually emitted by a LED unit, but the phrase can easily be mistaken for a laser source, owing to the “home made” definition by the author.

Here is another example from the study titled: Taly A B, Sivaraman Nair K P, Thyloth Murali T, Archana J. Efficacy of multiwavelength light therapy in the treatment of pressure ulcers in subjects with disorders of the spinal cord: A randomized double-blind controlled trial. Archives of Physical Medicine and Rehabilitation. 2004; 85 (10): 1657-1661.

In a study by Taly [1424] thirty-five subjects with spinal cord injury, with 64 pressure ulcers (stage 2, n=55; stage 3, n=8; stage 4, n=1), were randomized into treatment and control groups. Mean duration of ulcers in the treatment group was 34.2±45.5 days and in the control group, 57.1±43.5 days. Treatment group received 14 sessions of multi wavelength light therapy, with 46 diodes of different wavelengths from a gallium-aluminum-arsenide laser source, 3 times a week. Energy used was 4.5 J/cm^2. Ulcers in the control group received sham treatment. Healing of the ulcer, defined as the complete closure of the wound with healthy scar tissue, time taken for the ulcer to heal, and stage of the ulcer and Pressure Sore Status Tool score 14 days after last treatment. There was no significant difference in healing between the treatment and control groups. Eighteen ulcers in treatment group and 14 in control group healed completely. Mean time taken by the ulcers to heal was 2.45±2.06 weeks in the treatment group and 1.78±2.13 weeks in the control group. Time taken for stage 3 and 4 ulcers to reach *stage 2 was 2.25±0.5 weeks in treatment group and 4.33±1.53 weeks in control group. Multi wavelength light therapy from a gallium-aluminum-arsenide laser source did not influence overall healing pressure ulcers. Limited evidence suggested that it improved healing of stage 3 and 4 pressure ulcers.*

The word “laser” is actually used in the abstract, but reading closely it is obvious that the equipment contains LED:s.

Lasers - better than LED:s?

The scientific documentation for laser phototherapy has been, and remains superior to that of non-coherent light sources. When coherent and non-coherent sources have been compared, the outcome has been in favour of the coherent sources, with very few exceptions. Admittedly, these studies have not succeeded well in using the same light parameters for coherent and non-coherent sources. So the situation is, for the time being, in favour of coherent light. A lot of reference is still used to *in vitro* studies, showing that it is the wavelength and energy density that counts. For the *in vitro* situation this is correct, and to some extent also for open wounds and mucosa. For bulk tissue, however, the situation is different. Unfortunately many manufacturers have been quoting *in vitro* studies as proof of a general equality between coherent and non-coherent light.

The come-back of the LED:s

In recent years a lot of very qualified research has been published in the field of LED light therapy. There is no longer any doubt about the efficacy of LED light therapy in itself. However, so far only superficial and transparent tissues have been documented, while deep tissue conditions such as DOMS have failed. And still today there is not one study correctly comparing coherent and incoherent light for any deep tissue condition. Further to that, finding equal light parameters for laser and LED is difficult and most studies have great variations in the energies applied in the two groups. The correct conclusion is generally that LED worked fine, which is good enough, but not that one of the two was better than the other. However, the controversy over the LED:s has subsided and today coherent and incoherent light therapies can be used in their own right, within the documented fields of application. The aim of this chapter is to underline the “come-back” of the LED:s. Other parts of this books deal with the different mechanisms of the two types of light more in depth.

Literature examples

Cytochrome c oxidase

Previous studies using 670 nm light-emitting diode arrays suggest that cytochrome c oxidase, a photoacceptor in the NIR range, plays an important role in therapeutic photobiomodulation. If this is true, then an irreversible inhibitor of cytochrome c oxidase, potassium cyanide (KCN), should com-

pete with LED and reduce its beneficial effects. This hypothesis was tested on primary cultured neurons in a study by Wong-Riley [1499]. 670 nm treatment partially restored enzyme activity blocked by 10-100 micromol KCN. It significantly reduced neuronal cell death induced by 300 micromol KCN from 83.6 to 43.5%. However, at 1-100 mm KCN, the protective effects of LED decreased, and neuronal deaths increased. 670 nm significantly restored neuronal ATP content only at 10 micromol KCN but not at higher concentrations of KCN tested. Pretreatment with 670 nm enhanced efficacy of the irradiation during exposure to 10 or 100 micromol KCN but did not restore enzyme activity to control levels. In contrast, 670 nm was able to completely reverse the detrimental effect of tetrodotoxin, which only indirectly down-regulated enzyme levels. Among the wavelengths tested (670, 728, 770, 830, and 880 nm), the most effective ones (830 nm, 670 nm) paralleled the NIR absorption spectrum of oxidized cytochrome c oxidase, whereas the least effective wavelength, 728 nm, did not. The results are consistent the hypothesis that the mechanism of photobiomodulation involves the up-regulation of cytochrome c oxidase, leading to increased energy metabolism in neurons functionally inactivated by toxins.

Delayed Onset Muscular Soreness (DOMS)

Several studies have failed to observe an effect of LED therapy for this indication.

Douris [1745] performed a randomized double-blind controlled study with 27 subjects, assigned to one of three groups. The experimental group received 8 J/cm^2 of phototherapy each day for five consecutive days using super luminous diodes with wavelengths of 880 and visible diodes of 660 nm at three standardized sites over the musculotendinous junction of the bicep. The sham group received identical treatment from a dummy cluster. The controls did not receive treatment. The study was completed over five consecutive days: on day one baseline measurements of RANG and upper arm girths were recorded prior to DOMS induction. On days 2-5, RANG, girth, and pain were assessed using VAS and the McGill Pain Questionnaire. The experimental group exhibited a significant decrease in pain associated with DOMS compared to the control and sham groups based upon the VAS at the 48-h period. The McGill Pain Questionnaire showed a significant difference in pain scores at the 48-h period between the experimental and the sham groups. There were no significant differences day to day and between the groups with respect to girth and RANG.

Further literature: [1674, 1675, 2342, 2343]

Dermatology

Weiss [1605] describes the experience over the last 2 years using 590 nm LED photomodulation within a dermatologic surgery environment. Practical use of non-thermal light energy and emerging applications in 3,500 treatments delivered to 900 patients is detailed. LED photomodulation has *been used alone for skin rejuvenation in over 300 patients but has been effective in augmentation of results in 600 patients receiving concomitant nonablative thermal and vascular treatments such as intense pulsed light, pulsed dye laser, KTP and infrared lasers, radiofrequency energy, and ablative lasers. LED photomodulation reversed signs of photoaging using a new nonthermal mechanism.*

Hatching

The objective of the study by Yeager [1602] was to assess the survival and hatching success of chickens exposed in ovo to far-red (670 nm) LED therapy. Fertile chicken eggs were treated once per day from embryonic days 0-20 with 670 nm light at a fluence of 4 J/cm^2. In ovo survival and death were monitored by daily candling (after Day 4). The researchers observed a substantial decrease in overall and third-week mortality rates in the light-treated chickens. Overall, there was approximately a 41.5% decrease in mortality rate in the light-treated chickens. During the third week of development, there was a 68.8% decrease in the mortality rate in light-treated chickens. In addition, body weight, crown-rump length, and liver weight increased as a result of the phototherapy. Light-treated chickens pipped (broke shell) earlier and had a shorter duration between pip and hatch. These results indicate that 670 nm phototherapy by itself does not adversely affect developing embryos and may improve the hatching survival rate.

Further literature: [1503]

HSV-1

Dougal [2352] performed a prospective, randomised, placebo-controlled, clinical trial to evaluate the efficacy of a 1072 nm light-emitting diode device for the treatment of HSV-1. In total, 87 patients with recurrent HSL were recruited and randomly divided into two groups. Subjects received a 3-min treatment with either 1072 nm infrared light therapy or placebo (sham) light therapy three times/day for 2 days. The devices used for both groups were identical in appearance and could not be differentiated by volunteers or researchers, and 1072 nm light is invisible to the human eye. The primary endpoint was healing time, which was taken as the time for the HSL lesions to resolve fully and for the underlying skin to become completely re-epithelialized, and the secondary endpoint was lesion crusting. The median time to healing for the active group was 129 h, compared with 177 h for the control group, which was significant. There was no difference between the two groups for median time to lesion crusting.

Mucositis

The purpose of a study by Whealan [1803] was to determine the effects of prophylactic near-infrared light therapy from light-emitting diodes in pediatric bone marrow transplant (BMT) recipients. 32 consecutive pediatric patients undergoing myeloablative therapy in preparation for BMT were *recruited. LED therapy consisted of daily treatment at a fluence of 4 J/cm² using a 670 nm LED array held to the left extraoral epithelium starting on the day of transplant, with a concurrent sham treatment on the right. Patients were assessed before BMT and every 2-3 days through posttransplant day 14. Outcomes included the percentage of patients with ulcerative oral mucositis (UOM) compared to historical epidemiological controls, the comparison of left and right buccal pain to throat pain, and the comparison between sides of the buccal and lateral tongue OMI and buccal pain. The incidence of UOM was 53%, compared to an expected rate of 70-90%. There was also a 48% and 39% reduction of treated left and right buccal pain, respectively, compared to untreated throat pain at about posttransplant day 7.*

Muscle function

Patients with chronic obstructive pulmonary disease (COPD) are susceptible to early muscle fatigue. Light-emitting diodes therapy (LEDT) has been used to minimize muscle fatigue in athletes and healthy subjects. The aim of the study by Miranda [2316] was to investigate the acute effects of LEDT on muscle fatigue and perception of effort in patients with COPD during isometric endurance test of the quadriceps femoris (QF). Ten patients underwent a single LEDT and sham application, 48 h apart, in a randomized crossover design. The LEDT and sham were applied in three localized areas of the QF (rectus femoris, vastus lateralis, and vastus medialis). Before and after exposure to LEDT and sham, the patients performed an isometric endurance test (60 % of the maximum voluntary isometric contraction), until the limit of tolerance concomitant to surface electromyography recording (median frequency as mean outcome). The slope obtained from linear regression analysis of the median frequency (MF) over endurance time was also used as an endurance index. Endurance time increased significantly after exposure to LEDT as compared to sham. A greater decline in MF was observed during isometric endurance test after sham, compared to LEDT. The slope of the MF over time was lower post-LEDT compared to post-sham. The dyspnea score corrected for endurance time was lower post-LEDT, but similar for fatigue both post-LEDT and post-sham. A single application of LEDT minimizes muscle fatigue and increases isometric endurance time.

The aim of the study by da Costa [2322] was to test, between two bouts of exercise, the effects of LED therapy and cryotherapy regarding muscle damage, inflammation, and performance. Male Wistar rats were allocated in four groups: control, passive recovery (PR), cryotherapy (Cryo), and LED therapy. The animals were submitted to 45 min of swimming exercise followed by 25 min of recovery and then a second bout of either 45 min of exercise (muscle damage analysis) or time to exhaustion (performance). During the rest intervals, the rats were kept in passive rest (PR), submitted to cold water immersion (10 min, 10 degrees C) or LED therapy (940 nm, 4 J/cm²) of the gastrocnemius muscle. Blood samples were collected to analyze creat-

ine kinase activity (CK), C-reactive protein (CRP), and leukocyte counts. The soleus muscles were evaluated histologically. Time to exhaustion was recorded during the second bout of exercise. After a second bout of 45 min, the results demonstrated leukocytosis in the PR and Cryo groups. Neutrophil counts were increased in all test groups. CK levels were increased in the Cryo group. CRP was increased in PR animals. The PR group presented a high frequency of necrosis, but the LED group had fewer necrotic areas. Edema formation was prevented, and fewer areas of inflammatory cells were observed in the LED group. The time to exhaustion was greater in both the LED and Cryo groups, without differences in CK levels. CRP was decreased in LED animals. The investigators conclude that LED therapy and cryotherapy can improve performance, although LED therapy is more efficient in preventing muscle damage and local and systemic inflammation.

The goal of the study by Borges [2483] was to determine the effect of light-emitting diode phototherapy at 630 nm on muscle recovery after a damaging eccentric exercise. Seventeen healthy young male volunteers, without previous experience with eccentric exercise, were included in a randomized double-blinded placebo-controlled trial. They were divided into a LEDT (n = 8) and a placebo group (n = 9). To induce muscle damage, subjects performed 30 eccentric contractions with a load of 100 % of maximal voluntary isometric contraction strength of the elbow flexors of the non-dominant arm. LEDT group subjects received biceps brachii phototherapy (630 nm; total energy density, 20.4 J/cm^2) immediately after the exercise bout. The LEDT in the placebo group was aimed at the muscle, but it remained turned off. Isometric muscle strength, muscle soreness, and elbow range of motion (ROM) were measured before and at 24, 48, 72, and 96 h the after eccentric exercise bout and compared between groups. The results showed that the muscle soreness, muscle strength loss, and ROM impairments were significantly reduced up to 96 h after a damaging eccentric exercise bout for the LEDT group compared with the placebo group. A single LEDT (630 nm) intervention immediately after a damaging eccentric exercise was effective in terms of attenuating the muscle soreness and muscle strength loss and ROM impairments.

Nerve conduction

A randomised controlled study was conducted by Vinck [1592] through measuring antidromic nerve conduction on the peripheral sural nerve of healthy subjects (n=64). One baseline measurement and five post-irradiation recordings (2-min interval each) were performed of the nerve conduction velocity (NCV) and negative peak latency (NPL). Interventional set-up was identical for all subjects, but the experimental group (=32) received an irradiation (2 min at a continuous power output of 160 mW, resulting in a radiant exposure of 1.07 J/cm^2) with an infrared LED device, while the placebo group was treated by sham irradiation. Statistical analysis of NCV and NPL difference scores, revealed a significant interactive effect for both NCV and NPL. Further post hoc LSD analysis showed a time-

related statistical significant decreased NCV and an increased NPL in the experimental group and a statistical significant difference between placebo and experimental group at various points of time. Based on these results, it can be concluded that LED irradiation at the wavelength and dosage used, applied to intact skin at the described irradiation parameters, produced an immediate and localized effect upon conduction characteristics in underlying nerves.

Retinal damage

The study by Eells [1504] was undertaken to test the hypothesis that exposure to monochromatic red radiation from light-emitting diode (670 nm) arrays would protect the retina against the toxic actions of methanol-derived formic acid in a rodent model of methanol toxicity. Using the electroretinogram as a sensitive indicator of retinal function, it was demonstrated that three brief (2 min, 24 s) 670 nm LED treatments (4 J/cm^2), delivered at 5, 25, and 50 h of methanol intoxication, attenuated the retinotoxic effects of methanol-derived formate. This study documents a significant recovery of rod- and cone-mediated function in 670 nm-treated, methanol-intoxicated rats. It is further shown that 670 nm irradiation protected the retina from the histopathologic changes induced by methanol-derived formate. These findings provide a link between the actions of monochromatic red to near-IR light on mitochondrial oxidative metabolism in vitro and retinoprotection in vivo. They also suggest that photobiomodulation may enhance recovery from retinal injury and other ocular diseases in which mitochondrial dysfunction is postulated to play a role.

Studies were conducted by Tang [2321] in streptozotocin-induced diabetic rats and in cultured retinal cells. Diabetes-induced retinal degeneration was assessed functionally, biochemically and histologically in vivo and in vitro. The authors observed beneficial effects of LED on the neural and vascular elements of retina. Daily 670 nm treatment (6 J/cm^2) resulted in significant inhibition in the diabetes-induced death of retinal ganglion cells, as well as, a 50% improvement of the ERG amplitude (photopic b wave responses). To explore the mechanism for these beneficial effects, Tang examined physiologic and molecular changes related cell survival, oxidative stress and inflammation. LED did not alter cytochrome oxidase activity in the retina or in cultured retinal cells. LED inhibited diabetes-induced superoxide production and preserved MnSOD expression in vivo. Diabetes significantly increased both leukostasis and expression of ICAM-1, and PBM essentially prevented both of these abnormalities. In cultured retinal cells, 30mM glucose exposure increased superoxide production, inflammatory biomarker expression and cell death. PBM inhibited all of these abnormalities. In conclusion, 670 nm LED ameliorated diabetic retinopathy in vivo and reduced oxidative stress and cell death in vitro.

Oh [2318] evaluated the clinical efficacy of LED photomodulation in reducing erythema resulting from ablative fractional CO2 laser resurfacing.

Randomly selected facial halves of 10 Korean subjects (Fitzpatrick skin type III-IV) were treated using a 635 nm wavelength LED array immediately after full-face fractional laser skin resurfacing. Each participant was subsequently treated with LED daily for the following 7 days. Clinical photographs, subjective physician assessment, and chromometer erythema index were used to track the results, with clinical improvement assessed using a 5-point grading scale. The post-laser erythema resolved faster on the experimental side than the control side, with improvements noted according to physician assessment and chromometer erythema index. Statistically significant improvements between the two sides were first noted on day 4. Treatment using a 635 nm wavelength LED array decreases the intensity and duration of post-fractional CO2 laser treatment erythema.

Sleeping quality

Zhao [2192] wanted to determine the effect of red light on sleep quality and endurance performance of Chinese female basketball players. Twenty athletes of the Chinese People's Liberation Army team took part in the study. Participants were divided into red-light treatment (n = 10) and placebo (n = 10) groups. The red-light treatment participants received 30 minutes of irradiation from a red-light therapy instrument every night for 14 days. The placebo group did not receive light illumination. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed, serum melatonin was assessed, and 12-minute run was performed at preintervention (baseline) and postintervention (14 days). The 14-day whole-body irradiation with red-light treatment improved the sleep, serum melatonin level, and endurance performance of the elite female basketball players. The authors found a correlation between changes in global Pittsburgh Sleep Quality Index and serum melatonin levels. This study confirmed the effectiveness of body irradiation with red light in improving the quality of sleep of elite female basketball players and offered a nonpharmacologic and noninvasive therapy to prevent sleep disorders after training.

Temporomandibular disorders

The study by Panhoca [2482] aimed to evaluate the effects of red and infrared LEDs on: (1) tissue temperature in ex vivo and (2) pain relief and mandibular range of motion in patients with TMD. Thirty patients between 18 and 40 years old were included and randomly assigned to three groups. The two experimental groups were: the red LED group and the infrared LED group. The irradiation parameters were 150 mW, 300 mW/cm², 18 J/cm², and 9 J/point. The positive control group received an infrared laser (780 nm) with 70 mW, 1.7 W/cm², 105 J/cm², and 4.2 J/point. LED and laser therapies were applied bilaterally to the face for 60 s/point. Five points were irradiated: three points around the temporomandibular joint (TMJ), one point for the temporalis, and one near the masseter. Eight sessions of phototherapy *were performed, twice a week for 4 weeks. Pain induced by palpating the masseter muscle and mandibular range of motion (maximum oral aperture) were measured at baseline, immediately after treatment, 7 days after treatment, and 30 days after treatment. There was an increase in tissue temperature during both the red and the infrared LED irradiation in ex vivo. There was a significant reduction of pain and increase of the maximum oral aperture for all groups. There was no significant difference in pain scores and maximum oral aperture between groups at baseline or any periods after treatment. The current study showed that red and infrared LED therapy can be useful in improving outcomes related to pain relief and orofacial function for TMD patients.*

Transcranial irradiation

In a literature review Rojas [2317] writes: Transcranial brain stimulation with low-level light/laser therapy (LPT) is the use of directional low-power and high-fluency monochromatic or quasimonochromatic light from lasers or LEDs in the red-to-near-infrared wavelengths to modulate a neurobiological function or induce a neurotherapeutic effect in a nondestructive and non-thermal manner. The mechanism of action of LPT is based on photon energy absorption by cytochrome oxidase, the terminal enzyme in the mitochondrial respiratory chain. Cytochrome oxidase has a key role in neuronal physiology, as it serves as an interface between oxidative energy metabolism and cell survival signaling pathways. Cytochrome oxidase is an ideal target for cognitive enhancement, as its expression reflects the changes in metabolic capacity underlying higher-order brain functions. This review provides an update on new findings on the neurotherapeutic applications of LPT. The photochemical mechanisms supporting its cognitive-enhancing and brain-stimulatory effects in animal models and humans are discussed. LPT is a potential non-invasive treatment for cognitive impairment and other deficits associated with chronic neurological conditions, such as large vessel and lacunar hypoperfusion or neurodegeneration. Brain photobiomodulation with LPT is paralleled by pharmacological effects of low-dose USP methylene blue, a non-photic electron donor with the ability to stimulate cytochrome oxidase activity, redox and free radical processes. Both interventions provide neuroprotection and cognitive enhancement by facilitating mitochondrial respiration, with hormetic dose-response effects and brain region activational specificity. This evidence supports enhancement of mitochondrial respiratory function as a generalizable therapeutic principle relevant to highly adaptable systems that are exquisitely sensitive to energy availability such as the nervous system.

Wound healing

The purpose of the study by Whelan [1503] was to assess the changes in gene expression of near-infrared light therapy in a model of impaired wound healing. Polyvinyl acetal (PVA) sponges were subcutaneously *implanted in the dorsum of mice. LED treatments were given once daily, and at the sacrifice day, the sponges, incision line and skin over the sponges were harvested and used for RNA extraction. The RNA was subsequently analyzed by cDNA array. The study revealed certain tissue regenerating genes that were significantly upregulated upon LED treatment when compared to the untreated sample. Integrins, laminin, gap junction proteins, and kinesin superfamily motor proteins are some of the genes involved during regeneration process. These are some of the genes that were identified upon gene array experiments with RNA isolated from sponges from the wound site in mouse with LED treatment.*

The effects of infrared and red pulsed monochromatic non-coherent light, with varied pulsations and wavelengths, on the healing of pressure ulcers were evaluated in the prospective, randomized, controlled study by Schubert [1513]. Elderly patients (>or=65 years) with Stage 2 or 3 skin ulcers were enrolled and assigned to one of two groups. Both groups were given the same standard ulcer therapy. One group was also given phototherapy with pulsed monochromatic infrared (956 nm) and red (637 nm) light. Treatments lasted 9 min each time using a regimen with pulse repetition rates varied between 15.6 Hz and 8.58 kHz. Patients were followed for 10 weeks or until the ulcer was healed, whichever occurred first. The ulcer surface area was traced weekly. Patients treated with pulsed monochromatic light had a 49% higher ulcer healing rate, and a shorter time to 50% and to 90% ulcer closure compared with controls.

In view of promoting the wound-healing process in diabetic patients, a preliminary in vitro study by Vinck [1594] investigated the efficacy of green light emitting diode (LED) irradiation on fibroblast proliferation and viability under hyperglycemic circumstances. To achieve hyperglycemic circumstances, embryonic chicken fibroblasts were cultured in Hanks' culture medium supplemented with 30 g/L glucose. LED irradiation was performed on 3 consecutive days with a probe emitting green light (570 nm) and a power output of 10 mW. Each treatment lasted 3 min, resulting in a radiation exposure of 0.1 J/cm^2. A Mann-Whitney U test revealed a higher proliferation rate in all irradiated cultures in comparison with the controls.

In another study by Vinck [1593] cultured fibroblasts were treated in a controlled, randomised manner during three consecutive days, either with an infrared laser or with a LED light source emitting several wavelengths (950 nm, 660 nm and 570 nm) and respective power outputs. Treatment duration varied in relation to varying surface energy densities (radiant exposures). Statistical analysis revealed a higher rate of proliferation in all irradiated cultures in comparison with the controls. Green light yielded a significantly higher number of cells than red and infrared LED light than the cultures irradiated with the laser; the red probe provided a higher increase than the infrared LED probe and the laser source. However, the doses for LED:s and laser were not the same.

Al-Watban [1541] determined the effect of polychromatic light-emitting diodes (LED) in burn healing of non-diabetic and streptozotocin-induced diabetic rats. The polychromatic LED is a cluster of 25 diodes emitting photons at wavelengths of 510-543, 594-599, 626-639, 640-670, and 842-879 nm with 272 mW output power. Age-matched rats (n=30) were used. Streptozotocin was used for diabetes induction. Rat weight, hyperglycemia, and glycosuria were monitored for the first 3 days and weekly thereafter. Rats were anesthetized and shaved after 1 week of diabetes. Burn areas of 1.5 ± .03 cm^2 were created using a metal rod pre-heated up to 600°C that was applied for 2 sec. Diabetic and non-diabetic rats were randomized into the following treatment groups: control, 5, 10, 20, and 30 J/cm^2. Light treatment commenced after burn infliction and was repeated three times per week. Burn areas were measured daily. Burn healing was impaired significantly during diabetes by -46.17%. Polychromatic LED treatment using 5, 10, 20, and 30 J/cm^2 incident doses influenced healing by 6.85%, 4.93%, -4.18%, and -5.42% in the non-diabetic rats; and 73.87%, 76.77%, 60.92%, and 48.77% in the diabetic rats, relative to their controls, respectively. The effect of polychromatic LED in non-diabetic rats was insignificant; however, it simulated the trend of stimulation and inhibition seen using low-level lasers. Significant stimulation observed in the diabetic rats demonstrated the usefulness of polychromatic LED in diabetic burn healing.

Minatel [2123] tested the hypothesis that combined 660 and 890 nm LED phototherapy will promote healing of diabetic ulcers that failed to respond to other forms of treatment. A double-blind randomized placebo controlled design was used to study 23 diabetic leg ulcers in two groups of 14 patients. Group one ulcers were cleaned, dressed with 1% silver sulfadiazine cream and treated with "placebo" phototherapy twice per week. Group two ulcers were treated similarly but received 3 J/cm^2 dose. At each of 15, 30, 45, 60, 75, and 90 days of healing, mean ulcer granulation and healing rates were significantly higher for group two than the "placebo" group. While "placebo" treated ulcers worsened during the initial 30 days, group two ulcers healed rapidly; achieving 56% more granulation and 79.2% faster healing by day 30, and maintaining similarly higher rates of granulation and healing over the "placebo" group all through. By day 90, 58.3% of group two ulcers had healed fully and 75% had achieved 90-100% healing. In contrast, only one "placebo" treated ulcer healed fully by day 90; no other ulcer attained > or =90% healing.

The study by Neves [2319] analysed the effect of non-coherent light therapy (light-emitting diode-LED) with or without silver sulfadiazine (sulpha) on the healing process of third-degree burns. In this study, 72 rats with third-degree burns were randomly divided into six groups (n = 12): Gr1 (control), Gr2 (non-contact LED), Gr3 (contact LED), Gr4 (sulfadiazine), Gr5 (sulfadiazine + non-contact LED) and Gr6 (sulfadiazine + contact LED). The groups treated with LED therapy received treatment every 48 h (640 +/- 20 nm, 110 mW, 16 J/cm^2; 41 s with contact and 680 s without con-

tact). The digital photometric and histomorphometric analyses were conducted after the burn occurred. The combination of sulpha and LED (contact or non-contact) improved the healing of burn wounds. These results demonstrate that the combination of silver sulfadiazine with LED therapy (lambda = 640 +/- 20 nm, 4 J/cm², without contact) improves healing of third-degree burn wounds, significantly reduces the lesion area and increases the granulation tissue, increases the number of fibroblasts, promotes collagen synthesis and prevents burn infections by accelerating recovery.

Lev-Tov [2320] shows that infrared LED fluences of 80, 160 and 320 J/cm² resulted in statistically significantly less fibroblast proliferation than in controls, without statistically significantly less cellular viability. LPT at high fluences can effectively inhibit fibroblast proliferation in vitro without altering viability and holds promise for the treatment of scars.

Our comments: A nice example of the therapeutic window - less is more!

Fushimi [2427] investigated the effects of red (638 nm), blue (456 nm), and green (518 nm) LEDs on wound healing. In an in vivo study, wound sizes in the skin of mice were significantly decreased on day 7 following exposure to green LEDs, and complete reepithelialisation was accelerated by red and green LEDs compared with the control mice. To better understand the molecular mechanism(s) involved, Fishimi investigated the effects of LEDs on human fibroblasts in vitro by measuring mRNA and protein levels of cytokines secreted by fibroblasts during the process of wound healing and on the migration of HaCat keratinocytes. The results suggest that some cytokines are significantly increased by exposure to LEDs, especially leptin, IL-8, and VEGF, but only by green LEDs. The migration of HaCat keratinocytes was significantly promoted by red or green LEDs. In conclusion, the study demonstrates that green LEDs promote wound healing by inducing migratory and proliferative mediators, which suggests that not only red LEDs but also green LEDs can be a new powerful therapeutic strategy for wound healing.

Further literature: [720]

2. Linear polarised light

Shibata [1558] examined the anti-inflammatory effect of infrared linear polarised light irradiation on the MH7A rheumatoid fibroblast-like synoviocytes stimulated with the proinflammatory cytokine interleukin IL-1. Expression of messenger ribonucleic acids (mRNAs) encoding IL-8, RANTES (regulated upon activation, normal T cell expressed and secreted), growth-related gene alpha (GRO) and macrophage inflammatory protein-1 (MIP1) was measured using real-time reverse transcription polymerase chain reaction, and the secreted proteins were measured in the conditioned media using enzyme-linked immunosorbent assays. It was found that irradiation with linear polarised infrared light suppressed IL-1-induced expression of

IL-8 mRNA and, correspondingly, the synthesis and release of IL-8 protein in MH7A cells. This anti-inflammatory effect was equivalent to that obtained with the glucocorticoid dexamethasone. Likewise, irradiation suppressed the IL-1-induced expression of RANTES and GRO mRNA. These results suggest that the irradiation of the areas around the articular surfaces of joints affected by rheumatoid arthritis (RA) using linear polarised light may represent a useful new approach to treatment.

There are reports of erythrocyte deformability improved by HeNe laser irradiation. In the study by Yokoyama [1573] human erythrocyte samples stored for three weeks were adjusted to 30% hematocrit. Erythrocyte deformability presented as the filter filtration rate was measured. There was no difference of the filter filtration rate between control group without irradiation and the group of 125 mJ/cm^2 exposure level at a wavelength of 830 nm. However, the groups of 625 and 1,250 mJ/cm^2 exposure levels at a wavelength of 830 nm showed higher filter filtration rates compared to the control group. Linearly polarised near-infrared irradiation in a range of 625-1,250 mJ/cm^2 exposure level at a wavelength of 830 nm improved the deformability status of human stored erythrocytes.

The study by Basford [1575] was designed to assess the physiological effects of irradiation on the stellate ganglion function in normal subjects and people with complex regional pain and to quantitate its benefits in people with upper extremity pain due to Complex Regional Pain Syndrome I (CRPS I, RSD). This was a two-part study. In the first phase, six adults (ages 18-60) with normal neurological examinations underwent transcutaneous irradiation of their right stellate ganglion with linearly polarised 0.6-1.6 micron light (920 mW, 88.3 J). Phase two consisted of a double-blinded evaluation of active and placebo radiation in 12 subjects (ages 18-72) of which 6 had upper extremity CRPS I and 6 served as "normal" controls. Skin temperature, heart rate (HR), sudomotor function, and vasomotor tone were monitored before, during, and for 30 minutes following irradiation. Analgesic and sensory effects were assessed over the same period as well as 1 and 2 weeks later. Three of six subjects with CRPS I and no control subjects experienced a sensation of warmth following active irradiation. Two of the CRPS I subjects reported a >50% pain reduction. However, four noted minimal or no change and improvement did not reach statistical significance for the group as a whole. No statistically significant changes in autonomic function were noted. There were no adverse consequences. The irradiation was well tolerated. There is a suggestion in this small study that treatment is beneficial and that its benefits are not dependent on changes in sympathetic tone.

Otsuka [1578] performed linear polarised light irradiation near the stellate ganglion in a 55 year old female with Raynaud's sign. She was suffering from cold and numb pain in bilateral fingers for 1 year. Stellate ganglion block and laser therapy near the stellate ganglion were not sufficient to relieve this symptom. Polarised light irradiation near the stellate ganglion induced a sting stimulation and warm sensation in her hands. Thermograms *revealed a remarkable increase in temperature of her hands. The results imply that ed light irradiation near the stellate ganglion increases blood flow of forearms and relieves Raynaud's sign.*

Wajima [1577] evaluated the effect of linear polarised light irradiation around the stellate ganglion area on skin temperature and blood flow in healthy adult volunteers. The researchers carried out two experiments. In study I, they investigated one-sided irradiation around the stellate ganglion area or posterior neck on the skin temperature of the bilateral nasus externi and earlobes. In study II, they investigated one-sided irradiation around the stellate ganglion area or posterior neck on the skin temperatures of both hands and skin blood flow on the irradiated side. In study I, irradiation around the stellate ganglion area increased skin temperature on the irradiated sides of the nasus externi (wings of the nose), and in study II, skin temperature and blood flow were increased on the irradiated side of the hands. These results suggest that linear polarised light irradiation around the stellate ganglion area would be useful and beneficial in clinical therapy.

Further literature: [1686, 1687, 1688]

Broadband polarised light (VIP)

See references: [1611, 1612, 1613, 1614, 2030, 2031, 2032]

Chapter 7
Veterinary use

Veterinary medicine is another field in which the laser enthusiast can find further uses for his or her laser. All the common laser types are effective, and GaAs is particularly good for deep-lying tissue.

The scientific documentation in the field of veterinary medicine is extensive, with over one thousand published studies on animals. In most cases, effects have been observed. Most of these studies have involved animals for whom a veterinarian would not ordinarily be called in the event of problems - rats, mice, rabbits, guinea pigs, etc. However, at the present time some documentation is also available on dogs and horses.

Fortune hunters and unscrupulous sales representatives managed to give the laser treatment of trotting horses a bad reputation during the 1980s. In the veterinary field, as in so many others, the reaction was to throw the baby out with the bath water. It is not the laser that is at fault, but often the deficient knowledge of the user and the poor quality of the equipment. A sound knowledge of equine medicine is necessary to achieve good results, in the same way as in human medicine.

Courtesy: Therese Andersen

Horses are more sensitive to laser light than humans. High local power density - and especially super pulsed lasers - bring about a reaction (including sometimes a pain reaction) when the light enters the vicinity of an injury or problem area. This is particularly true of GaAs lasers and at high pulse or pulse-train frequencies. If the horse reacts strongly, it is suitable to start with a low pulse frequency before going to the higher levels. This reaction in horses can also be used to locate a problem. In trotting and sport in general, the practitioners of laser therapy with the right training and the right equipment are enthusiastic about the results. The economic incentives are obvious. Dogs, cats and other household pets can also be treated with lasers with good results. As with pharmatecuticals, dosage must be adapted to the size of the animal and the type of fur.

Lindholm [562, 1280] has treated more than 500 horses with a defocused CO_2-laser. The results have been 80% positive in treatment of vertebral joint problems, but the treatment is significantly less effective for tendinitis. The clinical outcome of defocused CO_2-laser therapy for acute traumatic arthritis reveals at least an equal therapeutic effect compared with conventional therapy.

A common problem, and one that is even more pronounced in the treatment of race-horses because of the amounts of money involved, is, as we have discussed elsewhere, that laser treatment can radically alleviate pain after just one or two applications. In a couple of cases, when people without medical expertise have observed that the horse's limp has disappeared and ordered hard training, the result has been an exacerbation of the injury rather than a healing. This problem is to some extent associated with treatment of human athletes, too.

When treating horses and dogs, it must be born in mind that their coat can be essentially impenetrable to light. By measuring light absorption in various types of coats, we have determined that between 50% (thin, light coat) and more than 99% (brown hair and the coat of an Icelandic pony) of the light is absorbed by hair and skin. This absorption is essentially independent of wavelength, which is not the case as regards penetration of tissue. Further, the skin (beneath the coat) may be more or less strongly pigmented, which also affects light penetration.

The negative effects of hair on light absorption can obviously be eliminated by shaving the areas to be treated [2461]. Horse owners do not always want it to be obvious that their horse is under treatment, and shaving entails certain difficulties as well. For these reasons, it is not uncommon to give laser treatment through the hair. This presents no problem if the laser instrument is designed to do so, in which case the light is carried down through the hair by optical fibres or the like - much as a comb contacts the skin under the hair. Unfortunately many instruments used for veterinary treatment are not intended specifically for that purpose, but rather for treatment of humans, and their efficacy is therefore often limited.

Any type of fur absorbs a lot of the laser energy before reaching the skin, so to obtain a reasonable effect, unless the fur is shaved, irradiation has to be performed in contact and as close to the skin as possible. This can be obtained by using fairly thin probes or probes with protruding lenses, and moving them slightly around with a bit of pressure. For humans, it is easy to confirm this by keeping a reasonably strong laser in contact in the hairy neck area. Unless the hair is white or at least grey, there will be a hot sensation or even pain. But by slightly moving the probe around, the heat sensation and the pain will disappear. This is true for hairy animals as well, but they cannot verbally tell you that the therapy is uncomfortable.

Al Watban [2323] has studied the loss of energy for lasers in the range 442 - 830 nm. Shaved mice were placed in plexiglas boxes. The reflection of the Plexiglas varied between 6.6 - 11 % while reflection by the skin varied between 65 - 82.5 %. This means that there was a loss of energy between 61.6 and 93.5 % before the light reached the skin. And this is where human therapy starts! Some manufacturers have tried to overcome this problem by using large probes (lowering the power density) and recommendation of moving them around. But the large probe has difficulties of getting into the fur. Other manufacturers recommend water cooling to compensate for the high power of their lasers. It would be much better, and less expensive, to reduce the power and adapt the probe.

Figure 7.1 Treatment of joint inflammation

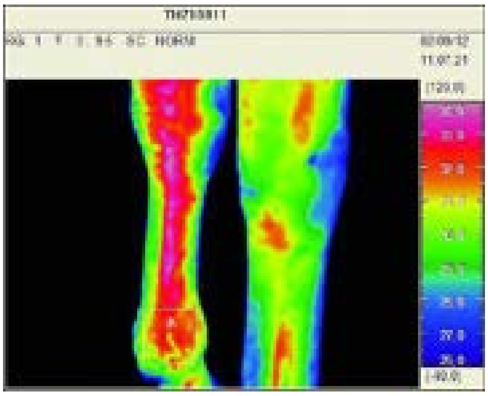
Laser probe with eight protruding laser diodes for veterinary use

Figure 7.2 Laser probe for veterinary use.

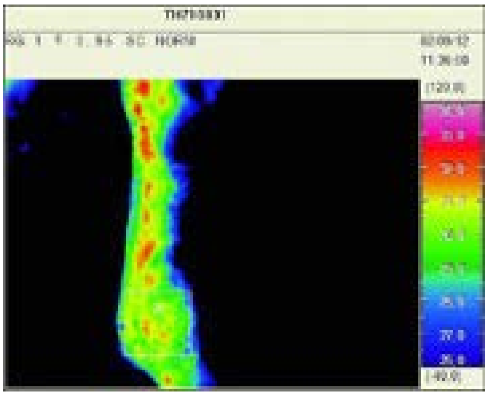
Heat camera measurement

An interesting method is to use a heat camera in diagnostics. It can also be used to objectively study effects of laser treatment. In the following pictures a heat camera was used to follow the reaction after laser therapy of an oedema outside the fetlock joint caused by a hard blow.

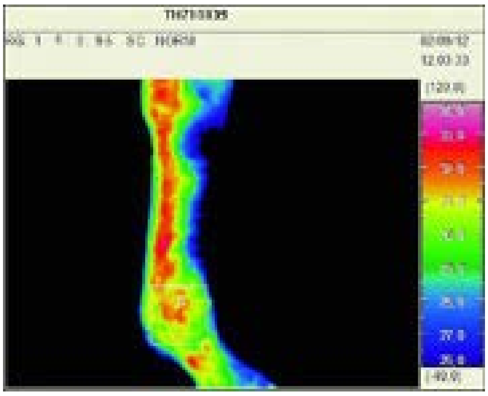
The first picture shows the temperature distribution about 15 minutes before laser treatment.



Within the square (marked "A") the maximum temperature is 32.9 °C. The average temperature is 31.5 °C. The following picture is taken 5 minutes after the treatment:



Within the square (marked "A") the maximum temperature is 31.8 °C. The average temperature is 30.0 °C. Next picture is taken 33 minutes after the treatment.



Courtesy: Lindströms Digital Infrared Thermal Imaging

It is amazing how quickly the inflamed tissue reacts. The fur is not cut or shaved off, hence the temperature difference is even higher on the skin under the fur.

<u>Laser parameters:</u> The average output power of the laser probe is measured to 62 mW (four GaAs-laser diodes, each with 13 watt peak power, 150 ns pulse duration, pulse train modulated with basic frequency 16 kHz, 50% duty cycle and envelop frequency 2500 Hz).

<u>Treatment parameters:</u> Treatment was done over the whole inflamed area. That area was about 5 × 40 cm (200 cm^2). Treatment time was 4 minutes. This gives a treatment dose of about 0.075 J/cm^2, which is rather normal for the GaAs-laser type.

For more information see “Thermography” on page 160.

7.1 Case reports

Many readers of our previous books have asked for more information on veterinary LPT. We have therefore asked Dr. Carrie Althouse, DVD, MS, CCRP to submit a few clinical cases in detail. These cases will illustrate how LPT can be used for veterinary conditions. Fairly powerful lasers have been used and might for some animals be needed to compensate for the reduction of absorption due to the presence of a fur.

Case 1: Charlie,
a 4 yr 11 mth old neutered male Morkie, presented for an evaluation for physical rehabilitation. Charlie's presenting complaint is persistent left hind limb lameness. The owner's goal is to decrease lameness on the left hind leg.

On physical examination, Charlie has bilateral medial patellar luxation, grade 1-2 on the left and grade 2-3 on the right. Joint effusion and some instability was present in the left stifle. Pain was present in the hip flexors, quadriceps, and lumbar epaxials. PROM was within normal limits in both stifles though he resents full extension of both stifles and direct palpation of the left stifle.

The initial plan was to utilise low level laser therapy to reduce pain and gradually implement a program of physical strengthening. All laser treatments were performed using an 810 nm 500 mW laser probe.

Charlie's hair was parted, the probe's convex lens placed in contact with the skin, with slight pressure applied and held stationary for the full emission duration per point. The control unit was set to 'CW' (Continuous Wave), except as noted, and the emission duration per point varied as applicable.

Probe Parameters:

Output Power	500 mW
Wavelength	810 +/-5 nm
Aperture Diameter	16 mm
Spot Size (Skin Contact)	17 x 2.9 mm (rectangular)
Power Density at Skin	1.0 W/cm^2

Initial treatment, Day 1: 40 seconds to each of four points over the left and right stifles; 30 seconds to trigger points in left and right hip flexors until comfort was achieved (2 treatments on the right, 3 on the left); 30 seconds to lumbar epaxials/dorsal nerve roots on the left and right; 20 seconds to lumbar spinal cord; 20 seconds to left and right gastrocnemius muscles and TL trigger points. Stretching (lumbar NAGs) was performed following treatment. Charlie was wary and slightly resistant to initial treatment.

Treatment 2, Day 7: Owner feels that Charlie may be a little bit better. He is still picking up his leg, but not as frequently as before. On physical examination he is still off-loaded onto his right hind. At a walk he has a 2/5 to a 5/5 lameness as his speed increases. He will pick up the left hind leg at least 50 percent of the time. Moderate muscle spasm and pain is noted in the left hip flexor, mild in the right. Plan: Ice to left hip flexor for 10 minutes. Laser: 30 seconds x 3 rounds to the left hip flexors at CW; 20 seconds to the entire dermatome with inclusion of the dorsal nerve roots; 20 seconds to the right stifle, hip and dorsal nerve root. Charlie was encouraged to stand on a balance pad for 3 minutes with his patellas in place with gentle weight shifting.

Treatment 3, Day 14: Owner reports significant improvement since his last visit. Charlie took off running after a squirrel, for the first time in years, both yesterday and today (the owner had thought "he had outgrown the habit"); only occasional skipping is noted on the left hind at increased speeds. Mild spasm only noted in the left hip flexor, right hip flexor now comfortable. No trigger points noted in the TL spine, decreased effusion in the left stifle, increased comfort through full PROM in both stifles. Plan: laser for 20 seconds per point to 4 points around each stifle and hip and to each dorsal nerve root. 20 seconds to LS spine. Lumbar NAGs to stretch. Introduction of strengthening and proprioceptive exercises: cavaletti rails on the ground (Charlie reluctantly navigated 2 rails) and standing on an inflatable peanut for 2 minutes.

Treatment 4, Day 21: Owner reports continued improvements. Charlie has been more willing to walk, has rarely picked up his left hind leg and seems peppier. He still refuses to try steps either at home or in clinic. No trigger points noted. Laser for chronic pain, 10 seconds to 4 points around left and right stifles and hips; 20 seconds to left and right hip flexors with hip extension; 20 seconds to dorsal nerve roots left and right; 20 seconds to quadriceps muscles left and right. Joint mobilisation of the stifle and hip on the left and right sides. Active exercises: cavaletti rails crossed on the floor: today well navigated. Charlie still refuses to step up onto a 2 inch block. Standing on the balance pad for 2 minutes with weight shifting.

Treatment 5, Day 28: Owner reports that Charlie has been getting around much better and feels that he has lost weight due to his increased activity level. He still has trouble jumping on the furniture but did use steps to climb onto the bed for the first time in a long time. He is starting to stand on his hind legs. He is notably more energetic and interactive. On physical examination there is minimal spasm in the hip flexors or quadriceps and he is comfortable through full PROM. Plan: laser pulsed (10 Hz, 250 mW average power), 30 seconds to left and right stifles and hips (4 points each), left and right quadriceps and hip flexors; CW for 20 seconds to lumbar dorsal nerve roots and LS spine. Active exercises: navigate cavaletti rails crossed on the floor, front feet on balance pad with weight shifting; standing on peanut; crawl under a rail at 6 inch height. Charlie will still not step up onto the scale.

Treatment 6, Day 35: Owner reports that Charlie is doing great! In the last week he sought out his once favorite toy and invited games of tug o' war which he has not done in years. He also sought out his favorite bone and started carrying it around the house. Owner thinks he may have attempted to climb the stairs. He is using the ottoman to climb onto the sofa. He is much more interactive and playful. Family has noted that he now stretches his back legs when he wakes up. On physical examination he is comfortable with 0-1/5 lameness at a walk and 1-2/5 lameness at a trot. Laser: 20 seconds to left and right stifles and hips at four points each, hip flexors, lumbar dorsal nerve roots. Active exercise: navigated cavaletti rails criss crossed on the floor with confidence, walked under obstacles, stood on the peanut for 5 minutes and stepped up onto the scale on his own 5 times!

Case 2: Dudley,
7 ½ year old neutered male pug mix diagnosed 6 months prior with intervertebral disk disease. He had been treated unsuccessfully with a combination of carprofen, tramadol, methocarbamol, and gabapentin.

He presented to the Rehabilitation service for evaluation for additional treatment options. He had been stiff, especially after sleeping in his crate, hiding, decreased activity, refusing to go on walks, not sitting squarely but rather on his pelvis, holding up his right hind leg when sitting on his pelvis, and general discomfort in his hind end.

On physical examination, Dudley had effusion and crepitus in both stifles with the right worse than the left, pain at end range of motion in both stifles, reaction to palpation at the TL junction and lumbar epaxials, resentment of tail elevation with snapping, discomfort on full extension of left and right hips, decreased spinal mobility especially at the TL junction. He was diagnosed with TL pain and restriction, lumbar restriction, trigger points in the left and right hip flexors, left and right iliopsoas pain, and osteoarthritis of the left and right stifles.

Dudley's owners elected to try physical rehabilitation including low level laser therapy, joint mobilisation, stretching, and adjunctive treatments (TENS, heat, cold, trigger point release) as indicated. All laser treatments were performed using an 810 nm 500 mW laser probe and an 810 nm 4x 750 mW nm cluster probe.

Dudley's hair was parted to enable the convex lens of each probe to be placed in contact with the skin with slight pressure applied, and the probe was held stationary for the full emission duration per point. The control unit was set to 'CW' (Continuous Wave), and the emission duration per point varied as applicable.

Probe Parameters:

Output Power	1 x 500 mW
Wavelength	810 +/-5 nm
Aperture Diameter	16 mm
Spot Size	17 x 2.9 mm (rectangular)
Power Density at Skin	1.0 W/cm^2

Multi Probe Parameters:

Output Power	4 x 750 mW
Wavelength	810 +/-5 nm
Aperture Size	35 mm
Spot Size per Laser	13.3 x 3 mm (rectangular)
Power Density at Skin	4 x 1.875 W/cm^2
LED guide lights	660 nm, nominal output

Initial treatment, Day 1: 500 mW probe was applied for 30 seconds per point to each of the left and right hip flexors, 2 repetitions; 20 seconds to the TL junction, 2 repetitions; left and right stifles (4 points) and quadriceps muscles, iliopsoas insertion at lesser trochanter, and LS; 4 x 750 mW multiprobe was applied for 20 seconds per site to multiple sites across the spine to include the epaxial muscles of the thoracic and lumbar spine, left and right hips and supporting musculature. Lumbar NAGs were applied with mobilisation at L4-6. He was stretched gently over a small inflatable peanut, and the owner was taught how to perform cookie stretches to increase spinal mobility and passive range of motion to all joints of the hind limbs to improve joint health and mobility. Methocarbamol was discontinued.

Treatment 2, Day 7: Owner reports improvement. They have discontinued gabapentin. Dudley was still not sitting "normally" and was still refusing to go for walks. Reaction was still noted at the TL junction and in the left and right hip flexors. He still resents tail elevation. End of extension was still resented in left and right hips and stifles. Laser: 500 mW probe 30 seconds to each of left and right hip flexors from medial and lateral aspects; 20 seconds to each stifle at 4 points circumferentially, iliopsoas insertion, lumbar epaxials on the left and right from TL junction to LS, and to trigger point at right T6 for 2 repetitions, and to LS. Lumbar NAGs were performed, cookie stretches, and standing on the balance pad.

Treatment 3, Day 14: Owner reports that Dudley is doing great. He has more energy and generally seems to feel better. He is now playing with his housemate and seems to be considering taking walks. He occasionally sits with his right foot elevated. He is more willing to do his cookie stretches. Exam findings: no spasm in hip flexors, minimal reaction to TL palpation, tolerates full range of motion in left and right stifles, and tail elevation, increased mobility at TL junction. Laser: 4x 750 mW mulitprobe for 20 seconds each site from T6 to tail base. 500 mW probe for 20 seconds to LS, hips circumferentially, stifles circumferentially. Dudley navigated through cavaletti rails scattered and stacked on the floor, and stood with his front feet on the balance pad to encourage hind leg strengthening. Tramadol was discontinued.

Treatment 4, 21 days: Owner reports that Dudley now only receives Rovera once daily and is not on any additional medications. Dudley continues to do well. He was willing to walk around a lot outside the hospital prior to treatment. He is spunky and interactive. His general demeanor is much more relaxed and interactive. On examination there was no reaction to spinal or epaxial palpation, he was comfortable through full range of motion in hips and stifles. Laser: 500 mW probe 20 seconds to left and right stifles and hips circumferentially; hip flexors medially and laterally including iliopsoas insertion and lumbar epaxials. Omega fatty acids added.

Treatment 5, 35 days: Owners report that Dudley is doing great. He is now going for walks and only occasionally lifts his right hind leg when sitting. He receives Rovera only when he seems stiff which is occasional when getting out of his crate. Laser: 500 mW probe 20 seconds per point to multiple points thoracic and lumbar spine and epaxial muscles; 10 seconds per point to multiple points left and right hips and stifles circumferentially. He is now on maintenance therapy every 4 weeks.

Case 3: Claude,

a 1 ½ year old neutered male Bulldog Mix, 63 lbs. History: 2 week history of limping on the left hind leg. He was diagnosed with a partial tear of the left ACL by an orthopedic surgeon at an area referral hospital. The owners elected to not have surgery performed, and instead conservative management of the tear, including low level laser therapy.

On presentation, there was effusion in the left stifle, slight cranial draw with no cranial thrust, pain on hyperextension of the left stifle, and mild spasm in the thoracolumbar epaxial muscles. He was partial (Grade 2-3/5 lameness at a walk) weight bearing on the left rear with offloading onto the right rear at rest. He would occasionally sit with the left rear abducted and extended but could execute a proper sit. Thigh circumference is equal.

All laser treatments were performed using the same lasers as in case 2. Claude's hair was parted to enable the convex lens of each probe to be placed in contact with the skin with slight pressure applied, and the probe was held stationary for the full emission duration per point. The control unit was set to 'CW' (Continuous Wave), and the emission duration per point varied as applicable.

Initial treatment, Day 1: Laser was applied using the 500 mW probe for 40 seconds per point to 8 points around the left stifle and 20 seconds to the dorsal nerve root and supporting dermatome. Owners were instructed to limit exercise to controlled leash walks of 10 minutes 4-6 times a day, weight shifting, and cookie stretches.

Treatment 2, Day 3: Laser 500 mW probe for 40 seconds per point to 8 points around the left stifle and 20 seconds to the dorsal nerve root and supporting dermatome

Treatment 3, Day 5: Laser 500 mW probe 30 seconds each to 8 points around the left stifle and 20 seconds to the dorsal nerve root and supporting dermatome.

Treatment 4, Day 12: Improved weight bearing and activity lameness score 2/5 at a walk, slight offloading at a stand (2-3/4). Institute body awareness exercise using low cavaletti (2 inch high) rails over 2 rails. Front feet on a balance pad for 30 second holds. Laser 500 mW probe for 30 seconds each to 8 points around the left stifle and 20 seconds to the dorsal nerve root.

Treatment 5, Day 19: Owner reports that Claude is doing very well. He is comfortable on full ROM of left and right stifles with a grade 1-2/5 lameness at a walk and 0-1/4 at a stand. There is no pain on hyperextension of the left stifle and minimal effusion. Exercises were increased to include 3 cavaletti rails, standing on a peanut, and sit to stands with proper positioning. Laser 500 mW probe for 20 seconds each to 6 points around the left stifle.

Treatment 6, Day 33: Claude continues to do well with no sign of lameness. He is walking 15 minutes a day and starting to play with no onset of lameness. The left stifle is comfortable through full range of motion. His activity level is increased to short (less than 5 minutes) sessions of free play, standing on the peanut, front feet on the balance pad, and 3 cavaletti rails. Laser 4x 750 mW multiprobe for 10 seconds each to 4 sites around the stifle and the dorsal nerve root.

Treatment 7, Day 40: Claude has been playing more at home with no pain or lameness. On physical examination he is comfortable. Exercises expanded to include stepping up onto a 5 inch riser, standing across 2 peanuts, cavaletti rails space 12 inches apart, and front feet on a riser with no lameness or discomfort. Laser 4x 750 mW multiprobe for 10 seconds per site to 4 sites around the left stifle and the dorsal nerve roots.

Treatment 8, Day 54: Claude continues to do extremely well. He is minimally restricted at home other than not being allowed to jump excessively. His exercise is expanded to include walking over 2 peanuts, weight shifting on the peanut, and stepping on and off a 5 inch riser. Laser 4x 750 mW multiprobe for 10 seconds to each of 4 sites around the left stifle and dorsal nerve roots. His left stifle stable. He is allowed to restart play groups with strict supervision and no rough housing at the owner's discretion.

Treatment 9, Day 68: Maintenance evaluation: doing well in daycare with no lameness noted on the left rear. No evidence of offloading of the left hind leg, no pain on range of motion. Laser 500 mW probe for 10 seconds to each of 8 points around the stifle and dorsal nerve roots.

Day 80: Claude presents from daycare for lameness on the right hind. Mild joint effusion and instability with pain on full extension of the right stifle is noted. The left stifle is stable and comfortable. The owners have elected to try management with laser therapy, adequan, and omega supplements as they understand that Claude is at risk for continued cartilage damage and osteoarthritis.

Literature:

Ghamsari [1120, 1121] made perforating wounds on 32 teats in eight diary cattle. Four different suture patterns were used and evaluated. Four of the eight groups were additionally treated with HeNe laser, 3.64 J/cm^2. It was found that wound healing was accelerated in the groups treated with laser. The epidermis in the laser groups more closely resembled normal epidermis and collagen fibres were denser, thicker and better arranged.

Ghamsari [1192] created full thickness wounds on the cranial surface of the teats. Teats were distributed into four groups; group A and B wounds were closed with a Gambee pattern, group C and D wounds were closed with three-layers of continuous suture pattern. Group B and D wounds were treated with 3.64 J/cm^2 of LPT using a helium-neon system continuous wave (632.8 nm) output of 8.5 nW. The teat wall in non-LLLT groups was significantly thicker than in LPT groups on day 7, 14 and 21. The mean blood flow differences between control and sutured sites in LPT groups were significantly lower than those in non-LPT groups. The morphology of the epidermis *in LPT groups more closely resembled the normal epidermis than that of non-LPT groups. Collagen fibers in LPT groups were denser, thicker, better arranged and more continuous with existing collagen fibers than those in non-LPT groups. The mean tensile strength was significantly greater in LPT groups than in non-LPT groups.*

Laser therapy of mastitis has been successfully used for dairy cattle and Herzog [1002] reports good effects on 66 individuals, using 830 nm, 30 mW, 0.5-2 J per point. On the other hand, Stoffel [1004] reports that HeNe laser, 25 mW had no effect on bovine mastitis. However, the irradiation area of 7.5 cm in diameter produces a very low energy density.

Herman [151] has studied the effects, in vitro, of Nd:YAG laser therapy on articular cartilage in cattle and has shown bio-chemically that laser light influenced the healing process.

Rochkind [561] subjected 17 dogs to laminectomy and transection of the spinal cord at D12-L1. An autograft of the left sciatic nerve was then implanted into the injured area. Neurorrhaphy was performed on the right sciatic nerve. Seven dogs did not receive any additional treatment and served as a control. The other 10 were treated transcutaneously with 16 mW of HeNe laser light for 20 days (high doses) over the operated area. The 7 dogs in the control group became paralysed as expected. The 10 dogs that underwent the same operation but were immediately treated with a laser were able to stand after 7-9 weeks, and could walk a few steps after 9-12 weeks. The histological picture obtained from the dogs 21 days post operation showed no rejection and no prominent scar tissue at the site of contact between the spinal cord tissue and the transplanted nerve. Moreover, new axons and blood vessels originating in the spinal tissue extended into the graft. These were seen only in the laser treated group and not in the control group, in which scar tissue had developed at the site of transection.

The clinical effects of intra-articular betamethasone together with hyaluronic acid (ßM/HA) and treatment with a defocused carbon dioxide laser on acute traumatic arthritis of the fetlock joint were assessed in a study by Lindholm [1280]. The horses in these studies were selected using a thorough lameness examination, including intra-articular anaesthesia, abolishing the lameness. This investigation comprised an observer-blind study, including 10 sport horses (10 joints), and a prospective study, including 180 sport horses (333 joints). In both studies, the material was divided into two groups treated with either ßM/HA or a carbon dioxide laser. The treatment doses were 12 mg of ßM, 20 mg of HA and 60 J/cm² of CO_2-laser over the treated area, respectively. Convalescence before training was 21 days for both groups in the observer-blind study. In the prospective study, convalescence in the ßM/HA group was 21 days but was only 7 days for the laser-treated group. In the observer-blind study, three of five treated joints recovered in both cohorts. In the prospective study, the groups had significantly different recovery rates - 68% of the ßM/HA-treated joints and 80% of the carbon dioxide laser-treated joints. These results indicate that the defocused *carbon dioxide laser should be an applicable mode of treatment of acute traumatic synovitis in horses.*

Although laser therapy has been very successfully used in treating horses, there are some studies showing little or no effect. In a study by Petersen [1153] GaAlAs laser was administered to full thickness skin wounds (3 × 3 cm) induced surgically on the dorsal aspect of the metacarpophalangeal joints of 6 crossbred horses in a randomised, blind, controlled study. Wounds that received a daily laser dosage of 2 J/cm^2 were compared with nontreated control wounds on the opposite leg. There were no significant differences in wound contraction or epithelialisation between the laser treated and the control wounds. Laser therapy had no clinically significant effect on second intention wound healing.

Our comment on this is that it seems that the wounds were induced surgically on healthy individuals, which means that the tissue was healthy and the healing capacity therefore close to optimal. The immunological condition of the tissue and of the individual is a significant factor in the effectiveness of laser therapy. Furthermore, it is not an optimal situation with controls in the same individual due to the influence of possible systemic effects.

Gomez-Villamandos [425] induced duplicate pharyngeal mucosal ulcers in 12 horses. Using a fibroendoscope, one of the two injured sides was treated daily with a HeNe laser at 8 J/cm^2. On day 7, histological samples were taken from two horses. Irradiated lesions cicatrised after 10.5 days and non-irradiated lesions after 18. A histological study showed coagulation, necrosis and oedema at the control site. However, in the samples from the irradiated lesions, no inflammatory oedema, numerous active fibroblasts, connective tissue or intensive epithelial regeneration were observed.

And what if the dog owner has an accident with his pet? Jih [1544] describes a case of a large linear atrophic dog-bite scar on the chin of greater than 2-year duration, treated for three sessions at 4- to 6-week intervals with a 1450 nm diode laser. Fifty to seventy-five percent improvement in the appearance of the scar resulted after three treatments with the 1450 nm diode laser. No adverse effects were noted from the treatment. The patient subjective rating of scar improvement was more than 50%. The 1450 nm diode laser may provide a non-invasive, non-ablative and effective alternative for the treatment of atrophic traumatic scars.

For animal breeding LPT can be quite valuable when artificial insemination is used, since LPT can improve the quality of sperm cells, documented by i.a. Corral-Baqués [1269, 1557,2379, 2410].

Draper [2418] performed a prospective study to determine if LPT and surgery for intervertebral disk herniation encourage ambulation faster than surgery alone. Thirty-six dogs with acute paraparesis/paraplegia due to acute intervertebral disk herniation were evaluated and given a modified Frankel score. Dogs with scores 0 to 3 were included in the study. Dogs were assigned to the control group (1) or the laser treatment group (2) based on alternating order of presentation. All dogs underwent surgery for their herniated disk. Dogs in group 2 were treated postoperatively with LPT daily for five days, or until they achieved a modified Frankel score of 4. A 5×200 mW 810 nm cluster array was used to deliver 25 W/cm^2 to the skin. All dogs were scored daily by the investigators using the modified Frankel scoring system. The time to achieve a modified Frankel score of 4 was significantly lower in the LPT group (median 3.5 days) than the control group (median 14 days).

The purpose of the research by Santiago [2438] was to study the influence of LPT on the process of bone repair after expansion of the midpalatal suture. The sample for this case-control experimental study was 11 dogs. They were randomly divided into 2 groups, both of which underwent rapid maxillary expansion with a hyrax appliance. The animals in group 1 were also treated with laser therapy. They were killed, and histologic specimens of the palatal suture were prepared. A significant difference was observed in the quality of the palatal sutures between the animals in groups 1 and 2. The connective tissues of the sutures in the group 1 animals were similar to the original configurations, with more advanced osteogenesis and fibrogenesis, compared with those of group 2.

This study by Ryan [2461] was designed to test the hypothesis that transmission of LPT in horses is increased by clipping the hair and/or by cleaning the area to be treated with alcohol, but is unaffected by coat colour. A LPT probe (810 nm, 500 mW) was applied to the medial aspect of the superficial flexor tendon of seventeen equine forelimbs in vivo. A light sensor was applied to the lateral aspect, directly opposite the laser probe to measure the amount of light transmitted. Light transmission was not affected by individual horse, coat colour or leg. However, it was associated with leg condition. Tendons clipped dry and clipped and cleaned with alcohol, were both associated with greater transmission of light than the unprepared state. Use of alcohol without clipping was not associated with an increase in light transmission. These results suggest that, when applying laser to a subcutaneous structure in the horse, the area should be clipped and cleaned beforehand.

Further literature: [129, 130, 131, 132, 133, 134, 135, 137, 138, 139, 381, 391, 396, 425, 506, 1152, 2262, 2467].

Chapter 8 -
Contra indications

Older literature on lasers often repeats certain alleged contra indications related to laser treatment. There are in fact no absolute contraindications to LPT, but some relative contraindications and caveats, based upon common sense.

8.1 Pacemakers

As pacemakers are electronic and cased in metal they cannot be influenced by light, and this is therefore a misconception. Try influencing your CD player with a laser! This city tale can still be seen in some literature. It seems that safety regulations for lasers were, in many cases simply transferred from safety regulations for electrical devices.

8.2 Pregnancy

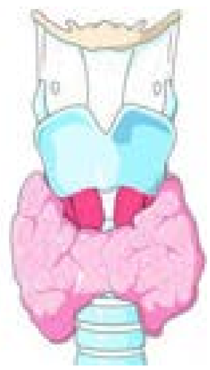
Pregnancy is another alleged contra indication. In this case, normal medical judgment with respect to the effect on the foetus should prevail. Large doses over the abdomen should perhaps be avoided, but the foetus will certainly not be any the worse off for its mother being rid of a sensitive tooth neck or a herpes sore. Avila [194] has demonstrated cell damage in chicken embryos after irradiation with a HeNe laser through an opening in the egg. We should bear in mind that the small chicken embryo received 5 mW of laser light for five minutes from a short distance through more or less transparent tissue. To give a human embryo the same dose per kilo of body weight via the mother's skin, weeks of treatment would be needed! The problem with both pacemakers and pregnancy is that they have long been presented as contra indications. If a complication unrelated to the use of a laser arises during or shortly after laser treatment, it is easy to blame the laser and the therapist is left with the burden of proof. It pays, therefore, to be prudent. Acupuncturists should therefore avoid the “forbidden” points with lasers as well as needles.

8.3 Epilepsy

Epilepsy is another alleged contra indication. Because pulsed visible light, particularly at pulse frequencies in the 5-10 Hz range can cause epileptic attacks, one should obviously be careful with instruments that use flashing visible light. It is rare, however, for therapeutic lasers to have pulsing visible light. Nothing is said in the literature on the subject of invisible pulsing light affecting epileptics, but some anecdotal accounts would suggest that it is best to be careful with GaAs when treating such patients. Simunovic [444] reports on GaAs treatment of an epileptic person who could only tolerate frequencies below 800 Hz.

On the other hand, the recent animal study by Radwan [2086] points into another direction - LPT might be a future treatment modality. The aim of the study was to investigate the effect of daily laser irradiation on the levels of amino acid neurotransmitters in the cortex and hippocampus in an epileptic animal model induced by pilocarpine. It has been claimed that at specific wavelengths and energy densities, laser irradiation is a novel and useful tool for the treatment of peripheral and central nervous system injuries and disorders. Adult male albino rats were divided into three groups: control rats, pilocarpinised rats (epileptic animal model), and pilocarpinised rats treated daily with laser irradiation (90 mW at 830 nm) for 7 d. The following parameters were assayed in cortex and hippocampus: amino acid neurotransmitters (excitatory: glutamic acid and aspartate; and inhibitory: gamma-aminobutyric acid [GABA], glycine, and taurine) by high-performance liquid chromatography (HPLC), glucose content, and the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), using a spectrophotometer. Significant increases in the concentrations of glutamic acid, glutamine, glycine, and taurine were recorded in the cortices of pilocarpinised rats, and they returned to initial levels after laser treatment. In the hippocampus, a moderate increase in aspartate accompanied by a significant increase in glycine were observed in the epileptic animal model, and these dropped to near-control values after laser treatment. In addition, a significant increase in cortical AST activity and a significant decrease in ALT activity and glucose content were obtained in the pilocarpinised animals and pilocarpinised rats treated with laser irradiation. In the hippocampus, significant decreases in the activity of AST and ALT and glucose content were recorded in the epileptic animals and in the epileptic animals treated with laser irradiation. Based on the results obtained in this study, it may be suggested that nearinfrared laser irradiation may reverse the neurochemical changes in amino acid neurotransmitters induced by pilocarpine.

A report from Epilepsy Services, Epilepsy Action [2369] only mentions pulsing light, not continuous light.



8.4 Thyroid gland

It has not been reported that LPT can cause irreversible damage, and because the thyroid is sensitive to light, this gland provides an interesting subject for research into hypo- and hyperthyroidism.The thyroid is often reported as a caveat but there are no studies confirming this and no such clinical experience.

Literature:

Hernandéz [285], using GaAs, reports that the decrease of T3 and T4 hormones after infrared laser irradiation might be explained by the changes in the cyto-skeleton and/or thyroglobuline synthesis.

Studies on mice by Parrado [159] indicate that the subject can suffer from disorders if irradiated with large doses. These authors irradiated for 15 consecutive days using GaAs, 46.8 and 140.4 J/cm^2. in the region of the thyroid gland. In a later recalculation of these doses, however, Azevedo [1625] shows that the actually doses were 3.12 and 9.36 J/cm^2. but that the cumulative doses were still very high.

Mikhailov [982] reports on the use of 890 nm laser treatment of autoimmune thyroiditis. 42 patients were given ten applications at 2.4 J/cm^2. The irradiated areas were the thymus projection zones (area of the sternum at a level of the second edge), vascular junction (left axillary area) and thyroid gland. A control group of similar size was given L-thyroxin, 100 mg/day. The clinical effect in all laser patients was a decreased feeling of squeezing in the field of the thyroid gland and a decrease of the facial oedema. The gland became softer palpatively and its size was reduced according to the ultrasound examination. The number of patients catching cold during the winter decreased. The immunoregulatory index (Th/Ts) normalised from 7.5 to 4.2%. The laser effect was still noticeable in 78% of the patients 4 months after treatment. This index was only slightly changed in the control group.

Peláez [484] showed that laser irradiation stimulated the growth and maturation of thyroidal endothelial cells in young mice, while in adult mice, it could cause thickening of the endothelium and reduction of capillary lumen.

The purpose of the study by Azevedo [1625] was to assess whether there were alterations in the thyroidal hormone plasma levels under infrared laser irradiation, in the thyroid gland region. Sixty-five albino male mice were used and assigned to five groups (n=13), with differences in the times that they were sacrificed. Irradiation procedures consisted of a diode laser emitting at 780 nm, at 4 J/cm^2, in contact mode, point manner. Blood was collected before irradiation (group 1), and then at 24 h (group 2), 48 h (group 3) and 72 h (group 4), and 1 week (group 5) after the third irradiation. The collected material was used for clinical analysis to evaluate the T3 (triiodothyronine) and T4 (thyroxin) hormones. Five animals were used for light microscopy analysis. A statistically significant hormonal level alteration between the first day and 7 days after the last irradiation was found. There were no morphological changes.

The aim of a study by Fronza [2408] was to assess the effects of LPT applied to a dental extraction socket on thyroid gland function in a rabbit model, based on serum triiodothyronine and thyroxine levels. Sixteen male rabbits were randomly distributed into two groups: a control group (non-irradiated animals) and an experimental group (irradiated animals: one irradiation point in the extraction socket of the lower incisor). Animals in the experimental group were irradiated with 830 nm, 40 mW, CW) for 13 days, every 48 h, at a dose of 6 J/cm^2 per session, resulting in a total dose of 42 J/cm^2. Serum triiodothyronine and thyroxine levels were measured in both groups before extraction and on the last day of observation (day 15). There *were no statistically significant differences between the groups in pre- and post-irradiation triiodothyronine and thyroxine values. With the irradiation protocol used in this study, LPT did not affect thyroid function in rabbits as assessed by circulating serum triiodothyronine and thyroxine levels.*

Chronic autoimmune thyroiditis (CAT) is the most common cause of acquired hypothyroidism, which requires lifelong levothyroxine replacement therapy. Currently, no effective therapy is available for CAT. Thus, the objective of a study by Höfling [1251] was to evaluate the efficacy of LPT in patients with CAT-induced hypothyroidism by testing thyroid function, thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and ultrasonographic echogenicity. A randomised, placebo-controlled trial with a 9-month follow-up was conducted from 2006 to 2009. Forty-three patients with a history of levothyroxine therapy for CAT-induced hypothyroidism were randomly assigned to receive either 10 sessions of LPT, 830 nm, 50 mW, fluence 707 J/cm^2*. (Laser group, n=23) or 10 sessions of a placebo treatment (Placebo group, n=20). The levothyroxine was suspended 30 days after the LPT or placebo procedures. Thyroid function was estimated by the levothyroxine dose required to achieve normal concentrations of T(3), T(4), free-T(4) (fT(4)), and thyrotropin after 9 months of postlevothyroxine withdrawal. Autoimmunity was assessed by measuring the TPOAb and TgAb levels. A quantitative computerised echogenicity analysis was performed pre- and 30 days postintervention. The results showed a significant difference in the mean levothyroxine dose required to treat the hypothyroidism between the L group (38.59±20.22 g/day) and the P group (106.88±22.90 g/day). Lower TPOAb and greater echogenicity were also noted in the L group. No TgAb difference was observed. These findings suggest that LPT was effective at improving thyroid function, promoting reduced TPOAb-mediated autoimmunity and increasing thyroid echogenicity in patients with CAT*

Further literature: [1214, 1663, 1664, 1665]

8.5 Children

Children - should they be treated with laser therapy? What about the growth plates?

Literature:

Renström [563] has successfully treated 30 children aged 11-15 for Morbus Schlatter. He treated their knees and lower legs with 60 mW, GaAs laser light at 30 Hz, pulse train modulated, and 0.1 J/cm^2*.*

Mb Schlatter has also successfully been treated by Paolini [945]. 15 young patients were given 30 sessions of GaAs laser therapy and the end result was compared to 15 patients who underwent conventional therapy, including surgery. The best results were obtained with laser therapy.

Ailioe [985] has used visible diode laser light for the treatment of the peripheral nerve system in newborns and infants.

Wollman [537] irradiated foetal brain cells in vitro using a HeNe laser. One single dose enhanced the appearance of brain cells around the treated aggregates. Two and three doses were correlated with 97% and 142% increases respectively. Rhodamine-labelled antibodies bound to receptors on cells indicated massive neurite sprouting and outgrowth of migrating brain cells in culture.

Cheetham [401] irradiated the healthy growth plates in young rats. One knee joint of each animal in the experimental group was irradiated three times a week at an energy density of 5 J/cm^2. The animals were examined histologically after 6 and 12 applications. There was no difference between the irradiated knee joints, the untreated contralateral knee joint or those in the sham-irradiated control group.

de Andreade [2176] writes: The longitudinal growth of long bones is attributed to epiphyseal growth. However, the effects of LPT in such structures has still not been studied extensively in the literature. Therefore, the aim of this study was to evaluate the use of LPT, 670 nm, at three different doses on the epiphyseal growth of the right tibia of rats. Twenty-one Wistar rats, aged four weeks, were subjected to the application of LPT, with dosage according to the group (G4: were submitted to the application of 4 J/cm^2; G8: were submitted to the application of 8 J/cm^2; G16: were submitted to the application of 16 J/cm^2). After completion of protocol they were kept until they were 14 weeks of age and then submitted to a radiological examination (evaluation of limb length) and euthanised. The histological analysis of the growth plates (total thickness and hypertrophic and proliferative zones) was then performed. Comparisons were made with the untreated left tibia. No differences were observed in any of the reviews (radiological and histological), when comparing the right sides (treated) to the left (untreated). It was concluded that the treatment with LPT within the parameters used caused changes neither in areas of the epiphyseal cartilage nor in the final length of limbs.

To determine the influence of LPT on femoral growth plate in rats, Oliveira [2177] used 30 rats, aged 40 days, and divided them into two groups, G1 and G2. In G1 the area of the distal growth plate of the right femur was irradiated at one point using 830 nm, 40 mW, energy density 10 J/cm^2. The irradiation was performed daily for a maximum of 21 days. The same procedure was done in G2, but the probe was turned off. Five animals in each group were euthanised on days 7, 14 and 21 and submitted to histomorphometric analysis. In both groups the growth plate was radiographically visible at all moments from both craniocaudal and mediolateral views. On the 21st day percentage of femoral longitudinal length was higher in G2 than G1 compared to basal value while hypertrophic zone chondrocyte numbers were higher in G1 than G2. Calcified cartilage zone was greater in G1 *than in G2 at all evaluation moments. Angiogenesis was higher in G1 than in G2 at 14th and 21st days.*

It is obvious that LPT dosage must be adapted to the weight of children but there is no indication in the literature suggesting that children, including neonatal babies, should not benefit from LPT.

8.6 Cancer

Cancer, or suspected cancer, should never be treated by anyone who is not a specialist. This is not because laser therapy would not have a stimulating effect but because the law, quite sensibly, does not allow anyone but an expert to treat cancer. As a palliative treatment in terminal patients, LPT could still be a very viable option for pain control and general stimulation. Treating the side effects of cancer treatment, such as radiation therapy, is on the other hand recommended [2115].

It has been speculated that the biostimulatory effect of LPT could cause undesirable enhancement of tumor growth in neoplastic diseases. The aim of the study by Frigo [2202] was to analyse the behavior of melanoma cells (B16F10) in vitro and the in vivo development of melanoma in mice after laser irradiation. The investigators performed a controlled in vitro study on B16F10 melanoma cells to investigate cell viability and cell cycle changes by the Tripan Blue, MTT and cell quest histogram tests at 24, 48 and 72 h post irradiation. Laser irradiation was performed three times (once a day for three consecutive days) with a 660 nm 50 mW CW laser, beam spot size 2 mm2, irradiance 2.5 W/cm^2 and irradiation times of 60s (dose 150 J/cm^2) and 420s (dose 1050 J/cm^2) respectively. There were no statistically significant differences between the in vitro groups, except for an increase in the hypodiploid melanoma cells at 72 h post-irradiation. This cancer-protective effect was not reproduced in the in vivo experiment where outcome measures for the 150 J/cm^2 dose group were not significantly different from controls. For the 1050 J/cm^2 dose group, there were significant increases in tumor volume, blood vessels and cell abnormalities compared to the other groups. LPT Irradiation should consequently be avoided over melanomas, as the combination of high irradiance (2.5 W/cm^2) and high dose (1050 J/cm^2) significantly increases melanoma tumor growth in vivo.

8.7 Haemophilia

Very little has been published on the issue of LPT for patients with haemophilia. It is known that LPT affects several rheological factors, but taking the scant knowledge into account, it is safe not to treat such patients, unless under medical supervision. For the time being, this is rather a caveat than a contraindication.

Literature:

The use of pulsed ultrasound (PUS) and LPT in patients with haemophilia has been recommended for supportive treatment of acute and chronic phases of haemarthrosis but its role has not been supported by experimental evidence. The purpose of the study by Ravanbod [2404] was to evaluate the effect of these modalities on joint swelling, friction and biomechanical parameters of articular cartilage. An experimental rabbit knee haemarthrosis model was used to test the hypothesis that LPT and PUS favourably impacted on the biotribological and biomechanical properties of cartilage after joint bleeding. To test this, 35 male albino rabbits weighing 1.5-2 kg were used. The left knee of 30 rabbits was injected with 1 mL of fresh autologous blood two times per week for four consecutive weeks to simulate recurrent haemarthrosis; five rabbits served as non-bleeding controls. Ten rabbits were treated with PUS and 10 with LPT and the remaining 10 were not treated. The treatments were started after 2 days and the treatment duration was planned for 5 days (sessions) in ultrasound and laser groups. A 810 nm laser, 25 mW, 1 J/cm^2 dosage for 200 s duration (5 J). The PUS treatment was applied with a duty cycle of 1/9, frequency of 1 MHz, and power of 0.4 W/cm^2 for 150 s. Joint perimeter was measured before the procedure at the beginning of therapies and after cessation of the procedure. Friction and biomechanical parameters were measured immediately after the killing of the animals. The results demonstrate that PUS was more effective in reducing knee joint swelling than LPT. Moreover, PUS had the unique ability of reducing the joint friction below normal values. However, it was not successful in returning the articular cartilage force and stiffness to normal state. LPT was more effective in increasing equilibrium force of the articular cartilage than PUS. However, neither therapy normalized this parameter. From these data, we conclude that PUS is more effective than LPT in reducing joint swelling and articular joint friction after experimental haemarthrosis, using the parameters of this study.

With 5 J per point, the dosage calculation seems unlikely.

8.8 Irradiation of the brain

Based on the findings by Ilic, below, it seems safe to irradiate in brain areas. When it comes to use the brain as the actual target of LPT, much remains to be explored. However, the effects on stroke are encouraging. Whether or not the intellectual capacity can be stimulated by laser irradiation is not documented, but is a fascinating field for investigations. In the meantime, it is prudent to stick to whatever brain capacity you have. What can be postulated is that brain damage will not occur when areas over the skull are being treated, for one reason or the other, but actually targeting the brain is so far not recommended due to insufficient documentation.

Literature:

In a study by Lapchak [1427] the rabbit small clot embolic stroke model (RSCEM) was used to assess whether laser treatment (7.5 or 25 mW/cm²) altered clinical rating scores (behaviour) when given to rabbits beginning 1 to 24 hours post embolisation. Behavioural analysis was conducted from 24 hours to 21 days after embolisation, allowing for the determination of the effective stroke dose (P50) or clot amount (mg) that produces neurological deficits in 50% of the rabbits. Using the RSCEM, a treatment is considered beneficial if it significantly increases the P50 compared with the control group. In the present study, the P50 value for controls were 0.97+/-0.19 mg to 1.10+/-0.17 mg; this was increased by 100% to 195% if laser treatment was initiated up to 6 hours, but not 24 hours post embolisation (P50=1.23+/-0.15 mg). Laser treatment also produced a durable effect that was measurable 21 days after embolisation. Laser treatment (25 mW/cm²) did not affect the physiological variables that were measured. This study shows that laser treatment improved behavioural performance if initiated within 6 hours of an embolic stroke and that the effect of laser treatment is durable.

The aim of the study by Ilic [1590] was to investigate the possible short- and long-term adverse neurological effects of LPT given at different power densities, frequencies and modalities on the intact rat brain. In a previous study on the effect of laser therapy for stroke in a rat model [1589], an optimal dose had been confirmed and now served as baseline dose 118 rats were used in the study. Diode laser (808 nm, wavelength) was used to deliver doses of 7.5, 75, 750 mW/cm² transcranially to the brain cortex of mature rats, in either continuous (CW) or pulse (Pu) modes. Multiple doses of 7.5 mW/cm² were also applied. Standard neurological examination of the rats was performed during the follow up periods post laser irradiation. Histology was performed at the light and electron microscopy levels. Both the scores from standard neurological tests and the histopathological examination indicated that there was no long-term difference between laser-treated and control groups up to 70 days post treatment. The only rats showing an adverse neurological effect were those in the 750mW/cm² (about 100-fold optimal dose), CW mode group. In Pu mode there was much less, heating and no tissue damage was noted. Long-term safety tests lasting 30 and 70 days at optimal 10x and 100X doses, as well as multiple doses at the same power densities, indicate that the tested laser energy doses are safe under this treatment regime. Neurological deficits and histopathological damage to 750 mW/cm² CW laser irradiation are attributed to thermal damage and not due to tissue-photon interactions.

In order to elucidate the metabolic modifications induced in rat brain by low power He-Ne laser irradiation in vivo, the variations in the biogenic amine levels in cortex, striatum and hippocampus were studied. Noradrenaline (NA), dopamine (DA) and serotonin (5-HT) Cassone [846] evaluated by HPLC-EC on irradiated rats, untreated rats (controls) and rats which had *undergone restraint stress (stressed). The results obtained on groups of four to eight rats assayed individually showed that irradiation caused a strong increase in 5-HT in striatum and hippocampus, a small but significant decrease in NA in cortex, and DA levels were not significantly affected. Restraint stress per se led to a considerable decrease in 5-HT and DA in striatum and hippocampus, but did not significantly alter the NA levels.*

Huang [2153] reviewed the use of transcranial LPT as a possible treatment for traumatic-brain injury (TBI). The author writes: The basic mechanisms of LPT at the cellular and molecular level and its effects on the brain are outlined. Many interacting processes may contribute to the beneficial effects in TBI including neuroprotection, reduction of inflammation and stimulation of neurogenesis. Animal studies and clinical trials of transcranial-LPT for ischemic stroke are summarised. Several laboratories have shown that LPT is effective in increasing neurological performance and memory and learning in mouse models of TBI. There have been case report papers that show beneficial effects of transcranial-LPT in a total of three patients with chronic TBI. Our laboratory has conducted three studies on LPT and TBI in mice. One looked at pulsed-vs-continuous wave laser-irradiation and found 10 Hz to be superior. The second looked at four different laser-wavelengths (660, 730, 810, and 980 nm); only 660 and 810 nm were effective. The last looked at different treatment repetition regimens (1, 3 and 14-daily laser-treatments)

The conclusion in a literature review by Demirtas-Tatlidede [2405] is: Different forms of non-invasive brain stimulation techniques harbour the promise of diagnostic and therapeutic utility, particularly to guide processes of cortical reorganization and enable functional restoration in traumatic brain injury (TBI). Future lines of safety research and well-designed clinical trials in TBI are warranted to determine the capability of NBS to promote recovery and minimize disability. .

Further reading: Irradiation of the brain, Chapter 4.

Further literature: [502, 1427, 1589, 1756, 1807, 1872, 1928]

8.9 Radiation therapy patients

Radiation therapy patients have been considered as contra-indicative for laser therapy. This is not entirely self-evident, in that the radiation they are subjected to has different characteristics from LPT. There are studies showing that laboratory animals receiving X-ray radiation made better progress if they received laser therapy first [147]. There are several studies in which effects on the immune system have been demonstrated. These effects have primarily been local. More and more studies are being published concerning laser treatment of circulating blood [180]. Changes in the components of the blood relating to the immune defence following laser treatment could obviously lead to effects in many other parts of the body, such as an improved defence against cancer. In fact, LPT appears to have a radioprotective effect on tissue, described by McGuff [1856] already in 1966 and confirmed by i.e. da Cunha [1812] 40 years later.

Literature:

Irradiation of a tumour with a low-level laser enhances the effect of chemotherapy. Tamachi [44], has studied the uptake of the cytotoxin 5FU in various experiments using rats. Laboratory rats that received 6 J/cm^2 of HeNe showed a greater uptake of 5FU than those who were given 5FU only. The irradiation causes blood vessels to dilate, allowing greater amounts of the anticancer drug to accumulate in the lesion. Hence laser therapy can minimise the required dose of the anticancer drug used.

Podolskaya [366] has used a HeNe laser on post-radiation reactions and injuries in lip skin and mucous membranes. The method has been more successful than previous medical treatments.

Kolomiyets [367] treated patients with precancerous changes in the gastric mucosa with a HeNe laser. Positive clinical and morphological effects were noted in 65% of the patients.

Soldo [371] studied the effect of GaAs laser radiation on murine sarcoma and found it to be anti-tumour on small tumours, probably due not to a direct effect on the tumour itself but rather to changes in the tumour-host relationship such as the immune defence.

Schaffer [468] irradiated mouse fibroblasts and human tumour cells with 805 nm laser. Both tissues received either 4 or 20 J/cm^2. With 4 J, an increase of mitotic activity in the healthy mouse cells could be registered, while at 20 J there was a slight decrease. The tumour cells were not stimulated by 4 J. 20 J, on the other hand, decreased the mitotic rate.

Funk [565] has investigated cytokine production following HeNe laser irradiation in cultures of human peripheral blood mononuclear cells. Cultured cells were irradiated for various periods at two selected intensities and then stimulated with various mitogens. When stimulating cells after irradiation, significantly increased levels (biostimulatory effect) of all cytokines were detected after 30 minutes of irradiation (18.9 J/cm^2), whereas after 60 min of irradiation (37.8 J/cm), cytokine levels were found to be significantly decreased (bioinhibiting effect).

Mucositis (painful mucosal wounds in the oral and pharyngeal mucosa) is an effect of radiation therapy for head and neck cancer patients. It has been shown that red laser can not only reduce this severe side effect but also prevent it if irradiation is given before radiation therapy. (See chapter 4.1.11 "Cancer" on page 224.)

Further literature: [1034]

8.10 Diabetes

Diabetes has been suggested as a contra indication. However, we have not found any evidence that laser therapy could aggravate symptoms. Laser treatment increases blood flow and is effective in wound healing. Laser therapy should therefore, on the contrary, be recommended as an additional treatment modality, e.g. for diabetic foot problems, according to Kleinman [477].

Since the experimental model of using healthy rats for wound healing studies has been questioned, rats with genetic diabetes have been suggested as a better model. Wound healing studies using this model [986, 1275, 1423, 1455, 1755, 1863, 1877, 1887] are promising, as well as diabetic wounded cells [1864, 1871, 1927, 1926, 1927]. Far from being a contra-indication, LPT to handle the circulatory side effects in diabetics appears to be a very good indication!

Literature:

An experiment by Radelli [470] on rats, using 904 nm GaAs laser, did not confirm any influence on the insulin-glycemic balance.

In a thermographic study by Schindl [478] carried out on patients with microanginopathic disorders, the improvement of blood flow started 15 minutes after the onset of laser irradiation and persisted up to 45 min after stopping the irradiation. A maximal temperature rise of 2.5° C was measured.

Kotani [501] compared the wound-healing rate in three groups of rats: 1. normal rats, 2. rats with experimentally induced diabetes mellitus, and 3. rats treated with doxorubicin. Doxorubicin inhibits the proliferation of fibroblasts and is used as an anti-cancer agent in medicine. 5.4 J/cm^2 of HeNe laser light was applied daily. In the diabetic group, irradiated wounds healed faster than non-irradiated. In the low dose doxorubicin group, healing was comparable to the non-irradiated control. In the group of healthy animals, irradiated wounds healed slightly faster but not statistically better than control. This again illustrates the importance of the condition of the tissue - healthy individuals will not improve greatly from laser therapy.

For further reading: (See chapter 4.1.18 “Diabetes” on page 254.)

8.11 Tatoos

Tatoos contain different pigments and even fairly low energies of laser light will be absorbed in these pigments. Depending on the type of pigment, a patient may experience heating or even pain when a therapeutic laser is used over a tattoed area. It is therefore prudent to start irradiation from a distance, then approaching the skin surface until the patient feedback decides to power density. Tatoos do not constitute a contraindication, but high intensities over tatoos will cause high absorption and may bring out a pain reaction.

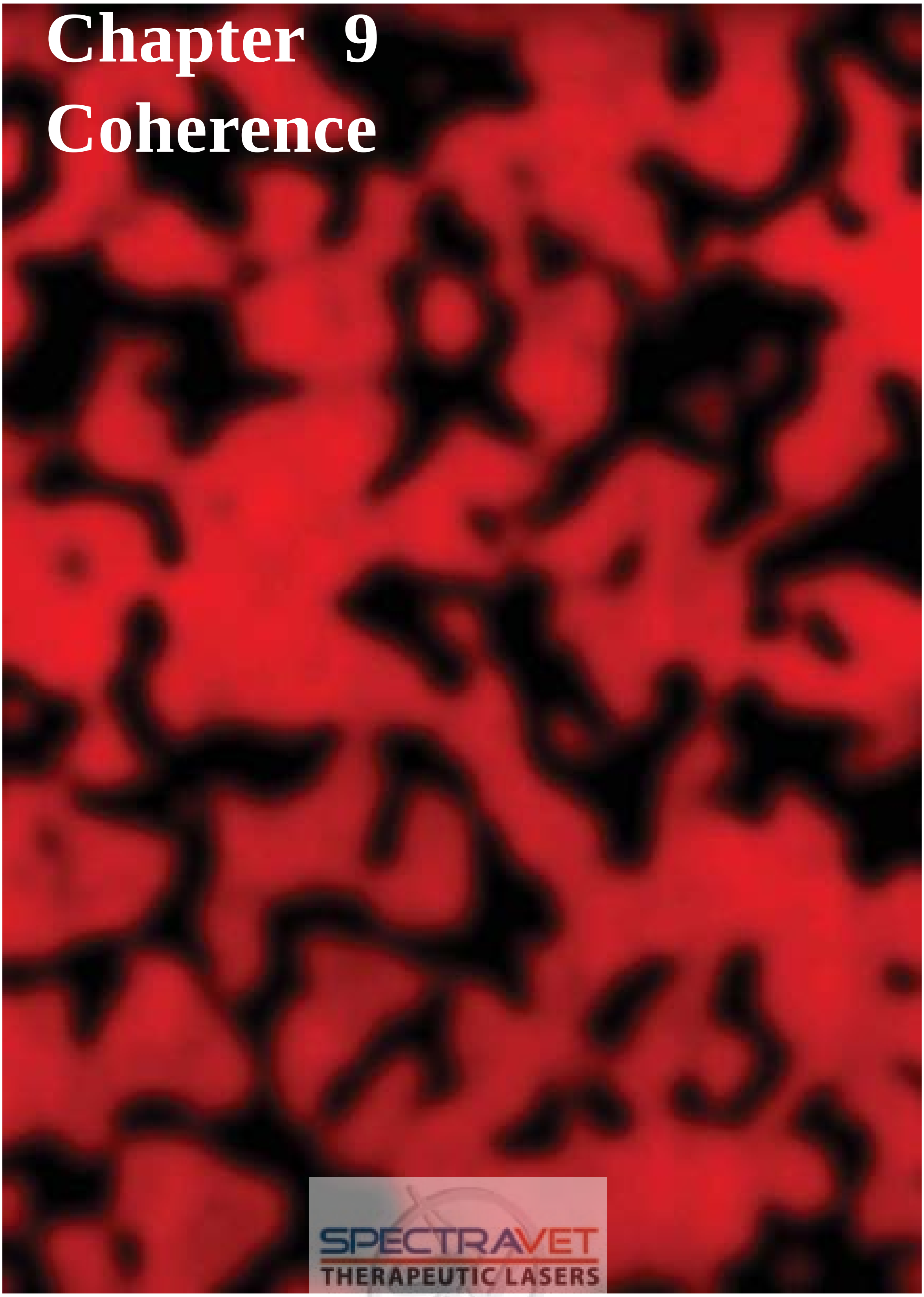
8.12 Light sensitivity

Light sensitivity is often listed as a contra indication for LPT. Looking through the literature, however, little is found to support this suggestion. A scan through PubMed gives no hints to a connection between LPT and photosensitisation. Rather, there are papers showing that LPT prior to radiation therapy has a preventive effect. The ultraviolet light, on the other hand, can cause photosensitivity [2152]. Up till now, this alleged contraindication has to be confirmed.

In the 2009 guidelines from the BMLA, the use of non-essential aesthetic lasers was contraindicated in patients receiving medication that causes whole-body photosensitisation as well as those causing local light sensitisation. Following this and anecdotal advice, many laser centres refuse to treat patients who are on known photosensitive medication. Therefore, specific patient cohorts that would benefit from laser therapy are being denied because of medications, such as long-term antibiotics for chronic facial acne. An article by Karstein [2523] reviews the published literature on lasers and photosensitive medications, the mechanisms of photosensitivity and the role of laser in its production. The aim is to analyse the available evidence regarding adverse reactions to laser treatment related to photosensitive medication. A PubMed review of published article titles and abstracts was performed using the search term Laser with each of the following terms individually: photosensitive, photosensitiser, photosensitizer, phototoxicity, photoallergy, complications, case-report, tetracycline, minocycline, amiodarone, nitrofurantoin and medication. Four publications were identified, none of which reported any complication in the use of laser in patients taking photosensitising medication. As there are no published accounts of adverse effects of laser in patients with photosensitive medication, we performed a review of the mechanism of photosensitivity by compiling a list of photosensitive medication and the peak wavelength of radiation required to activate the drug.

There are no absolute contraindications for LPT, only relative ones and caveats. As can be seen from the above, some alleged contraindications are pure nonsense; others are rather caveats due to legal implications - which are often based upon the nonsense! But it pays to be on the safe side and to be careful with epileptics and pregnant women, unless you are performing research. Another caveat is patients with *hereditary coagulation disorders*, because we still do not know how LPT affects the coagulation mechanisms, only that it does.

Chapter 9
Coherence



9.1 The role of coherence in laser phototherapy

By Tomas Hode, PhD

9.1.1 Introduction

The importance of coherence and laser speckles in LPT has been discussed over the last 30 years. Coherence [1] is often defined as a property of wave-like states that enables it to exhibit interference. In the case of light, this interference gives rise to laser speckles. This speckle field contains areas/ volumes of higher and lower intensity (Fig. 1). A speckle pattern can be subjective or objective: If visible laser light illuminates a wall paper or some other rough surface, the viewer will see laser speckles in the image plane [2]. If either the viewer or the illuminated target moves, the speckles will also change, and the direction of the perceived changes depends on the viewer's eyes. This is called a subjective speckle pattern, since the details of the pattern depends on the parameters of the viewing system (for example the shape of the eye). An objective speckle pattern is independent of the parameters of the viewing system, and can be imaged by using, for example, a photographic plate or optical sensor without an objective.

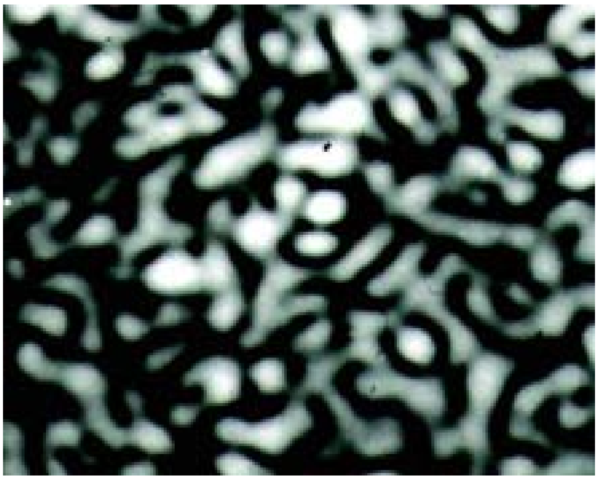


Figure 9.1 A b/w photograph of a speckle intensity pattern. Note that the areas of higher intensity represent constructive interference, and dark areas represent destructive interference. The average speckle size is in the order of a few micrometers. Photo by L. Hode.

It is well known that if a volume is filled with scattered laser light, a three-dimensional speckle pattern is formed in the volume of tissue that is reached by the scattered coherent light. It is also known that the coherence length decreases as a function of depth in the tissue, and that fluid movement within the tissue causes the speckle pattern to change with time. Historically, such speckles have been considered optical noise since they may interfere with various types of experiments. However, speckles can also be useful in various types of experiments. By analysing the movement of speckles on a surface illuminated by laser, it is possible to describe the movement within the tissue non-invasively. This has, for example, been applied when analysing surface deformation in real time using laser speckles [3]. Other practical uses of laser speckles are monitoring of velocity or flow fields, such as retinal blood-flow visualisation by means of speckle photography [4], and transmissive laser speckle imaging (Transmissive LSI), which is proposed as a diagnostic for rheumatoid arthritis [5].

Occasionally, however, it is purported that the coherence is lost as soon as the laser light enters the tissue, and that coherence therefore cannot have any therapeutic significance in phototherapy. Furthermore, it has become commonplace for manufacturers of non-laser light therapy devices to paraphrase as "light is light" the conclusions drawn in articles by Smith [6, 7], commented by Hode [8], and Enwemeka [9, 10]. The basic premise of the arguments was that the principal mechanism of phototherapy is photon absorption, and that it makes no difference [in the fundamental photochemical process] whether the light is coherent or not [11]. These arguments have been supported by in vitro studies [12, 13] as well as in vivo studies on wound healing [14] and other superficial indications [15] that seemingly indicate that LED phototherapy is as effective as laser phototherapy. On the other hand, several comparative studies have shown that laser phototherapy appears to be more effective than LED phototherapy in the treatment of deeper indications [16, 17], as well as in in vitro [18] and wound healing studies [19].

The question is important. If lasers are not needed to acquire an optimised therapeutic effect, then light emitting diodes or halogen lamps with band pass filters could just as well be used with a lower expense for the practitioner. Specifically, there are two main issues that need to be addressed: First, to what extent is coherence of laser light preserved when it penetrates skin and is diffusely scattered in tissue, and second, what is the significance of laser speckles in tissue (if any)?

Question 1: Is coherence lost in tissue?

First of all, it is important to clarify that coherence is not lost in a scattering media (such as tissue), only reduced. The fact that coherence is not lost upon the light entering the tissue can be demonstrated by a simple experiment [20], first demonstrated by L. Hode at The Ninth Congress of the International Society for Laser Surgery and Medicine in Los Angeles in 1991 in response to claims that coherence is entirely lost upon being diffusely spread in tissue [21, 22, 23]. This experiment is described elsewhere in this book, but for readers' convince, we summarise it here:

Anyone owning a red laser (for example a HeNe laser) can observe that coherence is not lost by conducting this simple experiment:

1) Press fresh ground beef, e.g. raw hamburger meat, between two glass plates so that a 5 - 10 mm thick slab of ground beef is formed.

2) Aim the light from a 5 - 10 mW red laser at the glass plates with the ground beef slab as shown in Figure 2. A red spot on the back of the minced beef will appear where the light has penetrated.

3) Place a small flashlight beside the laser so that the front end is pressed against the surface of the glass. The flashlight emits normal white light. This light also penetrates the ground beef and forms a light spot beside the one caused by the laser. The spot from the flashlight will also be red (red light is less absorbed than the other visible wavelengths).

4) Study both the red light-spots on the back of the slab from a distance of a few meters. The laser light-spot shows clear laser speckles, whereas the spot from the flashlight has no laser speckles. It is thus evident that coherence is not lost as the laser light penetrates the meat.

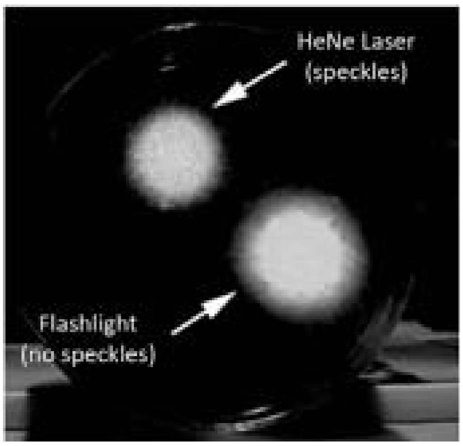


Figure 9.2 Light spots on the back side of a slab of minced meat through which the light from a HeNe laser and a flashlight has penetrated. The upper left spot originates from the HeNe laser, and the lower right spot originates from the flashlight. Both spots are red after their passage through the meat, which shows that red light has the best penetration of the visible light wavelengths. Infrared radiation penetrates even better. The figure shows that coherence of the laser light is not lost as the light penetrates the meat. The laser speckles can be clearly seen, and it is obvious that there is a difference between laser light and the light from a flashlight.

There is a common misconception that coherence is reduced or eliminated by fluid movement, which is based on the fact that speckles apparently cannot be seen with the naked eye when a laser shines through a finger, or on experiments that appear to demonstrate that speckle contrast is reduced or lost with fluid (e.g. blood) movement in the tissue. In fact, the speckle pattern is fully present in the tissue at any given moment, but it changes with the perturbations in the tissue. Faster movement in the tissue, such as blood in circulation and interstitial fluid flows, causes the speckle pattern to change configuration quicker. An example of such changes in the configuration of the speckle pattern can be found here: http://www.laser.nu/speckl.MOV. This is a film that was captured after shining laser light through a slab of ground meet, where the changes of the speckle pattern is caused by slight movements (fluids, cells, etc.) in the slab of meat. It is evident that the speckle patter is shifting over time, although this is not as fast as in a medium with, for example, blood perfusion, such as living tissue, where the movement is quite rapid compared to the slab of ground beef.

This phenomenon is well known and is in fact frequently used in various settings. For example, laser speckles can be used to quantify blood perfusion in highly scattering media: the lower the speckle contrast, the higher the blood flow velocity, essentially capturing the time-integrated speckle pattern at a fixed exposure time. In other words, since the speckle pattern changes during the time of exposure, a time integration will occur, and the faster the speckle pattern changes, the lower the speckle contrast will be for the same exposure time [24].

Surprisingly, it has been stated that this reduction in (apparent) speckle contrast indicates that the coherence of the light decreases with, for example, increased blood velocity (such as in living tissue). This is a misinterpretation of what the actual results of such experiments show. If an image is taken with a short enough exposure time, the speckle pattern will be quite clear. This also explains why a speckle pattern is not visually perceived when a laser shines through (for example) a finger: The reason is not because the coherence is lost due to the blood flow, but because the speckle pattern moves so fast that we are not able to register it.

The question, then, is how fast a movement of the speckle field is too fast to induce biological effects? Li and Champion [25] investigated the vibrational excitation and relaxation of laser-excited chromophores, and found, among other things, that 1) the average photoexcitation rate under photostationary conditions (for a 420 nm laser with average power of 15 mW/cm^2, giving a photon flux of ~1027 photons/sec and cm^2, an photon absorption cross section of 4×1016 cm^2 for the heme chromophore) corresponded to a photon absorption event every 8-9 ps, 2) that thermal saturation of both the chromophore and the protein occurred after ~100 ps, and 3) that the relaxation times for a chromophore-protein-solvent system were on the order of 10 ns once the influx of photons stopped. Since the lifetime of an individual speckle is on the order of a few ms when living tissue is illuminated with a laser, the speckle lifetime is clearly longer (nine orders of magnitude) than reaction times in photo-excitation events.

Having demonstrated that speckle patterns indeed occur when living tissue is illuminated with a laser, and that the lifetime of individual speckles is much longer than the reaction times in photo excitation events, the question then is why the presence of laser speckles in tissue would have a different or improved biological (therapeutic) impact than uniformly distributed (non-coherent) light?

Question 2: What is the significance of laser speckles in tissue (if any)?

Intensity thresholds

Several studies indicate that the effects of phototherapy depend not only on energy density [8, 26 and references therein], exposure time [27], and wavelength [26], but also on intensity [26, 28, 29].

The intensity thresholds have been shown to be in the order of 5-15 mW/cm^2 for monochromatic light sources and the biological responses either below or above these intensities appear to be limited. The exact reason as to why such intensity thresholds exist in phototherapy is not well investigated.

The thresholds can be viewed as the minimum rate (flux) at which photons need to be absorbed by the target molecules to reach a certain photobiological effect. The photon absorption rate depends on photon density (intensity) and absorption cross section of the target molecule. The photon absorption cross section, in turn, mainly depends on the wavelength, redox state, polarisation, and to some extent the temperature of the chromophore.

Hode et al. [30] performed a Monte Carlo simulation on the speckle intensity distribution in a scattering media (such as tissue), and found that intensities of up to 5 x mean can be expected in tissue (Figure 3). As a consequence, volumes of higher intensities will occur in the tissue at greater depths in the tissue than the average intensity otherwise would allow, thus increasing the effective depth of penetration of a laser as compared to a non-coherent light source with otherwise the same parameters (wavelength, power, etc.).

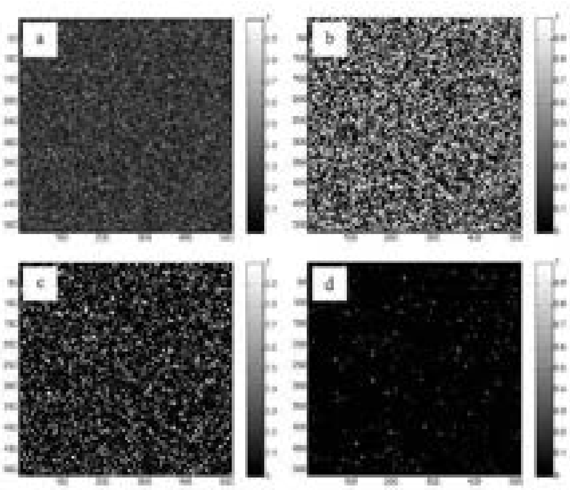


Figure 9.3 Simulation of intensity distribution of a speckle field in a highly scattering media (such as tissue). a) Polarised speckle pattern (see also fig. 2 below) with exponential intensity statistics. b) Regions with intensity greater than mean. c) Regions with intensity greater than 2 x mean. d) Regions with intensity greater than 5 x mean.

Polarisation

It is not only the intensity that differs between coherent and non-coherent light penetrating into tissue. The laser speckles so formed also differ from non-coherent light of the same intensity - it is locally polarised, or, at least, partially polarised. Speckles are a result of interference and interference only occurs if the interfering light is co-polarised and has some degree of coherence. If the E-fields contributing to the intensity at a single point are not aligned, there will be no constructive or destructive interference, i.e., no speckle. The laser speckles are formed also if the penetrating light from the illuminating laser is not polarised.

The simulations by Hode et al. [30] explored the statistics of the superposition of two orthogonally polarised statistically independent speckle patterns, specifically with regard to the degree of polarisation. The simulation showed that the degree of polarisation has a complex spatial distribution that looks somewhat like a speckle pattern, and the first order statistics are uniform. The results of the simulations suggest that even though an incident polarised beam becomes depolarised by the time it reaches a few transport mean-free paths as it penetrates the tissue, there still remains a complex spatial distribution of polarised light deep within the tissue (Fig. 4).

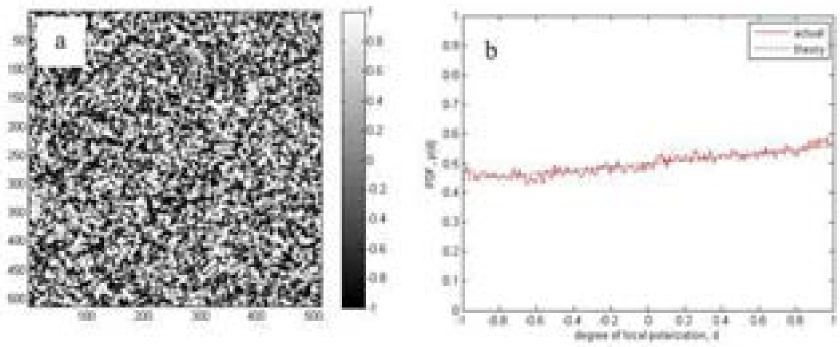


Figure 9.4 Simulation of degree of polarisation in a speckle field. a) Complex spatial distribution of the degree of polarisation somewhat similar to a speckle pattern. b) Distribution of the theoretical vs. actual degree of polarisation.

Interestingly, there is a polarisation dependence for the chromophore photon absorption cross section. Tolkachev [31] compared chromophore excitation in non-polarised vs. polarised light, and concluded that the maximum excitation occurs when the polarisation vector is parallel to the direction of the dipole moment of the chromophore (or close to it). Tolkachev [31] concluded that on an orientationally stable, fixed individual chromophore the excitation effect is two times larger than the effect of non-polarised light. In other words, the probability for photon absorption (cross section) is polarisation-dependent and up to two times as high if the direction of the polarised light is aligned with the dipole moment of the molecule.

Combining the effects of the intensity distribution and polarisation patterns in tissue, it can be concluded that the rate of photon absorption may increase with up to an order of magnitude compared to non-coherent light sources. In tissue, where the light absorption is high, these effects have a significant impact on the effective penetration depth. In a clinical setting, this increased effective depth of penetration can make the difference between having to rely on systemic effects vs. getting direct effects in the target tissue.

Superpulsing

Another factor that is typical for lasers, rather than LEDs and other non-coherent sources, is the ability to produce pulses with very high peak power. By so-called super-pulsing it is possible to simultaneously have high momentary photon density and low average power, thus giving low thermal influence. A continuous source for the same photon density would create a high temperature. A typical super-pulsed laser is the GaAs type laser (904 nm) with pulse lengths around 100-200 ns and peak powers up to 25-100 watts (Fig. 5). As a consequence of the high peak powers, the intensity in the tissue increases with an additional 1-2 orders of magnitude.

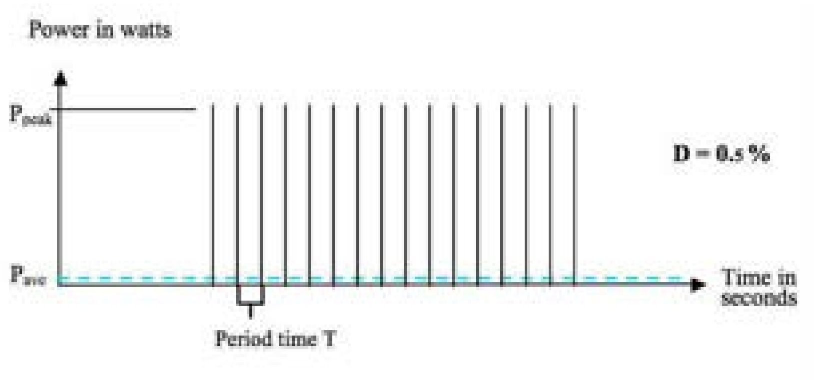


Figure 9.5 Diagramme of a super-pulsed GaAs laser pulse profile. Typical pulse widths range between 100-200 ns, with peak powers of up to 100 W. The average output power is significantly lower and generally range between 5 and 100 mW.

Biostimulating effects have also been noticed from skin treatment by means of IPL instruments. IPL instruments are wide band flash light devices, usually used for hair removal. The pulses from said devices are usually of rather high power (pulse energies of sometimes up to 100 joules over a surface of typically 3 cm^2 i.e. an energy density of >30 J/cm^2) and with typical pulse lengths of 3-5 ms. In the case of broad band light sources higher power densities (150-300 mW/cm^2) and energy densities (20-30 J/cm^2) are required [28], possibly because the relative intensity of the portion of the spectrum that is absorbed by the target molecules needs to be high enough to reach the 5-15 mW/cm^2threshold.

Dynamic environment
As previously discussed, a speckle field in tissue will change continuously due to e.g. blood flow. In an arbitrary point, the optical field will vary in intensity, temperature, degree of polarisation and direction of the Stokes vector in a random way, which may have clinical significance. For example, Horvath and Donko [32] measured the intensity differences in a speckle field, and concluded that although the actual temperature differences are low (in the order of micro-degrees), the thermal micro-gradients are very steep, which has the effect of increasing the rate of diffusion in accordance with Fick's equations. Furthermore, Rubinov [33] showed in a series of experiments that illumination of biological tissue by coherent laser light "unavoidably leads to strong intensity gradients of the radiation in the tissue due to speckle formation". This causes the appearance of inter- and intracellular

gradient forces whose action may significantly influence the paths and speeds of biological processes. In contrast to the photochemical action of light, which is accompanied by absorption of quanta and has a specific character (i.e. is characterised by a specific spectrum of action), the action of the gradient field is of non-resonant type. It is not accompanied by photon absorption and has a universal character - it depends weakly on the radiation wavelength, but requires a high degree of coherence". These effects will not take place with illumination by incoherent monochromatic light of the same intensity.

Length of coherence
A HeNe laser (a gas laser) can have a coherence length of several metres, whereas a diode laser of the same wavelength has a considerably shorter length of coherence. When treating in tissue contact, this would appear to have little importance. However, a study by Qadri et al. [34] showed that the results were in favour of the HeNe laser when compared to a diode laser of the same power and dose. HeNe lasers are no longer very common, but it is reasonable to believe that the energies quoted in HeNe studies should at least be increased by 100% if a diode laser of the same wavelength interval is to be used.

Summary

Coherence is a unique property of laser light, and it gives rise to a speckle field when an object is illuminated. It can easily be demonstrated that coherence is not lost in scattering media, such as tissue, which means that a three-dimensional speckle field will occur inside the tissue when illuminated by a laser. Furthermore, studies indicate intensities of up to five times the mean intensity occur in a speckle field. Together with the fact that polarisation patterns occur in speckle fields (independent of whether the light was originally polarised), and that the photon absorption cross section is polarisation dependent and up to two times more effective if the polarisation vector is aligned with the dipole moment of the target photoreceptor molecule, the rate of photon absorption can locally be up to an order of magnitude higher if a coherent light-source is used instead of a non-coherent light-source. Because of these intensity and polarisation distributions, the speckle pattern has a significant impact on the effective penetration depth of in vivo laser phototherapy (Fig. 6), since it becomes easier to reach the required intensity thresholds.

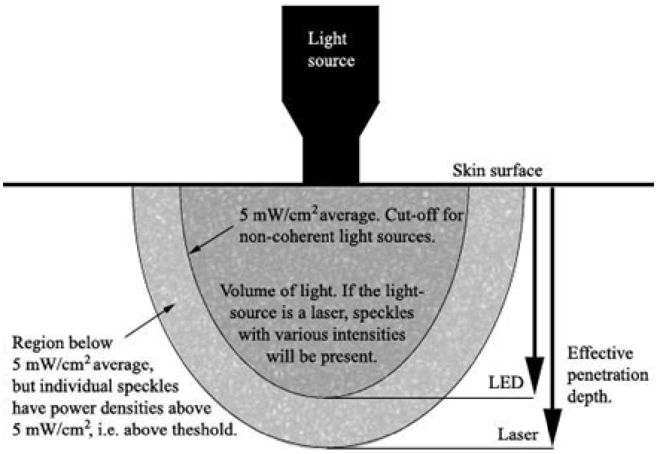


Figure 9.6 Illustration of the difference in effective penetration between coherent and non-coherent light-sources. For any given power density threshold (for example 5 mW/cm^2) there will be a depth at which the average intensity will be lower than the required power density for phototherapeutic effects to take place. However, in the case of coherent light (where a speckle field is present), there will be individual speckles with intensities of up to 5× the average intensity, which means that tissue situated deeper than the average power density threshold cut-off will be exposed to power densities above the phototherapeutic threshold. In other words, the effective penetration depth of coherent light-sources (i.e. lasers) is greater than for non-coherent light-sources (e.g. LED's).

Also, if a super-pulsed laser is used (e.g. GaAs laser, with peak powers between 5 and 100 W), intensities of additional 1-2 orders of magnitude will occur in the tissue. These observations are important for the clinical application of phototherapy. In deep tissue the intensity is lost to such an extent (as the light passes the tissue above) that it becomes hard to reach the necessary intensity thresholds of 5-15 mW/cm^2 [26, 28, 29]. With coherent light sources, and super-pulsed lasers in particular, the photon absorption rate is increased by up to 2-3 orders of magnitude, which translated into a clinical setting means an increased effective penetration depth of an additional 2-3 cm compared to non-coherent light sources.

These observations could also explain why LED phototherapy in many cases appears to be comparable to laser phototherapy for superficial indications such as wound healing [14], but not as effective as laser phototherapy in cases of deeper-seated indications [16, 17]. In LED phototherapy of superficial tissue (e.g. wounds, in vitro, etc.) the intensity-loss is not so much of a factor, and as a consequence it becomes easier to reach the required intensity thresholds than it is to reach the given thresholds in deep tissue. But a chronic wound is not only what meets the eye; large areas around the visible wound are affected by inflammatory processes and poor microcirculation. For these areas the laser seems to have advantages.

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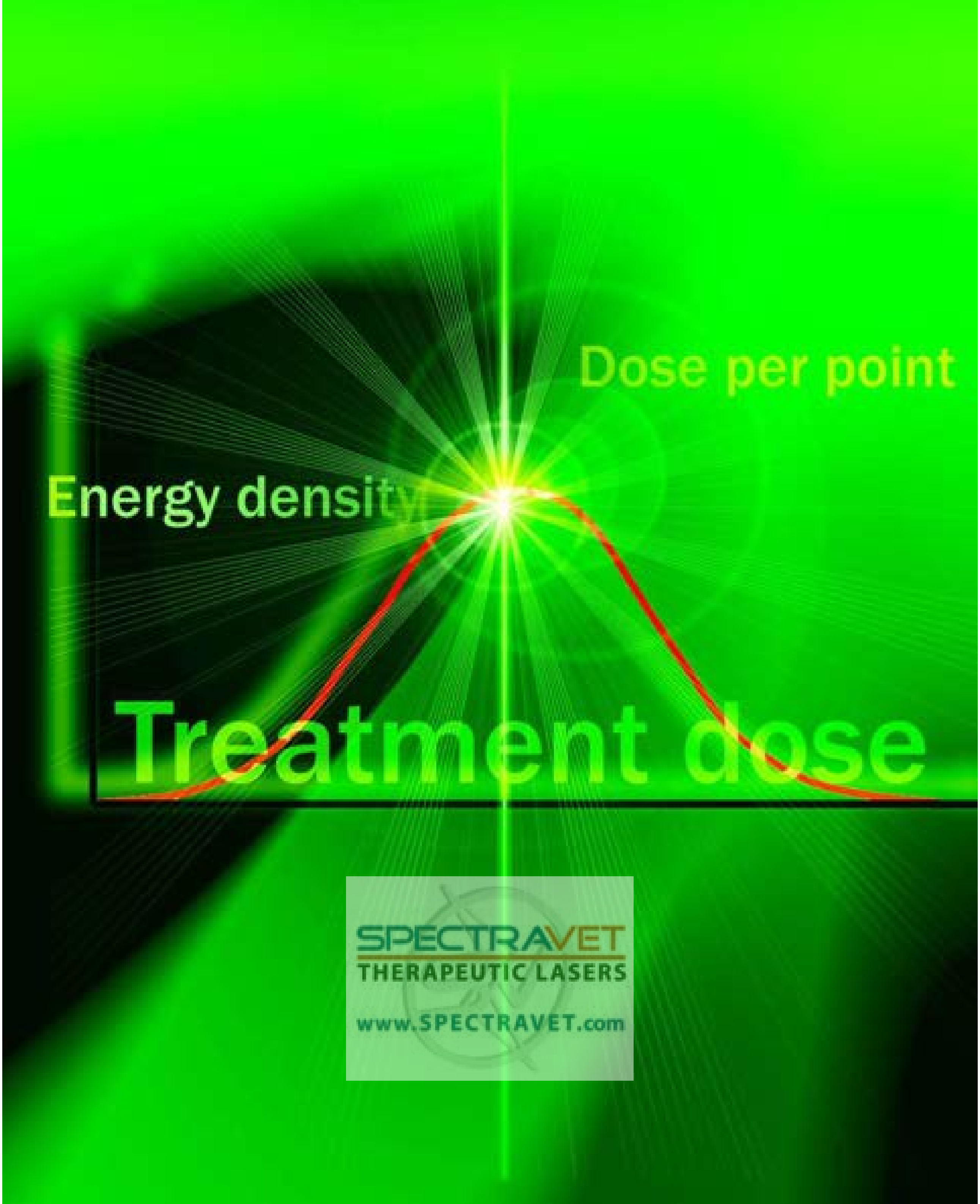
Chapter 10 - The difficult dose and intensity



We have previously pointed out that this book is not intended to be a tutorial in physics. However, we want to clarify some definitions in order to better understand the problems of dose and power density.

10.1 Basics about energy

For many people, the word energy means something else than it does for a physicist. A healer may say that he transfers “energy” to the patient. But that “energy” cannot be measured in the scientific sense. In this book, we will stick strictly to the form of energy that can be measured in joules (J). One of our most fundamental laws, valid in the entire universe, is the so called “principle of energy”. This law says:

Energy can never be created and never be destroyed.

Energy can occur in many forms. It was traditionally synonymous with “work”. Climbing up a hill takes a lot of work/energy. If my body weights 75 kg and I transport it from one level and up to a level 10 meters higher, I have performed an amount of work and increased my ***potential energy*** by

$$75 \text{ kg} \times 10 \text{ m} \times 9.81 \text{ m/s}^2 = \mathbf{73\ 600\ joules} = \text{potential energy}$$

Where 9.81 m/s^2 is the earth’s gravity constant
In this case I convert ***chemical energy*** in my body into potential energy. If I fall down from this height, I will convert that potential energy into kinetic energy.
If I travel with the speed of 10 m/s (36 km/hour) and my weight is 75 kg, then I have a ***kinetic energy*** of

$$0.5 \times 75 \text{ kg} \times (10 \text{ m/s})^2 = \mathbf{37\ 500\ joules} = \text{kinetic energy}$$

If I heat water with my electric heater and use 220 volts and 5 amperes for 100 seconds, then I have consumed ***electrical energy*** from the electric mains supply.

$$220 \text{ volt} \times 5 \text{ amp} \times 100 \text{ sec} = 110\ 000 \text{ Ws} = \mathbf{110\ 000\ joules} = \text{electric energy}$$

In this heater, this amount of energy is converted into the same amount of ***thermal energy*** which we can feel in the form of heat in the water.

A **laser** (or other radiation source) emits ***radiation energy*** in the form of a flow of photons, each with a well-defined energy. If its output power is 250 mW (= 0.25 W) and it is kept radiating for 2 minutes (= 120 sec), its emitted energy will be

$$0.2 \text{ W} \times 120 \text{ sec} = 24 \text{ Ws} = \mathbf{24\ joules} = \text{radiation energy}$$

Another example of energy conversion is when potential energy of the water in a water dam is first converted into the kinetic energy of moving water in a waterfall, which in turn is converted into electrical energy by means of a turbine connected to an electric generator. Even matter itself is a form of energy - ***material energy*** - following the famous equation

$$E = mc^2$$

formulated by Albert Einstein. In a nuclear reactor, matter is converted to thermal energy.

10.2 Output power

When you work with a laser, there are two fundamental things you need to know:

- Your laser type and its wavelength
- Its output power (for pulsed lasers - average and peak power)

If you don't know the output power of your laser, then you have no idea about the doses you administer - maybe you are just giving "homeopathic" doses or maybe you are giving too large doses.

Power is measured in watts, which is the same as joules per second, which is an energy flow. A strong laser has a high output power and a weak laser has a low output power. Power is in some way synonymous with "strength". However, power is not the same as intensity (see power density in next paragraph).

We have pointed out earlier that it is important to find out the real output of your instrument, which often is not what your brochure or manual claims. Output can decrease by ageing or by dirt in the aperture. The laser diode may even be broken (especially if it is infrared and invisible). The best precaution is to have a power meter, either built into the instrument or as a separate device.

10.3 Power density

Power density is briefly described in chapter 1.16.6 “Power density” on page 31 and in chapter 3.3.1.4 “Power density” on page 95. It is more or less the same as the "intensity" of the light and is measured in watts per cm^2 or milliwatts per cm^2 (in some literature watts per m^2). Intuitively we understand that if we spread out the light over a large area we will get a lower light intensity than if we concentrate it to a smaller surface. The power density (I) can be calculated as

$$I = \frac{P}{A} \qquad [\ W/cm^2\ ]$$

From this equation we can see that with constant output power from the laser (P), the power density (I) is inversely proportional to the surface (A) that it illuminates. In a practical situation, the power density is not constant over the illuminated surface - it has a two-dimensional distribution over the surface (even when a treatment probe is held in contact with the skin) and has a three-dimensional distribution inside the treated tissue.

In the picture below, we illustrate how the power density varies with the distance from the source in a divergent beam of a diode laser.

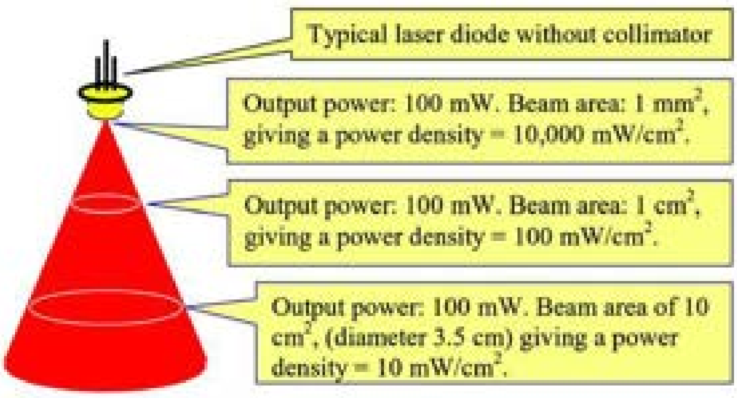


Figure 10.1 Typical beam from laser diode without collimator

Before leaving this subject, we illustrate the situation when a beam is focused - at the focal point we have an extremely high power density.

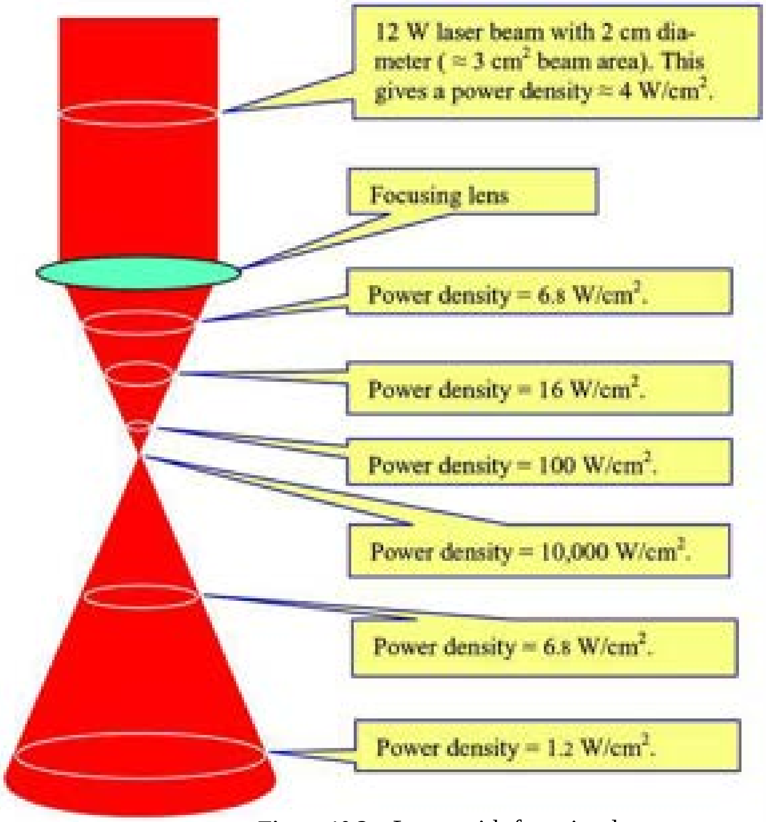


Figure 10.2 Laser with focusing lens

We have already mentioned that there are probes with focused light. When a surgical laser is used to cut tissue, this takes place near the focus point. Again: Looking at a specific situation with laser light penetrating into tissue, we will get scattering of the light, points and areas with high power density and other areas with low power density will occur. If this distribution of light is held constant for one second, we will have an energy density distribution that, in every point, is exactly the same number of joules as the number of watts in power distribution. If we keep the same situation going for ten seconds, we have an energy density (i.e. dose) that is ten times higher in every point reached by the light.

Like the power density, the energy density is not constant - it has a two-dimensional distribution over a surface (this is also true for the area hit by the laser light when a treatment probe is held in skin contact) and has a three-dimensional distribution in the treated tissue volume. (See chapter 3.5 “Other considerations” on page 139.)

10.4 The laser beam

The opening or glass surface through which the light comes out is called the "aperture". The beam from a laser tube or a laser probe does not usually have the same intensity in all parts of the aperture.

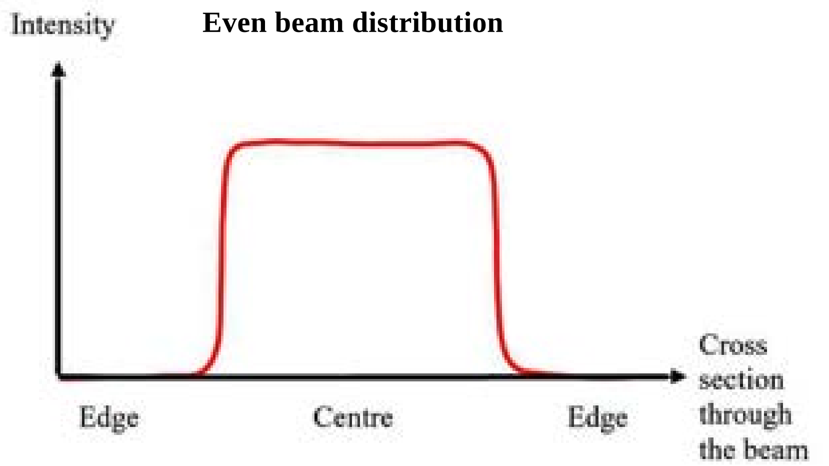


Figure 10.3 Even beam distribution

Usually it is stronger in the middle than at the edges. This often takes the shape of a so called Gaussian distribution (see the figure below).

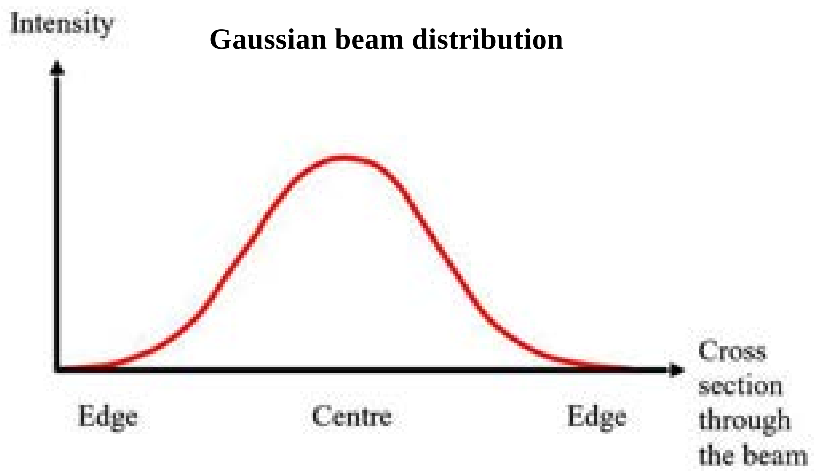
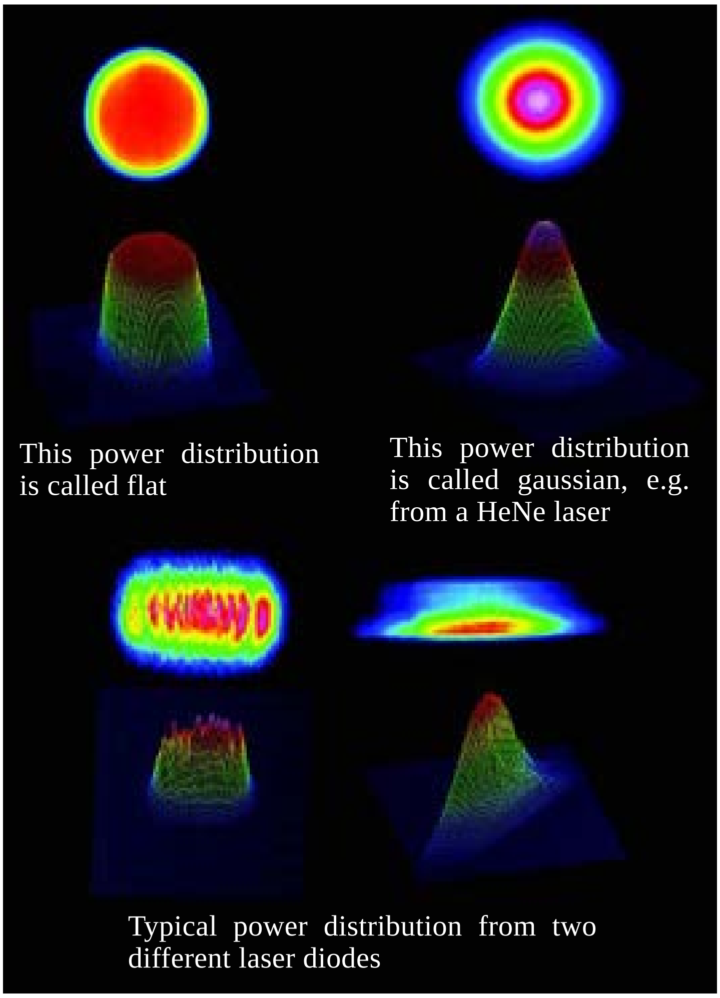


Figure 10.4 Gaussian beam distribution



In this figure we show two ways to demonstrate the power distribution in a laser aperture. Top figures in colour coded two dimensional picture and below each figure, the corresponding three dimensional picture.

Figure 10.5 Measured power distribution in typical probe apertures
Courtesy: James Carroll

The intensity distribution within the aperture is mainly of interest in scientific work, such as *in vitro* treatment, because in the treatment of tissue the light is strongly scattered. (See Figure 3.14 “Depth of penetration, direct contact” on page 141.) If, however, the beam is spread out over a larger surface (one or several square centimetres), then the intensity distribution is of importance.

10.5 The laser probe

In a practical situation, we have to look at our particular kind of laser probe (hand piece). There are many ways to design a probe:

a. In a gas laser (HeNe, Argon) a fibre is often used. It usually has a small diameter and ends at the top of the probe.

b. For diode lasers, the laser diode is usually situated inside the probe itself. In some probes the laser diode is unprotected and mounted at the very end of the probe in such a way that the glass surface of the diode is in contact with the skin during treatment. When irradiating from a distance, the light is divergent, which is advantageous from the point of view of eye hazards. But when the laser diode glass surface is in direct contact with the skin, we have a very small "light-spot" (typically in the order of one mm^2) which gives a very high power density. Further, the probe can be pressed against the skin, leading to tissue compression, which in turn causes the blood to move away from the beam. This will on the one hand increase the penetration depth and on the other lead to less effective treatment of blood cells than if the probe is not compressing the tissue.

c. In other probes the laser diode is mounted at some distance from the probe-end and there will be a distance (air) between the glass aperture of the laser diode and the skin. Depending on the distance and the angle of divergence of the laser light, the "light-spot" may be small or big with correspondingly high or low power density.

d. In some probes, the light from the laser diode is collimated by means of a collimator (lens system), resulting in a parallel and usually narrow beam. This gives us a choice of two options. In the first case, the glass surface of the collimator is at the extreme probe-end, making contact possible between skin and glass surface (compare point b). Here the cross section of the beam is usually larger than in case b. A typical cross section of such a collimated beam is in the order of 2 x 5 mm = 10 mm^2 = 0.1 cm^2. Remember that a collimated beam can be dangerous to the eyes, especially if it is invisible.

e. In the second case, the glass surface of the aperture can be situated at some distance from the probe-end with no possibility of skin contact. Instead of pressing against the skin with a glass surface, we often get a ring-shaped contact area. A consequence of this can be that some blood is trapped inside the ring, preventing penetration into the tissue. In this case the collimated beam can be dangerous to the eyes of patient and therapist, especially if it is invisible and carelessly aimed.

f. Another option is focusing the light from the laser diode through a lens. This focus can be placed inside the probe at the very end of the probe (possibly equipped with a glass surface) or slightly outside the end of the probe. Between the lens and the focal point the beam is convergent and after the focal point the beam is divergent, which is favourable from the point of view of risk to the eyes. The advantage of a focused beam is also that at or in the neighbourhood of the focal point the power density is high - at the focal point itself it can be extremely high (See Figure 10.2 “Laser with focusing lens” on page 679.)

g. A laser probe can have more than one source, in which case it is usually called a multiprobe. Multiprobes can have the laser diodes unprotectedly mounted at the end, (See Figure 7.2 “Laser probe for veterinary use.” on page 634.), or mounted inside in a multiprobe. In a multiprobe, the laser diodes are usually spaced over an area.

h. Combination probes where different types of lasers are mixed (e.g. visible and non- visible wavelengths, pulsed with non-pulsed etc.). In this case it has not been shown that simultaneous treatment with two or more laser types is advantageous.

i. Combination probes where one or several laser diodes are mixed with LEDs (here we don't mean LEDs which work solely as indicator lights). These require more research before we can safely accept them as useful. (See 11.1.2 “Comparisons between coherent and non-coherent light” on page 699.

10.6 Pulsed lasers

These have been discussed in, chapter 1.16.3 “Continuous and pulsed lasers” on page 28. A matter previously not commented on is the fact that if the laser is pulsed the power density is a function of time and can be divided into two figures: The peak power density (which in itself is not constant over the illuminated surface) and the average power density (with the same spatial distribution).

Specifically looking at the GaAs-laser, the peak power density is extremely high. Assume, for example, that the peak power of a GaAs-laser diode is 10 watts and that the diode is held in skin contact. Then, typically, the light is concentrated over a very small surface, e.g. 1 mm^2. This means that the power density in this small area is in the order of 10 W/mm^2 = 1000 W/cm^2. However, the average power density is of course much lower.

10.7 Energy density

Energy density is also named "dose" or "fluence". The difference between power density and energy density is simply the time. As mentioned above, the power density is measured in watts per cm^2. The energy density is measured in watt-seconds per cm^2, which is the same as joules per cm^2. For calculation of energy density. (See chapter 3.4.2 “Calculation of doses” on page 100.)

Looking at a specific situation with laser light penetrating into tissue, we will have points and areas with high power density and other areas with low power density. If this distribution of light is held constant over a certain time, we will have an energy distribution that, at every point, is exactly proportional to the power distribution. If we keep the same situation going for ten times as long, we have an energy density (i.e. dose) that is ten times higher at every point reached by the light.

10.8 Treatment dose

Again, the treatment dose (or the fluence) is the same as the energy density. We will mainly use the term dose. The dose is the most important treatment parameter. Dosage refers to the amount of energy per unit area applied to tissue surface or cell culture surface.

Biostimulatory effects of laser are governed by the Arndt-Schulz law of biology, i.e. weak stimuli excite physiological activity, strong stimuli retard it. Many therapists have the feeling that the more energy the better the result. But as can be seen from the diagramme below, what was originally a stimulating laser dose may become an inhibitory dose if you continue the irradiation beyond the optimal value. The optimal dose for biostimulation, based on current clinical experience, is 1-2 J/cm^2 in an open wound and 3-6 J/cm^2 when treating through overlaying skin (wavelength dependent). Dosage should also be adjusted according to individual response.

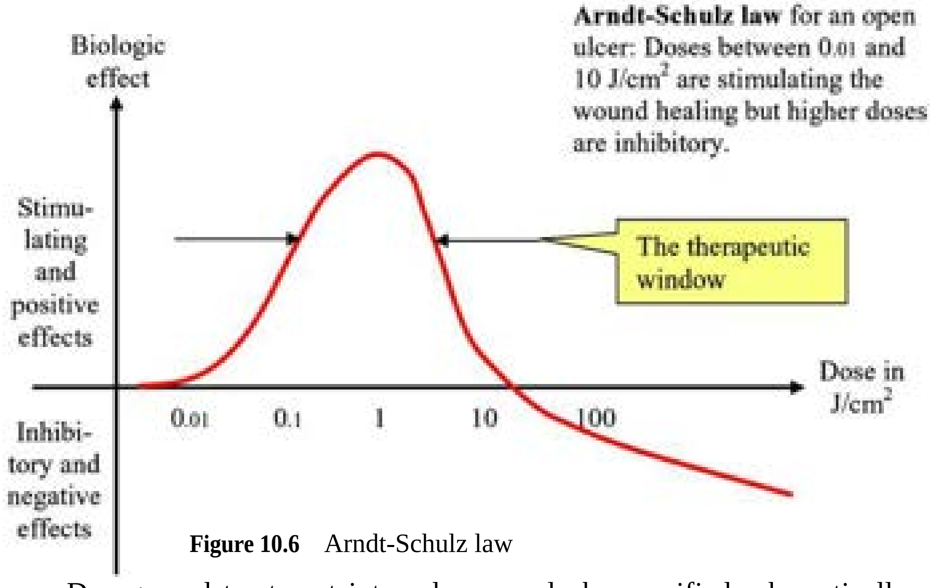


Figure 10.6 Arndt-Schulz law

Dosage and treatment intervals can only be specified schematically. This is because the various laser wavelengths and different treatment conditions mean that different doses must be given. People are receptive to laser treatment to varying degrees - some can "feel the laser right down to their toes", others are entirely impervious. It is appropriate to begin with a low dose for a new patient to ensure that you do not enter a biosuppressive dose range on the first treatment.

Generally, the dose is the amount of energy administered to a surface area of tissue. This is the same as the intensity multiplied by the time the illumination goes on and can be written:

$$D = I \times t \quad [\ J/cm^2\ ] \qquad \text{where} \qquad I = \frac{P}{A} \quad [\ W/cm^2\ ]$$

This equation tells us that if the intensity (I) is constant and t is the treatment time, then the administered dose is proportional to these factors. It also says that if we treat for a certain time (e.g. for 10 seconds) and we increase the intensity, then the dose is changed in proportion. So, we can give a certain dose using a strong laser for a short time or a weak laser for a longer time. Will then these two cases give the same result? Not necessarily there is a difference - the power density is different! With a ten times stronger laser we often get a better result (historically, therapy lasers have had a fairly low power density, far from the optimal value). The literature supports the hypothesis that higher power density yields better clinical results.

In pointing this out, it is not our intention to encourage therapists with low-powered instruments to scrap them in favour of newer, more powerful instruments. Their instruments will continue to be useful clinical tools if they are used with a proper understanding of the relevant facts. But remember this when it is time to buy a new laser.

Further, the dose D can be calculated as:

$$D = \frac{P \times t}{A} = \frac{E}{A} \quad [\ J/cm^2\ ]$$

where P is the laser's output power in watts, t is the treatment duration in seconds, E is the energy, and A is the area treated in cm^2. If the laser is pulsed, then the average output power in watts is to be used. P x t is the energy produced by the laser with output P, emitted over the time t. This can be written as E.

To make the equation part more complete, we add the treatment time formula from, see chapter 3.4.4 “Calculation of treatment time for a desired dose” on page 104. The most common situation in laser therapy is that we want to administer a certain dose D to a specified area A with our laser, having an output (or average output) power P, and we need to find the treatment time t for the laser probe at hand. We can look at two cases: superficial treatment or deeper treatment. For treatment of the skin, the following equation can be used:

$$t = \frac{D \times A}{P} \quad [\ sec\ ]$$

If, however, the problem to treat is situated at a deeper level (e.g. 1 cm or more) we have to compensate for the scattering and absorption losses on the way down from the surface to the problem volume. In a large volume, the light will be "diluted" in a manner of speaking. In reality, the light intensity decreases approximately exponentially with the distance from the surface. However, to use an exponential function in the calculation leads to complicated calculations and is not necessary because of the variations in tissue, type of indication and physical variations of the patient (skin, pigmentation, blood, bone etc) and the use of different treatment methods, see chapter 3.4.12 “Treatment method parametres” on page 117.

It would, however, be wrong not to take into account the rapid decrease of light intensity. Therefore, we suggest the use of a linear compensation as in the formula below. In this formula, which is simple to use, we have added the term (1+d) where d stands for the depth in centimetres and is limited to 1 = 0 to 4 cm.

$$t = \frac{D \times A}{P} \times (1 + d) \quad [\text{ sec }]$$

N.B.! The correct units to be used are: P in watts (not milliwatts), D in J/cm^2, the area A in cm^2 and the depth d in cm. The treatment time will then be expressed in seconds. Values 1 - 4 of the parameter d are only applicable to the infrared laser types (GaAs laser and GaAlAs lasers). For CO_2, HeNe and InGaAlP-lasers, use value d=0. For problems situated deeper than 4 cm in tissue, the dose is so low (even at long treatment times) that only systemic effects will do the job.

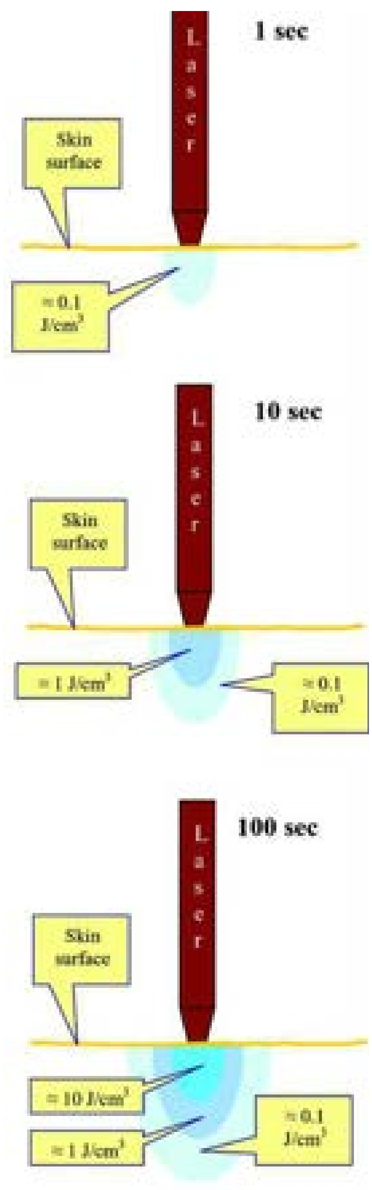


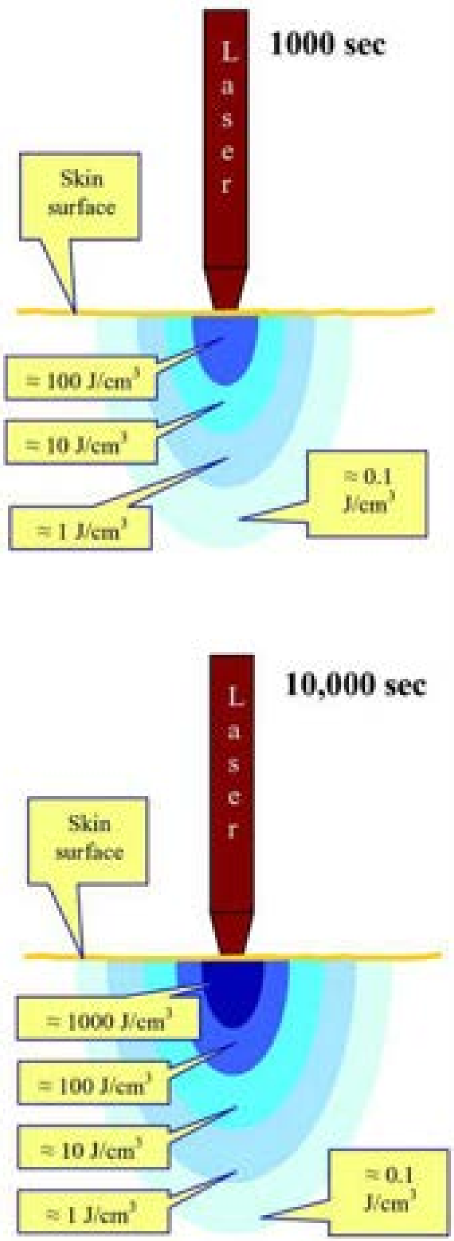
Figure 10.7 Laser on skin

When laser therapy was in its infancy in the early seventies, leading researchers such as Mester used doses in the range of 0.5 - 1.5 J for the treatment of wounds. They had access to 25 mW HeNe lasers, which were extremely expensive at the time - undoubtedly much too expensive to be used by anyone other than researchers and a handful of enthusiasts. It is nevertheless surprising that in the early eighties many companies introduced HeNe lasers with output powers of less than 1 mW and asserted that they were clinically useful. After fibre-optic losses, these instruments could deliver 0.1 mW or even less. This had a negative effect on clinical results, research and confidence in laser therapy. The joule suddenly disappeared from the landscape, its place being taken by the milli-joule.

When you hold the laser probe against the skin for **one second** and the laser probe has an output power of 100 mW, 0,1 joule enters into the tissue. The distribution of that energy is usually egg shaped as can be seen in the figure to the left. In the gray area a biostimulative dose within the therapeutic window will occur.

If we keep this set-up unchanged and keep the probe in the same position, with the same output power, for **ten seconds** instead of one second, we have put ten times more energy into the tissue and we will get a larger volume of tissue receiving doses within the therapeutic window. Also note that the dose decays exponentially from the area right beneath the probe and out against the outer regions.

In order to illustrate this further, let us assume that we keep this set-up unchanged and increase the time, holding the probe still and in skin contact for **one hundred** seconds instead of ten seconds. Now we have administered ten times more energy into the tissue, i.e. one hundred times more energy of laser light than in the case shown in the top figure. We will then get an even larger volume of tissue receiving doses within the therapeutic window.



When we previously talked about dose, we always used the unit J/cm^2. But the observant reader has already noticed that in the figures shown here, the dose is expressed in joules per volume, e.g. J/mm^3 or J/cm^3. In reality this is a more correct way of expressing the energy density in a volume and in most cases we do treat volumes. Only in the treatment of cell cultures can the volume be regarded as so small that joules per surface unit may be acceptable. Even when we treat a superficial ulcer we also, in reality, treat a volume rather than a surface.

In the figures to the left, the different colours represent different dose levels. The darker the colour the higher the dose (of course there are no such sharp edges in reality - it is a smooth and gradual change). In the volume in the figure to the left, the darkest blue area is shown as receiving about 1000 J/cm^3, but this does not mean that the shown volume is 1 cm^3, nor does it mean that it is the same dose everywhere in the volume; it is an average value.

In the bottom figure the difference in dose between the darkest and the lightest volume is in the order of 10 000 times. This may mean that no stimulatory effect, or even an inhibiting effect, may occur in the volumes receiving the highest doses.

Figure 10.8 Lasers on skin

However, this is not necessarily a problem as long as the tissue in those volumes is healthy - the laser light is not harmful to healthy tissue even at very high doses.

In an attempt to illustrate how the dose is distributed in treated tissue, we have shown a typical situation for two lasers with different wavelengths, one being less absorbed in tissue than the other. .

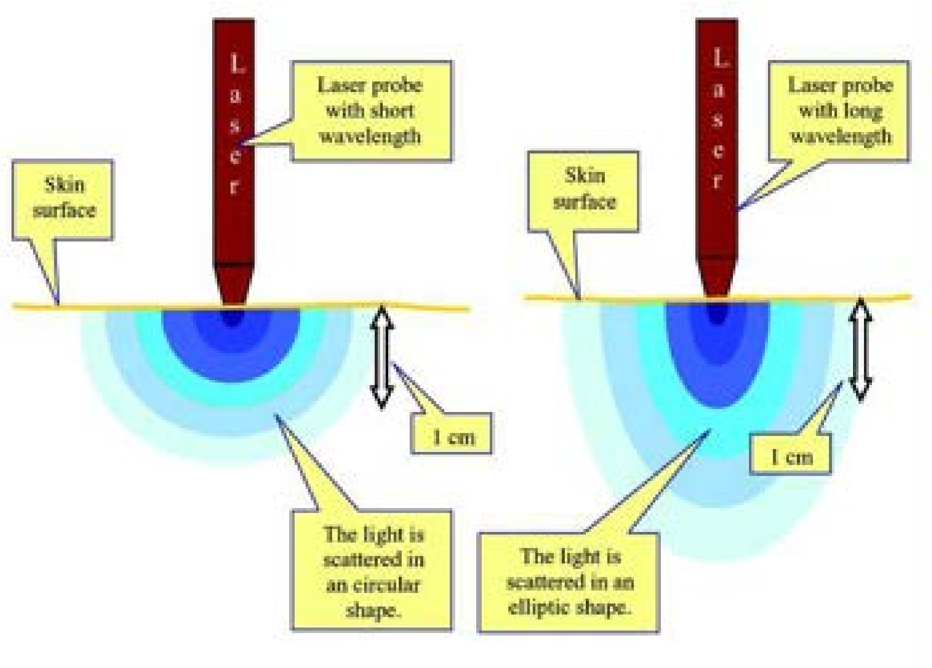


Figure 10.9 Lasers on skin, short - long wavelength

Two examples of treatment: Short wavelength light (wavelengths up to about 700 nm) is scattered more than long wavelength (700 to 1100 nm) light, resulting in different shapes of the "light ball" in the tissue underneath the skin surface. This is also the reason for the deeper penetration of most of the infrared lasers.

10.9 The dose does not depend on the intensity

What is not obvious is that with one and the same laser, dose and intensity are independent, even without changing the output power. To simplify the situation, we assume that the light from the laser diode is divergent and that the light cone is circular, (See Figure 10.1 “Typical beam from laser diode without collimator” on page 678.), and not elliptical and that, within the circle, it gives an even distribution of light all over the area hit by the beam. At different distances from the laser diode, the power density varies considerably. Just outside the glass covering of the laser diode (or end of a fibre) the power density is very high; it then decreases rapidly with the distance (inversely proportional to the square of the distance from the source).

If we want to treat a circular leg ulcer with a diameter of 3 cm (area 10 cm^2) we can choose the following alternatives:

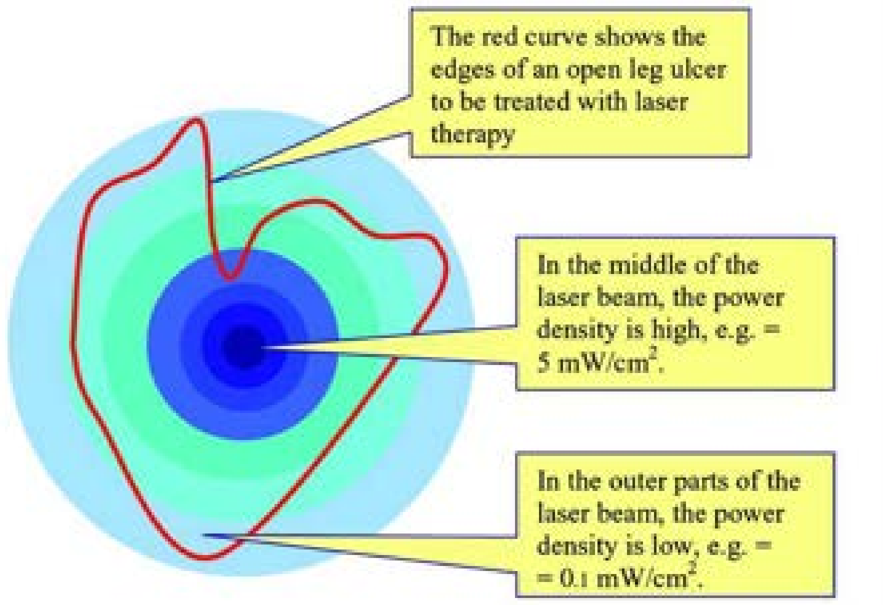


Figure 10.10 Treatment of an open leg ulcer

Figure 10.11 Illustration of technique for wound healing. Low intensities in non contact over the open wound, higher intensities in contact over adjacent skin areas.

1.We can use a treatment distance such that the beam covers the entire ulcer (as in figure 10.9), or …
2.… we can choose a short treatment distance (higher power and energy density) for the ulcer edges and a longer distance for the open parts of the ulcer (as in figure 10.10).
When treating an open wound, almost all the energy delivered reaches the intended target. The wound is naked and easily inspected, and the laser light goes directly into the relevant tissue without first passing through covering layers of skin, which, through absorption, diffusion, and reflection, remove a large percentage of the light. If the laser light is collimated, it makes no difference if it is delivered from a distance, since air does not absorb the light. If the laser light is not collimated, however, it should be delivered close to the surface to achieve proper power density and to avoid unnecessary complications in calculating the light intensity in the tissue.

Ready-reckoner.
For most people, mathematical formulas give negative associations. For the common therapist, it is, however, not necessary to use a calculator for every treatment. We have made the process easy. For the treatment of large areas, such as back, neck, shoulders, arms, knees, etc., we use "apples". If you cut an apple in two halves, the cut surface has an area of about 50 cm^2. Supposing that you know the laser type you have and its output power, you simply look up your laser in the table below and enter the depth of the problem: Is it deep or superficial? The table will show you the treatment time in minutes

per "apple" at different depths. (See Figure 3.8 “Apple ready reckoner” on page 105.)

Figure 10.12 Apple

Example 1: For an area the size of an apple using a GaAs-laser probe with an average output power of 60 mW at the chosen treatment frequency (N.B.: in many GaAs-lasers, the output power is frequency dependent) and a deep problem, you should treat for a minimum of 3 minutes. Is the area larger than an apple - e.g. the size of 4 apples - treat for 4 × 3 minutes as a minimum. Maximum treatment time: Choose twice the minimum value.

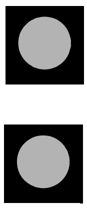
10.10 Dose per point

In the treatment of trigger points and acupuncture points the dose is often said to be a number of joules per "point", the assumption being that a point is something small. We have defined a "point" as an area that is 5 mm in diameter (= 0.2 cm^2) or less. This means that if we hit the skin with the light concentrated to this small area and administer 1 joule, we have given 1 J "per point", and if this "point" is 0.2 cm^2, the dose value is 5 J/cm^2 .

Diagrammatically this may appear as below:

If this is one square centimetre (1 cm^2) and 1 joule of energy is applied equally over its total area, then the energy density is 1 J/cm^2 in every point over the total area.

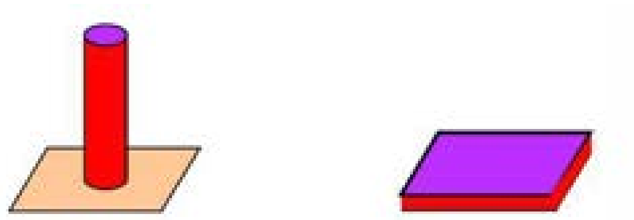
100 mW x 10 sec/1 cm^2 = 1 J/cm^2



If the round spot shown in the figure is the area of light from a laser probe applied in contact with the skin, held still during the exposure time and having an area of 0.1 cm^2, then the energy density is 10 J/cm^2 in every point over the spot area if 1 joule of energy is applied.

100 mW x 10 sec /0.1 cm^2 = 10 J/cm^2

However, the average over the whole 1 cm^2, is 1 J/cm^2.



Unevenly distributed light = unevenly distributed dose

Evenly distributed light = evenly distributed dose

Figure 10.13 Distributed light

Point treatment is used in the treatment of trigger points and in laser acupuncture. (See chapter 3.4.12 “Treatment method parametres” on page 117.) A suitable dose for a trigger or acupuncture point is one to four joules.

10.11 More about treatment technique

When treating a certain area, different techniques may be used. Some therapists use the "spot" technique, meaning that they hold the probe still, move it slightly, hold it still, etc. Others use a scanning technique, sliding the probe over the skin. Different figures can be used and it does not really matter what technique you use as long as you have a good idea about the doses you give. Whether one treats clockwise or anti-clockwise is of no relevance

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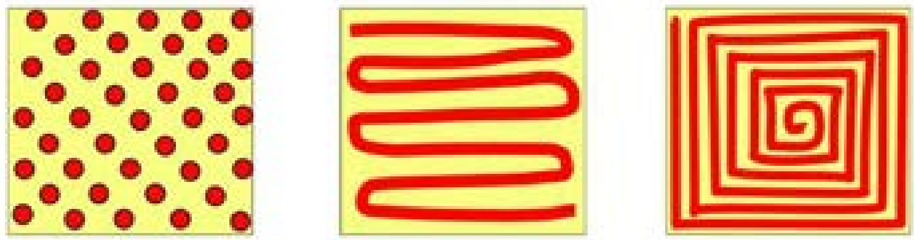


Figure 10.14 Treatment technique

The question at hand is not how many joules are delivered during a treatment session - that information may in fact be entirely irrelevant. The question is how many joules actually reach the diseased tissue. The two figures may be widely divergent.

When treating a known anatomical point located just beneath the skin, there are large dose differences depending on whether the light is delivered from a distance with a narrow collimated beam, from a distance with a divergent beam (spread out over a larger area), in contact with the skin, or in contact with added pressure. The difference between remote, contact and pressure treatment is great. The amount of energy (number of photons) reaching the inflamed tissue may vary a lot. Saying that "3 joules per point" were delivered may be meaningless for purposes of comparison. One therapist may end up delivering a dose (and/or power density) 100 times greater than that delivered by a colleague, although the same "dose" was given! Or, even if the dose is the same, taken as an average over a certain area, the power density can differ very much, giving different treatment results.

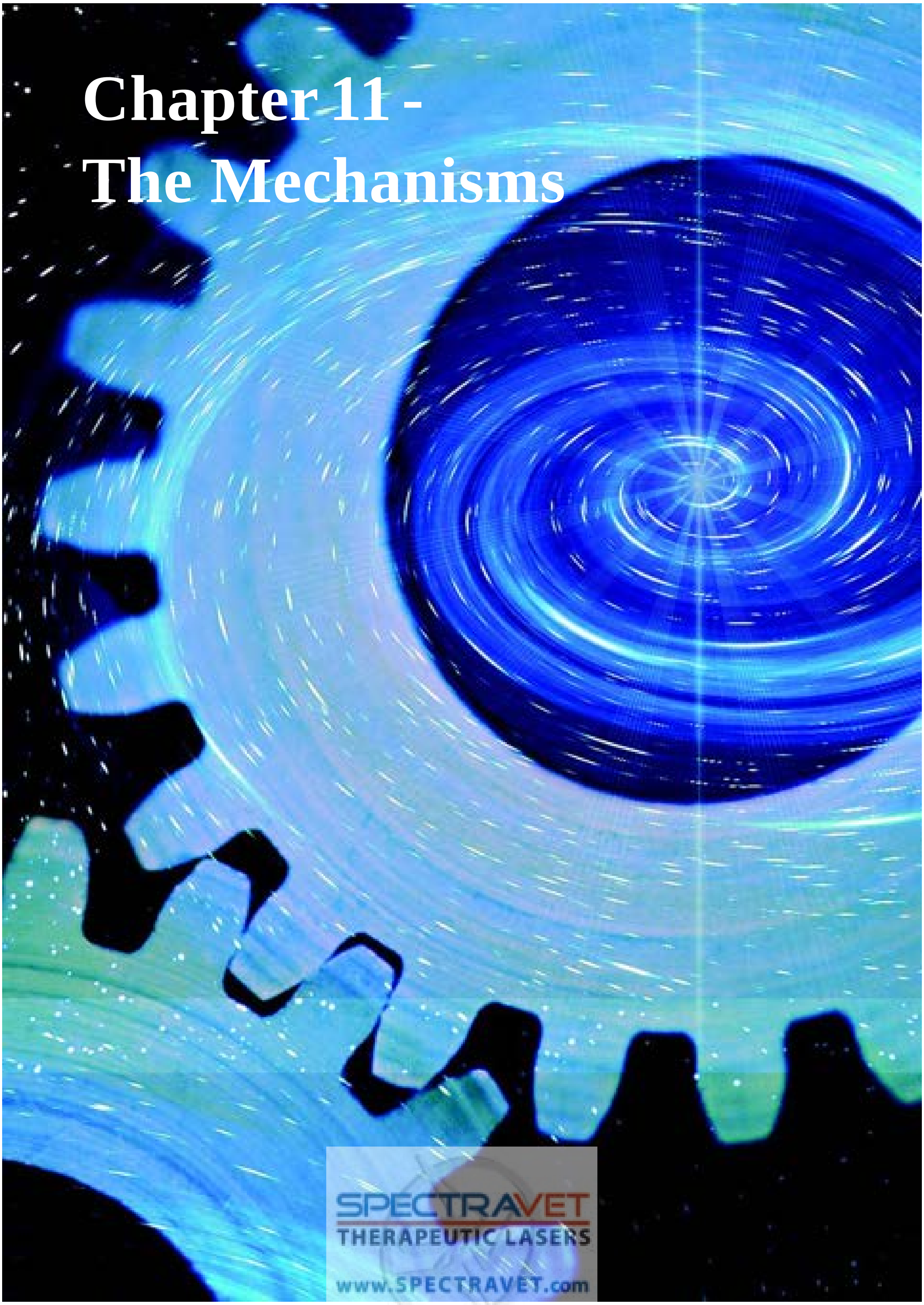
If the diseased tissue is deeper still, a new problem arises: where in the tissue is the treatment target?

Another important factor which comes into play is the skill of the therapist. If the diagnosis is correct, it is easier to know which tissue to irradiate. If the therapist has a good knowledge of anatomy, he or she will also know how to reach the tissue with the lowest possible energy loss. It may be necessary to place the patient in a particular position so that intervening muscles move out of the way and reveal the target. In such situations, the dose delivered by a qualified therapist may exceed that delivered by an unqualified colleague by a thousand-fold. Comparing the number of "joules delivered" in such a case is meaningless. It may very well be the case that therapist number one has found the right point and applied pressure to ensure minimum power loss. Therapist number two has irradiated from a distance, through an intervening layer of muscles, covering the target area by chance and luck. If therapist number two thinks that lasers are ineffective, we can understand why.

Technique and expertise mean a lot. This is clearly shown in a study by Ortutay [518]. The outputs of 13 different laser wavelengths (604-1219 nm) were compared in medical rehabilitation applications. The same pain alleviation effects were achieved regardless of wavelength or pulsing if the dose was controlled. The minimum dose for skin was 4 J/cm^2, but the location of the target in the tissue was always taken into account. It was sometimes necessary to increase the dose up to 20 J/cm^2 to compensate for absorption. If the target was deep, only infrared wavelengths were used in order to increase penetration. There is generally no point in increasing the dose if the wavelength has a low penetration factor; the penetration of the particular wavelength must be taken into account. However, as mentioned before, pain treatment needs higher doses than e.g. wound healing.

This study clearly shows that a "joule" is very much a relative concept. The dose recommendations in this book make the assumption that the joule is delivered in a more or less optimal manner. This means, in most cases of local treatment, that it is delivered as close to its anatomical target as possible.

Chapter 11 -
The Mechanisms



11.1 Are the biostimulative effects laser specific?

All forms of light affect the living organism. It has been shown that white light in certain doses influences seasonal depression conditions [240], see chapter 11.1.9 “Bright Light Phototherapy” on page 711. It is also known that it shows stimulating effect on collagen production in skin that can be used for treatment of wrinkles.

It is essential to clarify whether or not the biological effects obtained with laser therapy will appear only if the light source is a laser - that is, if the effects are laser specific. This is not just of theoretical interest. If one could just as well use a light bulb with a polarisation filter, so called Visible Incoherent Polarised light (VIP) - or ordinary Light Emitting Diodes (LED) of a certain colour or infrared light (such as in remote controls) - it would be considerably less expensive to manufacture therapeutic instruments. Some producers of therapeutic instruments claim that treatment with LEDs is as effective as laser treatment. Some producers even claim that LEDs are more efficient than lasers. They often make references to laser research in their marketing, obviously due to lack of support for LED effects.

We will discuss this problem closely in this chapter and the reader will, hopefully, feel more enlightened on the subject after having read this part of the book.

Furthermore, we will try to look into the mechanisms behind the healing laser light. But first we will take a look at the arguments advanced by some "non-believers".

11.1.1 Is it possible to prove that laser therapy doesn't work?

New knowledge and treatment modalities within medicine have not always been well received. When Louis Pasteur claimed that there are small microscopic beings that make meat decay, his contemporary colleagues scorned him. "But," said he, "have a look for yourselves in my microscope!" His colleagues laughed and said they would certainly not do that.

It is an interesting phenomenon that physicists have entered the debate in an attempt to prove that laser therapy just cannot work. As an example of this, we have chosen to discuss an article by King [12] who, like Greguss [233, 234, 235] before him, maintains that therapeutic lasers cannot work because it would be contrary to the laws of physics. King and Greguss claim that:

(A) In terms of their biological effect, lasers may just as well be replaced by a "normal light" with the same optical characteristics, due to the laser light's loss of coherence through scattering in tissue, and

(B) Laser light can have no medical effect, due to its minimal penetration in tissue.

We consider this to be a mistake, on the basis of the following:

Firstly: There have been quite a number of studies conducted on both people and laboratory animals [13, 14, 15, 16, 17, 158, 204, 205, 253, 332, 426, 493, 511, 659, 750, 851, 940, 1077, 1105, 1233] - even blind studies - in which the effect of laser light was compared with the effect of light from other sources, such as LED's. A significant effect was observed with lasers, which was not achieved with the other, less narrow-band light sources. Conclusion: Either all the investigators who conducted this research were mistaken, or the effects are specific to laser light.

Secondly: The coherence of laser light is not lost in tissue due to the phenomenon of scattering. Light is neither coherent nor incoherent but is more or less coherent (see the term "coherence" as explained above).

Thirdly: There is no "normal light" with the same optical properties as a laser, although if one did exist, it would of course produce the same biological effects as a laser.

Fourthly: The penetration of light into tissue is not minimal. This will be discussed later. (See chapter 11.1.8 “How deep does light penetrate into tissue?” on page 709.)

11.1.2 Comparisons between coherent and non-coherent light

In the literature there is good support for the hypothesis that at least some of the biostimulative effects in vivo are laser specific. In fact, we have not yet found even one single study indicating that non-coherent light is as efficient as coherent light for anything but for superficial structures. This does not mean that non-coherent light is not useful for therapy, only that it is less efficient and probably mainly useful on superficial structures.

Literature:

Bihari [13] treated three groups of patients with long-standing crural ulcers with HeNe, HeNe/GaAs and non-coherent unpolarised red light, respectively. Groups 1 and 2 demonstrated excellent healing, with group 2 slightly better than group 1, compared to group 3, which had a low effective percentage.

Kubota [14] found that an 830 nm GaAlAs laser increased flap survival area in a rat model. Laser treated flaps had better perfusion, a greater number of larger blood vessels and significantly enhanced flow rates. There was no difference between control and LED 840 nm groups.

Berki [15] used a HeNe laser to stimulate activation of cells in vitro. These effects (increased phagocytic activity, immunoglobulin secretion) were not seen when irradiating the cell cultures with normal monochromatic light of the same wavelength and doses.

Muldiyarov [16] used a HeNe laser on arthritis in rats and found that the laser exerted an evident therapeutic effect. Analysis of the cases where the rats were treated with ordinary red light revealed no essential differences from the control group.

Haina [17] compared the effects of HeNe-laser and incoherent light of the same wavelength. Experimental wounds were punched out in the muscle fascias of 249 Wistar rats. In the HeNe groups, the granulation tissue increased 13% at 0.5 J/cm² and 22% at 1.5 J/cm². The increase in the incoherent group was less than 10%.

Rochkind [158] compared five different wavelengths, giving a single transcutaneous irradiation to injured peripheral nerves. HeNe laser prevented the drop in functional activity following crush injury. 830 nm laser was less effective, 660 nm incoherent light was even less effective, and 880 and 950 nm incoherent light was completely ineffective.

Laakso [253] studied the relationship between laser therapy and opioids. In a double blind study, 56 selected patients with chronic pain conditions were treated with 820 nm laser therapy 25 mW, 670 nm laser therapy 10 mW, or 660 nm LED 9.5 mW. ACTH and ß-endorphin levels were significantly elevated in the laser therapy groups but not in the LED group.

Pöntinen [332] compared the effect of laser light (633 and 670 nm) and light from a LED-source (with 660 nm wavelength) on head skin blood flow in 10 healthy men, using laser doppler technology. Doses were from 0.1 to 1.36 J/cm². Skin blood flow was measured before, immediately after and 30 minutes after each treatment session at 4 sites on the scalp. The conclusion was that 670 nm laser induced a temporary vasodilatation and increased blood flow when the dose given was in the range of 0.12 - 0.36 J/cm². The non-coherent visible monochromatic irradiation with doses between 0.68 and 1.36 J/cm² decreased blood flow for at least 30 minutes after irradiation.

Lederer [426] found that "irradiation with coherent HeNe laser light affected leukocytes in migration inhibition assays. Incoherent light of the same wavelength and power density showed no influence."

Rosner [493] evaluated the ability of HeNe laser to delay posttraumatic optical nerve degeneration in rats. The optical nerve was crushed and irradiated through the eye. Interestingly enough, irradiation immediately before the injury was as effective as irradiation beginning soon after it. Non-coherent infrared light was ineffective or had an adverse effect. However, the non-coherent light had a wavelength of 904 nm, which makes comparisons difficult.

Nicola [511] developed a technique of causing highly reproducible inflammatory lesions on the skin of rats. HeNe laser with a dose of 1 J/cm² produced an acceleration of the healing process. Incoherent light of the same wavelength and dose was less favourable.

Onac [659] compared the effect of HeNe laser and monochromatic light at 618 nm. The intact skin of guinea pigs was irradiated with different doses. He not only compared the two different light sources but also compared them at different doses (from 0.63 J/cm² and up to 38.1 J/cm²) and came to the following conclusion: Non-coherent monochromatic red light irradiation leads to tegument trophicity at 4.96 J/cm² (but less than a HeNe-laser); lower doses have no effect (the HeNe laser does) whereas higher *doses cause focal epidermic hypertrophy. Thus, the therapeutic window seems to be narrower for monochromatic non-coherent light.*

Nicola [750] investigated the role of polarisation and coherence of laser light on wound healing in rats. There were four groups of wounds:
#1 was treated with coherent and polarised HeNe laser light (633 nm).
#2 was treated with non-polarised, coherent HeNe laser light (633 nm).
#3 was treated with polarised, low degree coherent light (633 nm).
#4 was untreated and served as control.

After the fourth treatment, lesions #1 had healed completely; lesions #2 had not healed completely but showed a more advanced healing process than lesions #3. The lesions #4 showed a poor degree of cicatrisation as compared to lesions #1, #2 and #3.

One investigation that unexpectedly strengthens our hypothesis that most treatments in vivo are laser specific, was published by Zhou [825]. The study concerns PDT (Photo dynamic therapy) using three light sources: a) copper-vapour pumped-dye laser, b) HeNe laser, and c) non-coherent red light (filtered from a halogen lamp), when irradiating the liver in normal mice. The mice (each group containing 18 - 20 mice) received hematoin derivative in a dose of 10 mg/kg intravenously, 24 hours prior to light irradiation. The mice livers were directly irradiated with different types of red light at a dose of 5, 10, 25, 50, or 100 J/cm^2, respectively. Forty-eight hours later the mice were killed and the depth of liver necrosis was measured using a computerised image-analysis system. No necrosis was found in the control liver irradiated with 500 J/cm^2 alone. The depth of photodynamic necrosis showed a light dose-dependent response. The mean depth of necrosis of all groups was compared statistically. The Cu-dye laser showed the best effect, while the non-coherent light showed the poorest. There were significant differences between non-coherent light and laser-irradiated groups, but not between Cu-dye and HeNe laser groups. The results indicate that of the light sources examined, the Cu-dye laser is most suitable to photodynamic therapy (PDT) of tumours. However, the halogen lamp with a special filter device may still be occasionally used as a light source in PDT if needed.

In a study by Paolini [940], 99 patients with shoulder tendinitis were divided into three groups. One received HeNe laser irradiation, one LED 660 nm irradiation and one anti-inflammatory medication. 25 sessions with either laser or LED were given. The outcome of the laser group was better than the pharmacological group and much better than the LED group.

Antipa [1077] compared the effect of: 1) GaAlAs laser, 720 nm 3 mW, 2) non-coherent light at 750 nm, 9 mW, and 3) placebo irradiation. 74 patients with sciatic problems were treated. The positive results were 66.6% for the laser group, 52% for the non-coherent group and 36.4% for the placebo group.

Simunovic [1134] compared the effects of 830 nm laser light with broadband, non-coherent, polarised light in the treatment of epicondylitis. Both groups of patients (n = 20) received 4 J/cm^2, 12 consecutive treatment *sessions, excepting weekends. 40% of the laser treated patients recovered fully, while in the non-coherent group no patients recovered fully.*

In a further study, Simunovic and Trobonjaca [709] compared the efficiency of laser therapy on lateral epicondylitis (tennis elbow) in 120 patients with:

a) transcutaneous electro-neural stimulation (TENS),
b) visible, incoherent polarised light (VIP) and
c) placebo "treatment" with a non working laser unit.

The number or treatment sessions per patient was twelve. The laser dosage was 4 J/point and the VIP-light dosage was 4 J/cm^2*. The results demonstrated that the laser therapy gave the highest percent of pain relief (>45% of lased patients reported 90-100% pain relief), TENS gave the second best pain relief. None of the patients in the VIP group reported 90-100% pain relief. The worst result was reported by the placebo group (<20% of average pain relief).*

We wish to underline that the studies above do not indicate that non-coherent light therapy for suitable indications and with sufficient energy densities is inefficient. It only shows that whenever compared, coherent light has come out on top. But indeed, the effect of non-coherent light therapy has been verified [1074], even in double blind studies [433, 941, 1232]. However, in these studies, non-coherent light was not compared with coherent light.

11.1.3 What is the importance of the length of coherence?

One of the first therapeutic lasers in the red spectrum was the helium-neon laser with a wavelength of 632.8 nm. In recent years red laser diodes in the range 630-660 nm (InGaAlP) have been replacing the HeNe laser. There are many advantages with diode lasers compared to gas lasers - smaller size, low voltage power supply, not fragile and much lower price. Lately, the red diodes can also offer higher power than most HeNe lasers. However, a HeNe laser has a spectral width of 0.01 nm compared to about 1 nm for a diode laser of the same wavelength. Correspondingly, a HeNe laser typically has a much longer coherence length - several centimetres and possibly up to meters - than diode lasers. In many therapeutic instruments using a HeNe laser, the light is transported through an optical fibre. This reduces the length of coherence considerably but anyway remains longer than that of a typical red laser diode.

Most therapeutic HeNe lasers are in the range 1-10 mW. Higher output is available but becomes expensive. Still the HeNe lasers have been successful during the years, in spite of their low power. Could it be that the superior length of coherence has something to do with it?

The aim of the study by Qadri [1606] was to investigate whether or not the length of coherence has any clinical significance. The study design was copied from a previous study by the authors [1185]. In that clinical split mouth study the effect of laser light on the gingival inflammation was investigated. The laser parameters used indicated that all clinical variables improved as well as some of the laboratory variables. In that first study one side of the mouth was treated with laser and the opposite side was used as control. In spite of the possibility of systemic effects, the clinical and laboratory findings suggested that the model could be a base for a study on the importance of the length of coherence.

In the second study a HeNe laser was used on one side of the mouth and an InGaAlP laser on the other side of the mouth. The output power of both lasers was 3.0 mW. The round aperture had a diameter of 4.0 mm, giving an aperture area of 0.122 cm^2. Supposing that the light intensity distribution is equal over the aperture area, the power density was 3.0 mW / 0.122 / cm^2 = 24 mW/cm^2. If instead the average intensity (power density) over 1 cm^2 including and surrounding the aperture (held in contact with the tissue) is calculated, we have 3.0 mW/1 cm^2 = 3.0 mW/cm^2. The lasers used were a custom made 3 mW HeNe laser (632.8 nm) and a diode laser (650 nm), equally of 3 mW. Both lasers had the same size of the aperture, allowing for equal power densities. The outputs of the lasers were controlled weekly using analogue power metres provided by the manufacturers. The lasers were selected in spite of the low output because they had identical features.

Treatment time was 180 seconds per point, resulting in a dose value in the aperture area of 180 sec × 24 mW/cm^2 = 4.3 $J//cm^2$. On the other hand, with the more common definition of dose, using averaging over $1/cm^2$ rather than over the area of the aperture, results in a dose of 180 × 3 mW/cm^2 = 0.54 J/cm^2.

Laser therapy started one week after baseline with one session every week for six weeks. Each buccal papilla of the teeth 13, 14, 15, 16, 17, 23, 24, 25, 26, 27 and in addition the lingual papillae of 16 and 26 were irradiated for three minutes each, representing an energy of 0.54 J per point, total energy per quadrant 3.24 J. Final measurements were performed one week after the last laser session. The irradiation was performed in light contact with the tissue.

The difference between the two lasers was obvious, in spite of the possible systemic effect. It is therefore suggested that the length of coherence is an important parameter in laser therapy. It is possible that increased dose from the diode laser could compensate for its shorter length of coherence but this is still an open field for research.

11.1.4 Hode's hamburger

Figure 11.1 Hode's hamburger

The literature gives no support to King's and Greguss' assumption that the coherence of laser light is lost when it penetrates tissue. We maintain that coherence is not lost.

It is, however, well known that the coherence length decreases in the event of diffuse reflection, but it does not drop to zero. We can firmly establish this by means of the following experiment, first demonstrated by L. Hode at The Ninth Congress of the International Society for Laser Surgery and Medicine in Los Angeles in 1991. Anyone with a HeNe laser can conduct this experiment.

1. Press newly minced fresh beef, e.g. raw hamburger meat, between two glass plates so that you have a 5-10 mm thick slab of minced beef.

2. Aim the light from a 5 - 10 mW HeNe or InGaAlP-laser (red visible light with a wavelength of 633 nm) at the glass plates with the minced beef slab as shown in the figure. You can see a red spot on the back of the minced beef where the light has penetrated.

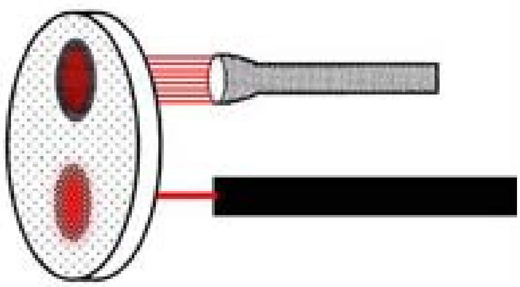


Figure 11.2 Set-up for Hode's hamburger experiment

3. Next, place a small penlight torch beside the laser and put its front end against the surface of the glass. The torch emits normal white light. This light also penetrates the minced beef and forms a light spot beside that caused by the laser. The spot from the penlight torch is also red, even though the torch emits white light. This is because the white light's blue, green and yellow colour components are absorbed, and only the red component penetrates.

4. Now study both the red light-spots on the back of the slab from a distance of a few metres. The laser light spot shows clear laser speckles which you can see if you slowly move your head. The spot from the torchlight has no laser speckles.

We can draw the following conclusions from this experiment:

A. Both light spots are red after their passage through the meat. This shows that red light has the best penetration of the visible light wavelengths. Measurements using instruments show that infrared radiation penetrates even better.

B. The coherence of the laser light does not disappear. The laser speckles can be clearly seen, and it is obvious that there is a difference between laser light and the light from a torch. This physical difference characterising the light after its passage through tissue can explain at least some of the research results mentioned above.

C. The HeNe laser beam is narrow and parallel (collimated) when it encounters the minced beef. After its passage through the meat, it is scattered considerably. If we use a laser with visible and highly divergent light (e.g. a diode laser) and place it close to the surface of the meat, we get the same light image on the back as with the collimated laser.

light image on the back as with the collimated laser. The collimation therefore has no significance for the light image in tissue [429].
It is easy to extend this experiment by including a red light LED. This gives the following result:

11.1.5 Hode's big burger

At the European Medical Laser Association 2nd International Meeting in Florence, October 28-31, 1999, L Hode presented an extended version of the same experiment using four light sources - HeNe laser, InGaAlP diode laser (650 nm), a cluster of 7 red LEDs (660 nm) and a normal small pocket torch. Two of the four red light spots showed laser speckles and two of them did not - guess which one!

Figure 11.3 Extended set-up

These nice and simple experiments can be performed by anyone who has a laser and a pocket light. Anyone can see the difference between the laser light and the non-coherent light after penetration of the tissue (meat).It is essential that one has a stable set-up so that movements do not distort the speckle pattern.

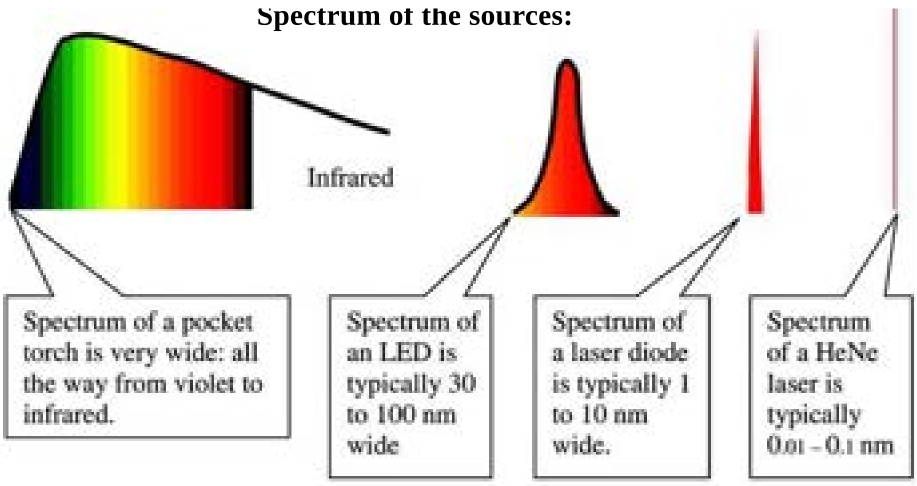


Figure 11.4 Different light sources have different spectra

Even though the laser diode has a much shorter coherence length than the HeNe-laser, the speckles are very pronounced in both laser spots. The LED has such a short coherence length that no speckles can be seen. The coherence length of a light source is more or less inversely proportional to its spectral bandwidth. This means that lamp light has a very short coherence length (in the order of nanometres) while a gas laser can have a coherence length of several metres.

We have noticed that in the treatment of ulcers, herpes and some other skin and mucous problems, a higher dose is needed when a diode laser is used than when a HeNe laser is used. This is most probably due to the difference in coherence length between those two sources.

11.1.6 Abrahamsson's apple

This is another experiment showing that the coherence of laser light does not disappear when spread diffusely.

If we direct a narrow beam from a HeNe laser at an apple, we can see a halo with a diameter of 1-2 cm around the intense target point. This halo occurs because the laser light is spread and reflected in all directions in the tissue of the apple, and consequently, some of it is also, after scattering, reflected out of the apple. If we look at the halo, we also see laser speckles (virtual speckles), which shows that the laser light retains its coherence after its passage through the tissue of the apple. Furthermore, the coherence of the laser light is much greater than the coherence of light from a red LED, for example, which does not exhibit clear speckles when directed towards the apple. The distribution of the laser light inside the apple is not homogeneous but grainy, due to interference, i.e. it consists of a three-dimensional speckle structure (real speckles).

Abrahamsson, at The Swedish Royal Institute of Technology in Stockholm, observed these speckles through a microscope and was probably the first to notice that the speckles on the surface of an apple move. He could relate this movement to particle movement within the cells of the apple.

The phenomenon has since been surveyed by French scientists [19], who studied the movement of the laser speckles and could differentiate two different forms of particle movement in the interior of the apple cells. As this is not possible with light sources other than laser, it is fairly obvious that there is a great difference in quality between laser light and incoherent light and that the coherence of laser light is not lost.

Kamikawa [359] shows in his article "Studies on low power laser therapy of pain" a picture of a finger that is transilluminated by a diode laser of 1 mW. The light from the laser passes through the finger and shows, on the opposite side, interference fringes. When the same experiment was done with an LED, no interference fringes appeared. This experiment also shows that coherence is not lost when laser light is diffusely scattered in tissue.

Enlarged real laser speckles recorded on a black and white film. Bright parts correspond to areas (volumes) with higher intensity than average.

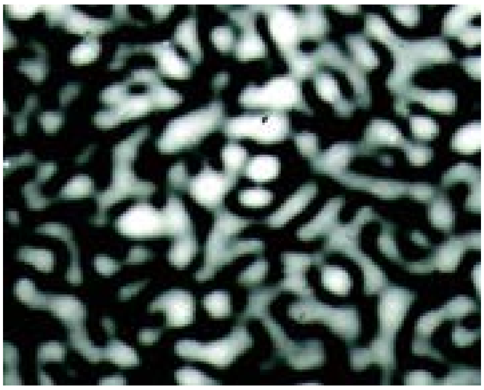


Figure 11.5 Enlarged real laser speckles
Photo: Lars Hode

11.1.7 Moonlight

King and Greguss also assert that, for example, the light from a HeNe laser (red visible light) only penetrates 1-2 millimetres into the skin and laser therapy can therefore have no effect, except for a very superficial one. They define the penetration as "the depth where the light intensity has dropped to 37% (=1/e of the intensity on the surface, where e = 2.7182) of the intensity on the surface".

Svaasand [27] has tried to lead the way in proving that the reported effects of laser therapy on tissue would contradict the laws of physics. He has calculated that at the depth inside the body of, for example, a shoulder joint, laser treatment gives a light intensity equal to that of moonlight. This is probably correct. However, laser therapy is not a case of broadband moonlight, but of highly monochromatic and, at least partially, polarised, coherent laser light, which even at low levels can impart interference effects. And what light intensity does it have to be? Would perhaps starlight level be enough? In theory, one single photon can actually start a chain reaction.

Let us make a little calculation: A fully adapted human eye can see about 10^{-9} lux. This corresponds to about 1.5×10^{-17} watts of visible power or about 30 photons per second of energy through the pupil of an eye. This little energy flow can create a minute nerve signal.

In a dark room, a 10 mW HeNe-laser can transilluminate a hand. A GaAlAs laser (820 nm) has even better transmission but its longer wavelength cannot be seen by the naked eye. It has to be measured by instruments. 2 cm down in tissue, only between 0.1% and 0.01% of the incident power remains. Suppose that we use the lower transmission value. Assume that the laser probe has an output power of 60 mW (0.060 watt) which is a power level often referred to in the literature. Assume further that said 60 mW laser light is concentrated to a 3 × 3 mm surface, i.e. gives a power density of 660 mW/cm^2. This means that 2 cm down in tissue the laser power is as low as $0.0001 \times 0.660 = 6.6 \times 10^{-5}$ $watt/cm^2$, i.e. 66 microwatts per cm^2. The rest of the power has been absorbed, been transmitted or, after scattering, been reflected away. An interesting question is now: How many photons per second (N) passing through the surface of 1 cm^2, equals 66 $microwatts/cm^2$?

$$N = 6.6 \times 10^{-5} \text{ watt / photon energy } (hv) =$$
$$= 6.6 \times 10^{-5} \text{ watt} / 3 \times 10^{-19} \text{ joules} =$$
$$= 2.2 \times 10^{14} \text{ photons / second} =$$
$$= 220.000.000.000.000 \text{ photons / second}$$

That is a tremendous amount of photons!

Let's look even deeper into the tissue: At a depth of 4 cm (thickness of an arm), the laser power is as low as 0.006 microwatts, with the same chosen absorption factor. This corresponds to 22 000 000 000 photons per second and cm^2, also a very large number. This is about 700 million times more than the 30 photons per second that it takes to produce the chemical reaction needed to create a nerve signal that we can notice.

At 6 cm depth we get 2.200.000 photons per cm^2 per second, which is 70.000 times more than the 30 photons per second that are capable of stimulating a nerve signal in a human eye. So, even at such large depths, theoretically, there is enough laser light energy to give rise to chemical reactions and secondary chain reactions.

11.1.8 How deep does light penetrate into tissue?

Figure 11.6 Transilluminated hand

It is easy to establish that the light penetrates deeper than 1-2 mm in tissue. If you hold your hand in front of a pocket torch, you can see that the light penetrates your fingers, and they are generally thicker than 1-2 mm. You will also note that the light which penetrates is red, so it is the red light in particular which penetrates, while the blue, green and yellow are absorbed. Infrared light is not visible, but it is easy to demonstrate that it penetrates deeper than visible light. Therapeutic lasers emit red or infrared light.

The depth of penetration of the red light has been studied in conjunction with a technique called PDT (photodynamic therapy) by which HPD (hematoporphyrin derivate), for example, is injected in the tumour area and then irradiated with laser light with a wavelength of 630 nm. It has been established [24, 25] that the depth of penetration is enough to get a biological response (necrosis) as far down as 10 mm in the tissue.

With the above mentioned definition, [37% =1/e of the intensity on the surface, where e = 2.71828 - (See chapter 11.1.7 "Moonlight" on page 707.) - the depth of penetration becomes totally independent of the laser's output, which means that the same depth value is achieved no matter how weak (or strong) the laser. The definition in question specifies, in actual fact, the relative penetration, while the decisive factor for the biological effect is the beam's momentary absolute value and, as has been mentioned, the absolute penetration. This is decisive for the intensity of the electric field across the cell membranes deep in the tissue.

Our understanding and experience, based on 20 years of experiments and practical work, is that laser therapy achieves direct biological effects at a depth of 1 - 4 cm in tissue, depending on the type of laser used, the laser's output, and other parameters. Further, systemic effects due to circulation of blood and of other forms of communication in the tissue, such as the transport of transmitters or signal substances occur at much deeper levels and, as a matter of fact, throughout the entire body.

If poor penetration would indicate that therapeutic lasers just could not work (according to Greguss and King), it would be even less logical for CO_2 lasers to have an effect. The penetration of CO_2-laser light is considerably poorer than that of the conventional therapeutic lasers. The calculation below shows the penetration of CO_2-laser light (wavelength 10.600 nm) into pure water:

Absorption coefficient 17 mm^{-1}
Scattering coefficient 0.0 mm^{-1}

Intensity as a function of depth in pure water $I = I_0 \times e^{-17 \times d}$

Depth in mm	Intensity in %
0.0	100.0
0.1	18.0
0.2	3.3
0.3	0.6
0.4	0.1
0.5	0.02

Table 11.1 Absorption

This means that, at the depth of 0.5 mm, 99.98% of the radiation is absorbed. As tissue does not consist of 100% water - rather, it contains between 70-90% - the penetration will be somewhat higher, but the difference is not so large since organic matter also strongly absorbs this wavelength.

Literature:

Gürsoy [429] made comparisons between 660 and 830 nm laser penetration in tissue, using CCD camera, radiometer and isotropic detectors. A 200 mW 830 probe could give a depth of 3.5 cm with a lateral spread of 2.7 cm. Both wavelengths were scattered widely regardless of the collimation. Attenuation in skin and muscle was equivalent. Less attenuation was observed in bone and salivary tissue.

Kolárová [1130] also used CCD camera technique to establish the penetration of 50 mW, HeNe laser light, 632.8 nm and 21 mW, 675 nm. In the thickest skin sample (19 mm with epidermis + dermis + subcutaneous fat from regio abdominalis) approximately 0.3% of the HeNe and 2.1% of the diode laser light penetrated. In granular tissue the penetration was about 2.5 times higher.

Jarry [782] performed in vivo dual wavelength differential spectrography on the hand of an adult male, using a collimated transillumination device. A pulsed laser with sufficiently high peak power and sufficiently low energy was employed so that transillumination could be realised without thermal damage. Spectrochemical analysis based on the absorbance of oxygen transporting molecules (OTM), i.e. haemoglobin in blood vessels and myoglobin in muscles, was performed along a 70 mm scanning line within the near-red infrared range. In other words, so much light penetrates the hand of an adult person that it is possible to measure the spectrum of the transmitted light!

Further literature: [1254, 2155]

11.1.9 Bright Light Phototherapy

It has been known for many years that daylight influences seasonal depressions. As early as in 1990 Rao [801] investigated the circadian profiles of melatonin in serum and serotonin in blood before and after 7 days of artificial light treatment in 30 patients with non-seasonal depression and 12 healthy subjects. Patients and volunteers were allocated at random to either dim (50 lux) or bright light (2500 lux) for 2 hours daily. Light treatment was found to marginally modify the circadian melatonin profiles of depressed patients and healthy subjects. However, it increased blood serotonin throughout the day. This increase was seen in all patients and in healthy subjects after bright as well as dim light. These results suggest that the influence of light is more pronounced on serotonin than on melatonin metabolism.

In 1991 Deltito [808] treated patients with either 400 or 2500 lux phototherapy for 2 hours on seven consecutive days. Unexpectedly, the result was the same regardless of the intensity of the light. The changes were judged to be quite clinically significant. All patients showing a response were noted to have maintained their response at a 3-month follow-up.

The same year [795] Petterborg examined the effects of a single exposure to a brief burst of bright light on serum melatonin in groups of healthy human volunteers of both sexes. They were treated with a 15-minute dose of bright light (350 cd/m^2) early in the evening during the winter months. Serial blood samples were collected from each person and the effect of the light dose on serum melatonin and cortisol levels was determined. Melatonin levels were significantly but only transiently suppressed by the light dose, while cortisol levels were not affected. These results demonstrate that short duration bright light treatment can influence the melatonin rhythm generating system in humans.

From these studies, it seems to be clear that it is the serotonin level that is mainly influenced, and to some extent the melatonin level as well.

It has been the general belief that mammals are not influenced by light except in the retina. Wetterberg [796] writes (1991): "The light which reaches the eye affects us both visually and non-visually. New results of treatment for depression show that strong artificial light has physiological effects on man ... "

Our opinion is that this is wrong. If it were only a question of sending light to a person's eyes, it would not be necessary to sit in a room with high intensity light - it would be quite easy to make "light goggles" with small built-in lamps. Among the "laser therapy society" it has been known for more than 30 years that our cells (other than those in the retina) and our tissue react to light and especially laser light!

However, in 1998 it also became clear to the non-laser therapy society, from the following experiment, that this opinion was wrong: Campbell and Murphy [786] investigated, in a randomised controlled trial, the effect of light irradiation on physiological and behavioural rhythms. The response to extraocular light exposure was monitored by measurement of body temperature and melatonin concentrations throughout the circadian cycle before and after light pulses presented to the popliteal region (behind the knee). A systematic relation was found between the timing of the light pulse and the magnitude and direction of the circadian phase shifts. These findings challenge the belief that mammals are incapable of extra-retinal circadian photo-transduction.

The literature is, as always, to some extent contradictory. We find the following:

BLT literature:	Our comments:
Rao [801]: Light treatment increases blood serotonin throughout the day. This increase is seen in all patients and healthy subjects after bright (2500 lux) as well as dim (50 lux) light. These results suggest that the influence of light is more pronounced on serotonin than melatonin metabolism. Treatment 2 hours daily.	Main influence on serotonin. This is also typical of laser therapy. It is surprising that the light intensity is not of greater importance. Maybe saturation is reached due to illumination of a large body area.
Rice [805] compared 2 weeks of light therapy with full spectrum white light with cool white light. Both treatment methods reduced depression scores, advanced the timing of the melatonin rhythm, and increased melatonin concentrations	Full spectrum white light also has a great deal of infrared radiation which cool light has not. Maybe the infrared part of the spectrum is of less importance. What about narrow band treatment or even laser light?
Wetterberg [819] writes "Light may be used to treat depression, sleep disorders, menstrual dysregulations and other illnesses with disturbed circadian and seasonal rhythms".	Treatment of menstrual dysregulations with laser therapy has successfully done by Takac [143]
Bylesjö [787]: Three of the 4 women reduced their net weight (1.5-2.4 kg) and improved in mood. 1500 lux.	It was actually popular to treat overweight with laser therapy in Sweden. We don't know how successful these treatments were. Maybe it works …

Table 11.2 BLT literature

BLT literature:	Our comments:
Thalén [790]: Ninety patients with major depressive disorders were treated with a luminance of 350 cd/m^2 (approximately 1500 lux) at **eye level**. Depressed patients with a seasonal pattern improved significantly more than those with a non-seasonal pattern.	In this report, too, we can see that the author believes that the effects are due to retinal illumination. Spectrum, bandwidth, coherence, pulsing, different areas to treat, treatment interval, etc., remain to be investigated.
Lewy [807]: Morning light was more anti-depressant than evening light.	Thalén [790]: There were no significant differences between morning and evening BLT.
Kripke [818]: Light therapy can be combined with standard therapies for treating non-seasonal depressions and appears synergistic.	Laser therapy also acts synergistically with other therapies.

Table 11.2 BLT literature

11.1.10 Similarities and differences

Both laser therapy and BLT are non-invasive, safe and painless light treatment methods. Most of the laser therapy effects have been known for 30 years. BLT has been used for less than 19 years (2002) and the mechanism is not yet known - just recently it was discovered that it does not only work through retinal effects.

Our belief is that BLT and laser therapy act in similar ways and may use the same mechanisms. We think that maybe a "laser solarium", using laser light in the visible red part of the spectrum, might be more efficient than BLT. It also seems that ordinary solariums have an anti-depressive "side-effect" and that this may be one of the reasons that they still are so popular in spite of all the alarming reports of their danger.

BLT increases serotonin levels [787, 800, 801, 806] and laser therapy increases serotonin levels [191, 247, 303, 496, 846, 847, 848, 849].

Literature:

Cassone [846] studied the metabolic modifications induced in rat brain by low power HeNe laser irradiation in vivo. Both the variations in the biogenic amine levels in cortex, striatum and hippocampus were studied. Noradrenaline (NA), dopamine (DA) and serotonin (5-HT) were evaluated by HPLC-EC on irradiated rats, untreated rats (controls) and rats that had undergone restraint stress (stressed). The results showed that irradiation caused a strong increase in serotonin (5-HT) in striatum and hippocampus and a small but significant decrease in NA in cortex, while DA levels were not significantly affected.

Loginov [847] investigated the effect of copper vapour laser therapy (578 nm) on the content of biogenic amines - serotonin and histamine and the state of the adenylcyclase (AC) system (content of cAMP, cGMP and AC activity) at the edge of a gastric ulcer. Direct effect of laser radiation (single dose 10-15 J.) produced a significant increase of serotonin, histamine, cAMP, AC activity and an insignificant increase of cGMP. Healing of the ulcerative defect after 5-6 laser therapy sessions was followed by a reduction of the content of serotonin and an increase of histamine, cAMP and AC activity. Loginov discusses the biostimulative effect of laser radiation by influencing the inflammatory-proliferative processes in the epitheliocytes in prolonged non-healing gastric ulcers.

11.2 Possible primary mechanisms

In order to facilitate an understanding of the mechanisms of laser therapy, we have chosen to separate what we call the primary mechanisms and the secondary mechanisms. The primary mechanisms relate to the interactionbetween photons and molecules in tissue, while the secondary mechanismsrelate to the effect of the chemical changes induced by the primary effects.

The fact that the biostimulative effects are dose dependent indicates that there may be thresholds involved in different mechanisms - a certain photon density is needed. There can be many reasons for this, one of which may be multiple photon action. If the effects simply were due to electron excitation and ionisation, there would be no thresholds - single photons would do the job. The table below shows examples of dose levels for different cell types and different wavelengths in vitro.

Wave-length in nm	Culture type	Measured activity	Stimulation dose, J/cm^2	Inhibition dose, J/cm^2	References
633	Chinese hamster	cAMP	0.01		Karu [F16]
630-633	Chinese hamster fibroblasts	Proliferation	0.1		Abdvakhitova [1230]
632.8	Human embryonic foreskin fibroblasts	Proliferation	0.01		Boulton [268]
632.8	Red blood cells	Deformability	-	>1	Yova [1229]

Table 11.3 Examples of different dose levels in vitro

Wave-length in nm	Culture type	Measured activity	Stimula-tion dose, J/cm²	Inhibition dose, J/cm²	References
632.8	HeLa	Clonogenicity	0.01 ~ 0.1	>1	Karu [1228]
632.8	Mouse mast cells	Cell granule release	2 - 4		Trelles [1227]
660	Hypertrophic scar-derived fibroblasts	Proliferation	2.4 - 4		Webb [615]
660	Human neu-trophils	Bacteria kill-ing	2.4 -4.8		Yu [1231]
694.3	Murine mela-noma cells	Growth rate	< 0.01	> 0.2	Carney [520] Hardy [1226]
812	Human buc-cal fibroblasts	Proliferation	0.45		Loevschall [75]
860	Human fibro-blasts	Succinic dehydroge-nase activity	2	16	Boulton [419]
904	Keratinocytes	Proliferation	0.25 - 4		Steinlechner [4]

Table 11.3 Examples of different dose levels in vitro

11.2.1 Polarisation effects

One important property of light is the polarisation. Any kind of light can be made polarised, simply by letting it pass a polarisation filter. It is easy to show that when non-coherent polarised light is penetrating and being scattered in tissue, the degree of polarisation rapidly decreases as a function of penetration depth.

(In a non scattering medium the polarisation can be kept high, see chapter 11.2.4 “Cell cultures and tissue have different optical properties” on page 717) When tissue (or any scattering medium) is illuminated with coherent light, polarised light will occur due to the formation of laser speckles (se below). This is independent of whether the incident light is polarised or not. If the incident coherent light (laser light) is polarised, this polarisation is evenly distributed. This degree of polarisation rapidly decreases as a function of penetration depth, but instead, laser speckles are formed by interference and then an uneven polarisation distribution has occured.

It has been documented that ordinary broadband non-coherent polarised light can give biostimulative effects on superficial problems like wounds and ulcers, but not deeper down in tissue. The Bioptron lamp is such a device. This further supports that some of the mechanisms are laser specific. See chapter 11.2.3 “Porphyrins and polarised light” on page 716.

11.2.2 What characterises the light in a laser speckle

The phenomenon of speckles is a form of optical noise. It was observed long before the laser arrived. As early as 1877 Exner [741] reported granulations in filtered mercury lamp light. When the first lasers came, the speckles became not only much more noticed but also a problem. Dennis Gabor, the "father of holography", published an article in 1970 with the title: "Laser Speckle and Its Elimination" in which he described different ways to get rid of speckles.

Speckles can be real or virtual. The three-dimensional structure of real speckles is manifest not only in an apple but also in a patient's tissue during irradiation with laser light. It arises as a result of interference between different beams with a random direction, amplitude and phase. In laser speckles, which have a higher intensity than the surrounding environment, the light is linearly polarised, or partially polarised (a mathematical description of partially polarised light is found in reference [850]), because the higher intensity has come about as a result of constructive interference, which occurs only if the interfering waves have the same polarisation. In this way, islands of polarised light appear in the tissue with an average size of a few tenths of a millimetre, that is, generally larger than the cells they surround. Interestingly enough, these islands occur regardless of whether the irradiating laser emits polarised or unpolarised light.

Literature:

Hode [743, 745] investigated 1972-1973 the possibility of using the inherent information in speckle fields to observe surface movements and deformation in real time.

Horvath [223] has actually measured the light distribution in tissue when illuminated with coherent and incoherent light. He used a small detector and could verify that there is a three-dimensional speckle structure of the light in the tissue if illuminated by laser light but not by incoherent light. This proves that the laser light, after penetration of tissue, is spatially coherent.

Literature: [744, 746]

11.2.3 Porphyrins and polarised light

If polarisation is important, can we not simply use polarised normal light? The answer is yes and no. If we illuminate cell cultures, the polarisation remains unchanged throughout the thin layer of cells. However, in the case of a highly scattering medium, such as living tissue, the polarisation is lost after a penetration of a millimetre or so. Therefore, if we polarise light from a pocket torch and use it to irradiate skin, the polarisation will disappear before it encounters the deeper-lying tissues. However, we could use polarised normal (broadband incoherent) light to treat open wounds and improve healing [272] (if we filter off all wavelengths shorter than 600 nm, since these have a negative effect on cells already stimulated). The light would directly encounter the cells in the wound, where there is no overlying skin to reduce or eliminate the polarisation. The positive effect of polarisation has been shown by Bolton [1284]. When macrophages were irradiated by visible 95% polarised light the fibroblast proliferation was greater than when irradiated with 14% polarised light.

Now, accepting that laser light gives rise to areas of polarised light in tissue (as earlier described), we might also ask the question: what is there in the body/tissue/cells that reacts to the light's polarisation? Are there polarisationsensitive elements?

Yes, there are. It is known that matrix-fixed chromophore molecules (e.g. the body's porphyrins) possess absorption dipoles and both absorb and emit (e.g. through fluorescence) linearly polarised light [20] of a determined polarity. Porphyrins are just one of the elements in the mitochondria's respiratory chain and are the molecules chiefly responsible for the absorption of blue and red light. The polarisation in the speckles created by laser light is significant here, and this could explain why the studies mentioned above showed different results with lasers and incoherent light sources. Some persons have the opinion that the respiratory chain is at the base of all effects that laser therapy might have. However, there are effects of e.g. HeNe laser irradiation on red blood cells in which there are no mitochondria [987]. As the cytochrome system in the mitochondria is influenced by photons [1312], it is logical to assume that other chromophores in the cell could be influenced by photons as well.

The conditions we have described above are in no way a complete list. We simply want to show, by looking at the physical conditions in more depth, that it is inappropriate (in the way chosen by some authors) to try to prove that laser therapy cannot work. It is reminiscent of the well-known proof, as deduced by mathematicians and physicists, that a bumblebee cannot fly because its wings are too small in relation to its body weight.

11.2.4 Cell cultures and tissue have different optical properties

In a number of studies in which the biological effects of monochromatic light from various sources have been compared, the following has been found:

1. In cell cultures (low scattering medium) laser light gives almost the same effect [33] as incoherent light (i.e. colour-filtered light from a light bulb or an LED of the same wavelength).
2. When tissue (highly scattering medium) is irradiated, laser light gives a stronger effect than incoherent light in all the studies so far conducted. In some of the studies, certain effects were also achieved with LEDs, but the studied LED-light-influenced phenomena were not as clear as with laser light of the same wavelength and the same dose. It should be noted that in four of these studies, adverse effects from LED light were seen [332, 493, 659, 825].

3 In a comparison between light of different kinds, cell cultures with T- and B-lymphcytes were irradiated with (a) polarised HeNe-laser light, (b) polarised narrow band incoherent light and (c) non-polarised narrow band incoherent light – all three with the same wavelength and dose. If the effect of the laser light (a) is set to 100%, the polarised narrow band incoherent light (b) gave 81% and the non-polarised narrow band incoherent light gave less than 1% effect [23].

4 Even polarised broadband light [272, 1284] has a clear effect on cell cultures and also affects open wounds and certain skin problems; however, it is not as effective as polarised laser light.

5 Under certain power density conditions, non-polarised broadband light can also have an influence on cells in cultures [252, 374]. Biostimulative effects have been noticed after treatment with so-called IPL devices (Intensive Pulsed Light, originally used for hair removal) with a spectrum limited to 600-1200 nm, power densities of 20-50 J/cm^2 and peak power density in the order of 1 kW/cm^2. This can indicate that multi photon actions may be of importance. (See chapter 11.2.13 “Multi-photon effects” on page 725.)

Karu [33] has demonstrated stimulating biological effects in cell cultures from monochromatic incoherent light. However, she has also shown that cell cultures which are first irradiated with laser light, and have consequently exhibited biological effects, and which are then irradiated with broadband (that is, non-monochromatic and incoherent) and laser light simultaneously, subsequently have their laser-produced biological effects reduced to almost nothing [22]. This indicates that there are more mechanisms at work here than simply the excitation of polarisation-sensitive chromophores.

It is important to understand the purely optical difference between irradiating tissue, which spreads light very diffusely, and a thin transparent cell layer in culture. If a thin layer of cells in culture is irradiated with polarised light, the polarisation is maintained right through the whole layer. This means that the cells are entirely surrounded by polarised light. Mester has shown that leukocytes in culture are affected by both polarised laser light and polarised incoherent light, but not by unpolarised incoherent light [23]. Our opinion is that many of the phenomena that hundreds of research scientists around the world have been able to establish as a result of laser irradiation of cells and tissue, are laser-specific in vivo, and that this is due to the coherence and/or narrow-band nature of the light, but not always laser specific in vitro.

11.2.5 The effect of heat development in the tissue

It has occasionally been asserted that the "possible" effects of laser therapy are due to the laser heating the tissue, and that one could just as well use a blanket, hot shower or a heat-lamp. Heat can of course be valuable many times, but in this context we have to look a bit closer into the matter.

11.2.6 Macroscopic heating

A heat-lamp has an output of 50-100 watts, while a therapeutic laser often has an output of 5-100 milliwatts (one milliwatt is a thousandth of a watt), that is, thousands of times weaker. All light that is absorbed by tissue is converted to heat, but it is not the heat itself that is of importance here. A blanket, hot shower or a heat lamp causes macroscopic heating of the skin and tissue - a rather even and smooth temperature distribution. Therapeutic lasers cause no perceptible heating, which heat-lamps obviously do and still there is a clear biostimulative effect, also on chilled tissue. So if it were just a question of heating the tissue, heat-lamps would give just as good or even better therapeutic results! It is true that a GaAlAs laser in the >100 mW range can cause sensations of heat on sensitive areas such as the lip, and on pigmented areas, but about 90% of the laser therapy described in the literature is performed with lasers in the <100 mW range.

11.2.7 The microscopic heat effect

However, the uneven, speckled light distribution in tissue causes local temperature differences. These have been calculated by Horvath [223]. Such temperature differences lead to local gradients in certain concentrations of substances, which in turn bring about transport of materials in the tissue in the manner described by Fink's equations. In other words, when tissue is irradiated with laser light, a microcirculation will be initiated, which is not the case during irradiation with non-coherent light sources, such as LEDs for example. Spanner [224] has shown that a temperature difference across a cell membrane of 0.01 °C causes a difference in pressure of 1.32 atmospheres, and this can mean that the distribution pattern of Na^+ and K^+ can be considerably influenced [225]. The local transient rise in temperature of absorbing biomolecules may cause structural (e.g., conformational) changes and trigger biochemical activity (cellular signalling or secondary dark reactions) [1373], [1374].

11.2.8 Mechanical forces

A very interesting experiment has been performed by Rubinov [1417]. He brings about a new approach to the understanding of biological activity caused by low-intensity laser radiation, in which coherence is a factor of paramount importance. This is based on the dipole interaction of gradient laser fields with cells, organelles and membranes. The laser intensity gradients in an object arise due to the interference of the light scattered by the tissue with the incident light beam (speckle formation). Apart from speckles, different types of light spatial modulation can be created deliberately, using different schemes for beam interference. It is shown that gradient laser fields may cause spatial modulation of the concentration of particles and increase their "partial temperature". Rubinov presents the results of experimental observation of trapping of different types of particles, including human lymphocytes, in the interference fields of the HeNe laser. The sweep-net effect on particles of different sizes when moving the laser field is demonstrated and crystal-like self-organisation of particles in the laser gradient field is observed. The influence of gradient laser fields on erythrocyte rouleaus, on the apoptosis of human lymphocytes as well as on their chromosome aberrations is demonstrated.

It may be concluded from the experimental studies that the influence of an interference laser field with a correctly chosen period can stimulate the repair system of a cell, increasing its viability.

Rubinov concludes further: *"Illumination of biological tissue by coherent laser light unavoidably leads to strong intensity gradients of the radiation in the tissue due to speckle formation. This causes the appearance of inter- and intracellular gradient forces whose action may significantly influence the paths and speeds of biological processes. In contrast to the photochemical action of light, which is accompanied by absorption of quanta and has a specific character (i.e. is characterised by a specific spectrum of action), the action of the gradient field is of non-resonant type. It is not accompanied by photon absorption and has a universal character, i.e. it depends weakly on the radiation wavelength, but requires a high degree of coherence. The use of different schemes of interference allows us to obtain different configurations and periods of spatial modulation of the laser light intensity. The application of such interference fields opens new possibilities for controlling fundamental biological processes and may lead to new technologies in laser therapy."*

No doubt that these effects of gradients are very essential. However, they can not be the only important effects occurring in laser illuminated tissue. Also photon absorption and other photon energy specific effects occur, see e.g. the reference [1279] below, but the effects of field gradients are laser specific and can also be (at least part of) the explanation of why so many different laser types (wavelengths) give similar biologic effects. The more we learn about this, the more we realise that the mechanisms behind laser biostimulation are very complex and the authors of this book doubt that we will ever know all details. Why are for instance about 10% of humans and animals resistant to laser therapy?

11.2.9 Excitation effects

The most obvious photochemical and photo-biological effects are due to excitation of photon absorbing molecules. In this field, a lot of work has been done by Karu. In the following section, we have, with her permission used some of her material and ideas.

Literature:

The stimulation of cellular ATP production has been suggested as one of the most important effects of laser therapy. In a study by Mochizuki [1279] the effect of 830 nm laser irradiation on the energy metabolism of the rat brain was observed. A diode laser was applied for 15 min with an irradiance of 4.8 W/cm². Tissue adenosine triphosphate (ATP) content of the irradiated area in the cerebral cortex was 19% higher than that of the non-treated area, whereas the adenosine diphosphate (ADP) content showed no significant difference. Laser irradiation at another wavelength (652 nm) had no effect on either ATP or ADP contents. The temperature of the tissue was increased by 4.4 - 4.7 °C during the irradiation of both wavelengths. These results suggest that the increase in tissue ATP content did not result from the thermal effect, but from a specific effect of the laser operated at the 830 nm wavelength.*

Karu [2019] irradiated a monolayer of HeLa cells with an He-Ne laser (632.8 nm, 100 J m², 10 s) and the amount of adenosine triphosphate (ATP) was measured by the luceferin-luciferase bioluminescent assay technique at different times (5-45 min) after irradiation. The amount of ATP in the log phase of cultured cells remained at the control level (0.79 +/- 0.09) x 10(-15) mol per cell) during the first 15 min after irradiation; it then increased sharply and, after reaching a maximum (170.8%) 20 min after irradiation, decreased slowly to the control level. The ability of monochromatic red light to induce an increase in the cellular ATP level was found to depend on the growth phase of the culture, being insignificant in the lag phase of cultured cells, increasing in the log phase of cultured cells and reaching a maximum (about 190%) in cells at the late logarithmic and early plateau phase.

The negligible effect of the presence of heat in laser therapy has been well demonstrated by Lanzafame [1447]. Pressure ulcers were created in mice by placing the dorsal skin between two round ceramic magnetic plates for three 12-h cycles. Animals were divided into three groups (n = 9) for daily light therapy, 830 nm, 5.0 J/cm² on days 3-13 post ulceration in both groups A and B. A special heat-exchange device was applied in Group B to maintain a constant temperature at the skin surface (30 degrees C). Group C served as controls, with irradiation at 5.0 J/cm² using an incandescent light source. Temperature of the skin surface, and temperature alterations during treatment were monitored. The wound area was measured and the rate and time to complete healing were noted. The maximum temperature change during therapy was 2.0 +/- 0.64 degrees C in Group A, 0.2 +/- 0.2 degrees C in Group B and 3.54 degrees C +/- 0.72 in Group C. Complete wound closure occurred at 18 +/- 4 days in Groups A and B and 25 +/- 6 days in Group C. The percentage of the wound closure at 14 days was 75. 4 +/- 7.2% and 77.7 +/- 5.6% for Groups A and B, respectively (NS differences). However, animals in Group C demonstrated a wound closure of 36.3 +/- 4.8%. These *results demonstrate that the salutary effects of laser therapy on wound healing are temperature independent in this model.*

The temperature increase in tissue of black as well as white mice was investigated by Stadler [1457]. Irradiation at 830 nm and 5.0 J/cm² fluence induced a small temperature increase at the surface and at 1 mm in depth. The smaller effects seen in white mice might be due in part to reflection. This suggests that the thermal effects of colour should be considered, particularly at higher fluences.

Further literature: [398, 460, 497, 1257, 1547]

11.2.10 Primary reactions due to excitation

There are several such possible primary reactions. When a photon is absorbed, it can transfer its energy to an electron. If the photon energy is high enough, it can change the energy state of the electron, e.g. from level S_0 to S_1. Also triplet states can be involved. It has also been shown that excitation can occur by means of multiple photon action.

The mechanisms that have been proposed are:

1 Changes in redox properties and acceleration of electron transfer. ("Redox properties alteration hypothesis" [1349]. Photo-excitation of certain chromophores in the cytochrome-*c*-oxidase molecule (like Cu_A and Cu_B or hemes *a* and a_3 [1351] influences the redox state of theses and, consequently, the rate of electron flow in the molecule. [1349]

2 NO release from catalyticcentre of cytochrome *c* oxidase. ("NO hypothesis") [1369]. It is thought that laser irradiation and activation of electron flow in the molecule of cytochrome-*c*-oxidase could reverse the partial inhibition of the catalytic centre by NO and in this way increase the O_2-binding and respiration rate.

3 Superoxide generation. ("Superoxide anion hypothesis"). It has been suggested [1411] that activation of the respiratory chain by irradiation would also increase production of superoxide anions and that the production of $^-O_2$ primarily depends on the metabolic state of the mitochondria. [1412]

4 Photodynamic action. ("Singlet oxygen hypothesis") [1367]. Certain photo-absorbing molecules like porphyrins and flavoproteins (some respiratory-chain components belong to these classes of compounds) can be reversibly converted to photosensitisers.

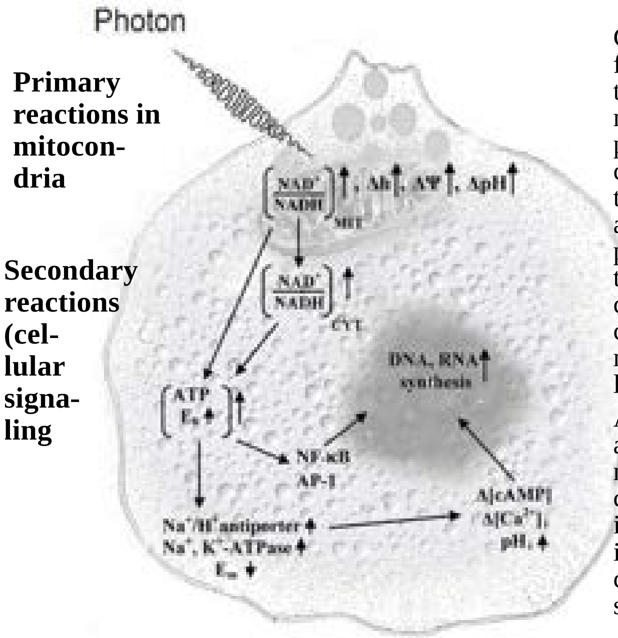
5 Changes in biochemical activity induced by local transient heating of chromophores. ("Transient local heating hypothesis") [1374]. When electronic states are excited with light, a noticeable fraction of the excitation energy is inevitably converted to heat, which causes a local transient increase in the temperature of absorbing chromophores.

The first two processes are of Redox type and the next two give rise to reactive oxygen species (ROS). The belief that only one of these reactions occur when a cell is irradiated and excited electronic states are produced is groundless. Rather, it is likely that more or less all of them take place. The question is, which mechanism is decisive?

Also; it is quite possible that all the mechanisms mentioned above lead to a similar result - a modulation of the redox state of the mitochondria (a shift in the direction of greater oxidation). However, depending on the light dose and intensity used, some of these mechanisms can prevail significantly. Experiments with *E. coli* provided evidence that, at different laser-light doses, different mechanisms were responsible - a photochemical one at low doses and a thermal one at higher doses. [1413]

11.2.11 Secondary reactions due to cell signalling

After the primary reactions in the mitochondria, a scheme of cellular signalling cascades (secondary reactions) occur in a mammalian cell. In the figure below, from Tiina Karu, $E_h \uparrow$ means a shift of the cellular redox potential to more oxidised direction. Further, the arrows ↑ and ↓ indicate increase or decrease of the respective values, brackets [ ] indicate the intracellular concentration of the respective chemicals.



Cytochrome-c-oxidase and flavoproteins like NADH in the respiratory chain in the mithocondria can act as photoreceptors. This can cause a short time activation of the respiratory chain and oxidation of NADH pool leading to changes in the redox state of both mitochondria and cytoplasm, changes in pmf (proton motive force), ΔΨ, Δph and leading to extra synthesis of ATP. Also a rise of Na^+/H^+ antiporter in the cytoplasmic membrane which causes a short term increase in pH_i and causing a change in the redox state of the cytoplasm, i.e. the redox state in the whole cell.

Figure 11.7 This figure is from Karu 1988. The process as described is of course simplified, but all steps are verified through experimental work.

These processes have been further verified. Yaou Zhang et al. [1416] used the cDNA microarray technique to investigate the gene expression profiles of human fibroblasts irradiated by low-intensity red light. Proliferation assays showed that the fibroblast HS27 cells responded differently to different doses of low-intensity red light irradiation at a wavelength of 628 nm. An optimal dose of 0.88 J per cm^2 was chosen for subsequent cDNA microarray experiments. The gene expression profiles revealed that 111 genes were regulated by the red light irradiation and can be grouped into 10 functional categories. Most of these genes directly or indirectly play roles in the enhancement of cell proliferation and the suppression of apoptosis (see also Rubinov, chapter 11.2.8 “Mechanical forces” on page 719). Two signalling pathways, the p38 mitogen-activated protein kinase signalling pathway and the platelet-derived growth factor signalling pathway, were found to be involved in cell growth induced by irradiation of low-intensity red light. Several genes related to antioxidation and mitochondria energy metabolism were also found to express differentially upon irradiation. This study provides insight into the molecular mechanisms associated with the beneficial effects of red light irradiation in e.g. the acceleration of wound healing by laser therapy.

11.2.12 Fluorescence - luminescence

Most people have at some time seen fluorescence. In discotheques, for instance, a UV-lamp is often set up to illuminate the guests. When the ultra-violet light hits our white shirt or our teeth, the invisible ultra-violet light is converted to visible light by means of fluorescence. Nice, bright porcelain crowns could suddenly "disappear", to the dismay of the owners. Modern ceramics have now adjusted to this embarrassing situation. In the old type of alarm clock, light energy from the bed lamp excited the phosphor molecules and the energy from the light was then stored for minutes or more and slowly emitted in the form of greenish light. This long-term storage is called phosphorescence.

Many animals have the ability to convert chemical energy into light energy - a process called luminescence. From this it is clear that light can change not only chemical processes in our bodies, but also that our cells can create light by a variety of different processes. It is also known that cells can communicate with each other by means of emitted and absorbed photons [753, 852].

Allan [853] discovered in 1972 that polymorphonuclear leukocytes emit photons during phagocytosis with a spectral maximum close to 600 nm. Nelson [854] found in 1976 that macrophages also emit light. Rosen [855] found experimentally that singlet oxygen is involved in the process; and Andersen [856] compared the emission spectrum from singlet oxygen with the spectrum from polymorphonuclear leukocytes in 1977 and found that they were more or less identical.

Part of the mechanisms of biostimulation can include fluorescence, phosphorescence or luminescence as possible means of communication between cells in different places.

Further literature: [448, 1000, 1001]

11.2.13 Multi-photon effects

Multi-photon effects are today more and more used in PDT, see chapter 11.6 “Photodynamic Therapy - PDT” on page 734 and in two-photon laser scanning microscopy by using a Ti:sapphire laser (superpulsed like the GaAs laser).

One possible explanation of the efficiency of the GaAs laser is action through multi-photon effects. The photon energy of the HeNe laser is 50% higher than the photon energy of the GaAs laser. However, in the extreme pulses of the GaAs laser, the photon density is very high, which is necessary for multi-photon action.

Literature

Shear [859] studied non-linear excitation of the neurotransmitter serotonin by means of Ti:sapphire laser light pulses. The results indicate that serotonin is photochemically transformed as a consequence of four-photon absorption to a photoproduct that then emits in the visible region via two-photon excitation. A minimum bound for the two-photon emission action cross-section was observed at 830 nm.

Maiti [860] measured serotonin distribution in live cells with three-photon excitation. Three-dimensionally resolved images were made along with measurements of the serotonin concentration from about 50 mM and up.

These investigations and many others, show that serotonin works as an optical target, especially for high photon density light pulses. With laser light (coherent) in particular, it is possible to achieve extra high intensity peaks due to interference.

11.2.14 Lasing effects in tissue

According to what is known as "The First Law of Photo Chemistry", light must be absorbed before photochemistry can occur. This is true if we are talking about energy transfer. But this does not mean that light cannot influence matter/tissue unless it is absorbed, since light can act as a catalyst. The existence of the laser is a proof of that. Lasing occurs when an excited atom is stimulated to emit a photon before emission occurs spontaneously. This takes place when a photon of the right energy (wavelength) enters the electromagnetic field of the excited atom: the incident photon triggers the electron energy shift and the energy difference is converted into electro-magnetic radiation and released by means of an identical second photon.

And **nota bene:** the trigger photon is not absorbed.

For a laser to work **-** i.e. to emit more photons of a certain energy than comes in, we must have an inverted population. In normal matter this is never the case. Living matter, however, has a very complex structure with a multitude of continuously ongoing chemical reactions where any conceivable level of energy is found. There are constantly excited molecules at every level of energy and it is not too unlikely for them to be triggered by incoming photons to release energy in the form of a photon while the triggering photon continues as it does in a laser. Hence, it seems possible that stimulated emission (laser action) can take place in tissue and that tissue itself can act more or less like a dye-laser.

There are currently thousands of different types of laser, and these produce light, UV or IR radiation of various wavelengths. Though a laser usually has one characteristic wavelength, it is sometimes possible to choose within a range of wavelengths. There are tuneable lasers where the wavelength can be changed, even during operation. Dye-lasers have a lasing medium that can be liquid and has a broadband amplification profile. Rhodamin, for example, has an amplification profile between 560-650 nm which covers both the wavelength of the HeNe laser and the InGaAlP lasers. Rhodamin is similar to porphyrin in optical property - it can easily cause fluorescence.

So, it is not unlikely that excited molecules in the tissue act like the medium in a dye laser and that this is triggered by the laser therapy. This could perhaps be part of the explanation of the rather deep effects of laser therapy. In particular, the CO_2-laser biostimulatory effect is very difficult to explain as the light is absorbed so superficially and also has such low photon energy. The wide-band action of tissue working as a dye laser can also make it easier to understand why biostimulation occurs for so many different wavelengths. Wide-band radiation, such as that from the sun, exhausts a lot of excited levels, thus inhibiting the effect of the laser therapy. Such sunlight induced extinction will only occur at depths that can be reached by that light. Secondary effects caused by laser treatment cannot be extinguished by sunlight or light from other sources.

11.2.15 Non linear optical effects

Theoretically, it is possible that non-linear optical effects can also occur in tissue. An example of a non-linear optical effect is the KTP (Kalium Titanyl Phosphate) crystal in the KTP laser (frequency-doubled Nd:YAG with 532 nm wavelength) which causes harmonic overtones, of which the first is used (532 nm is half the wavelength of the pumping light, in this case, Nd:YAG laser light - 1064 nm).

In order to achieve non-linear effects, high power density is needed. How high depends on the matter in question. We regard it as theoretically possible, but unlikely, that such phenomenon will take place in tissue. But if so, it is most likely to occur if lasers with high peak power, such as the GaAs laser is used, further intensified in bright speckle points due to interference.

11.2.16 Opto-acoustic waves

If intense light pulses are absorbed, acoustic waves may occur. In chapter 7 “Veterinary use” on page 631, we have noted that horses can "feel" GaAs laser light. It is possible that this is due to opto-acoustic waves.

11.3 Secondary mechanisms

11.3.1 Effects on pain

Pain is very complex in its nature. Since we are not specialists in this field, we have chosen to show that laser therapy influences many of the transmitter signal substances that we know are involved, such as endorphines, nitric oxide, bradykinine, serotonine etc, and also direct effects on nerves, e.g. C-fibres.

Literature:

Mizokami [247] has studied the change of serotonin in plasma in 63 patients with chronic pain. He used a GaAlAs laser, 830 nm, 60 mW output power. Patients achieving good pain relief from laser therapy were selected. On the first day of therapy, the change rate of plasma serotonin had a stable tendency to give a positive ratio. The treatment was applied every other day, resulting in a negative ratio from the tenth day of treatment.

Serotonin production was found to be enhanced when rat brains were irradiated with HeNe laser. In this study by Rossetti [502], the rats were exposed to stress. In both irradiated and control animals the ensymes aspartate transferase (AST), both cytosolic and mitochondrial, glutamate dehydrogenase (GIDH), and total superoxide dismutase (SOD) were monitored spectrophotometrically. In the brain of the irradiated rats there was a marked increase of total SOD, together with an appreciable decrease of cytosolic AST, and insignificant variations in mitochondrial AST and GIDH. In rats exposed to stress alone, the SOD decreased and the cystolic AST increased.

Montesinos [40] has shown that laser light affects the production of endorphins.

Honmura [188], by blocking opiates with naloxone, has been able to demonstrate that the pain-relieving effects of laser therapy do not depend solely on endorphins.

In a study on rabbits, Labajos [499] found an increase of ß-endorphine levels when a pain stimulus was given simultaneously with GaAs or HeNe laser.

Wakabayashi [190] has demonstrated that GaAlAs laser has a suppressive effect on injured tissue by blocking the depolarisation of C-fibre afferents.

Vizi [246] has demonstrated that ruby laser can enhance the release of acetylcholine.

A study by Mrowiec [432] indicates that nitric oxide is involved in the mechanism of laser therapy-induced analgesia. The analgesic effect of GaAs laser light in rats was prevented by an injection of I-NAME, an inhibitor of nitric oxide syntheses.

As mentioned earlier, Lubart [29] has demonstrated that singlet oxygen is produced in cells irradiated by HeNe laser. Singlet oxygen, in small amounts, is very important in biochemical processes and may be important in biostimulation. It is proposed that singlet oxygen is photo-produced by the natural porphyrins in the cells.

According to Lubart, only red (632 nm) and green (540 nm) light has an effect on the Compound Action Potential of the nerve. 904 nm laser light failed to produce this effect, supporting the theory that light with a wavelength in this region activates enzymes in the cell membranes while porphyrins act as photoreceptors in the visible range of the spectrum.

Friedman [375] reports that non-linearity in photo-biostimulation is a process where linear optical absorptions produce active chemicals such as cytoplasmatic H^{+} *and* Ca^{2+}*. These chemicals participate in chemical reactions, the rates of which depend on non-linearity of the concentration of these photoproduced chemicals, thus allowing very sensitive light control of non-linear biological reactions. Important contributions to neural excitability and growth include photostimulation of ATP production, which fuels the action potential and fills the synaptic ATP vesicles. ATP plays an important role as an extracellular neurotransmitter. With non-linear process, we do not mean non-linear optical effects as described in,* *(See chapter 11.2.15 "Non linear optical effects" on page 727.)*

In another study [377], the same author suggests a mechanism of stimulation of damaged cell cultures: Laser irradiation is assumed to intensify the formation of a trans-membrane electrochemical proton gradient in mitochondria. This enhances ATP production, which activates the Ca^{2+} *pumps, depleting the* Ca^{2+} *concentration in the cytoplasm and increasing the* Ca^{2+} *concentration gradient of the surrounding medium relative to the cytoplasm. This triggers enhanced* Ca^{2+} *influx into the cells via the* Ca^{2+} *ion channels of the cell membrane. In addition, with sufficient irradiation, the proton-motive force (pmf), due to the proton gradient, causes more* Ca^{2+} *to be released from the mitochondria by an "antiport" process. The additional calcium transported into the cytoplasm, together with other factors controlled by the pmf triggers mitosis and enhances cell proliferation. At higher doses, too much* Ca^{2+} *is released. This causes hyperactivity of* Ca^{2+} *ATP-ase and exhausts the ATP reserves in the cell.*

Brill [999] suggests the system of guanilate cyclase - cyclic guanosin monophosphate - NO-synthase as a primary photoacceptor.

Further literature: [1014]

11.3.2 Effects on blood circulation

Thermographic studies have shown that laser therapy can indirectly cause a higher temperature in the tissue, which is due primarily to an increased blood flow [170, 189]. In a number of studies [109, 190, 221], this rise in temperature has been measured in tissue irradiated with laser light, with the result that the temperature can rise by an average of 0.9 degrees over the area, and up to four degrees at certain points [14].

Literature:

Miro [301] has measured the effect of laser therapy on blood circulation in the nail bed and the mesenteric capillary flow. The increased blood flow continued for 20 minutes after the cessation of the laser treatment, even when the tissue was cooled.

Meada [460] measured the thermic changes after laser therapy using thermographic and thermometric methods. Excised skin in rats showed an increase of 0.4 °C, which remained constant during 30 minutes and was *noted equally on both the irradiated side and on the unirradiated contra lateral dorsum. There was no change in histology.*

Haina [497] reports a maximum temperature rise of 1 °C in human skin after HeNe irradiation of a density of 600 mW/cm², spot size 2 mm.

Sato [398] measured an increase in regional body temperature of 0.7 °C in a group of patients receiving active laser treatment for postherpetic neuralgia. Interestingly enough, there was no increase of temperature in the placebo group.

11.3.3 Stimulatory and regulatory mechanisms

In 1981 Mester [34] presented an article in which he summarised the research his group in Budapest had published: "The following model is proposed in order to explain the stimulating effects of polarised light (100% from a laser, 75% from a thermal light source): the electrical field intensity from the linearly polarised light changes the conformity of the double lipid layer in the cell membrane by means of electron polarisation of the lipids' electrical dipoles. One of the consequences of this is a change in the distribution of charge on the surface of the cell membrane, which can lead to changes in the lipid-protein bonds. Because the membrane acts as a biological amplifier, changes in the cell membrane affect every process associated with the cell membrane: the cell's energy production, its immunological processes, enzyme reactions, transport factors, etc."

11.3.4 Effects on the immune system

In the same article by Mester, the effects on the immune system were presented. In a study of the changes of the immune defence components by means of measurements before and after laser treatment, e.g. the alpha-I-lipoprotein content increased by 120%. The effect of laser therapy on macrophages is an indication of this claim [291].

Literature:

Dima [372] compared the activation of macrophages using HeNe laser, interferon and corynebacterium parvum. All three methods activated an intense phagocytic activity of the macrophages.

Yamaya [458] found that 904 and 830 nm laser enabled a rapid activation of the superoxide system, NADPH-oxidase.

Stadler [1031] irradiated human whole blood with 660 nm laser by using fluences between 0.1 and 5 J/cm². The lymphocytes were isolated after irradiation of the whole blood. As a control experiment, lymphocytes were first isolated and then irradiated with the same fluences. Lymphocyte proliferation was significantly higher in samples irradiated in the presence of whole blood compared with lymphocytes irradiated after isolation from whole blood. Free radical and lipid peroxide production also increased significantly when samples were irradiated in the presence of red blood cells.

Thus, the reaction of light with haemoglobin seems to be one of the keys in biostimulation.

Further literature: [1, 2, 214, 262, 273, 373]

11.3.5 Other interesting possibilities

An interesting hypothesis about the effect of laser therapy has been put forward by Reznikov and Pavlova, based on three separate studies [728, 729, 730]. Reznikov [857] gives the following description:

"Laser light could be considered as a trigger of an adaptive reaction because during evolution, this kind of "irritator" (stresser) is unusual, uncommon. There is not any physical agent besides laser light which we never experienced evolutionary - radiation, gravity, temperature, light, pressure, CO_2 or O_2 saturation, etc. Because of multiple exposures to changes of those conditions (effectors) during the evolution, listed effectors may induce stress only if they are approaching to damage (hazardous) range. The real therapeutic effect related to stress/adaptation, however, may be expected only if the effector does not add its own hazardous effect. Among all known cases it is possible only if laser light is applied at the low dose. Why?

Unlike other physical factors, the light with narrow spectral band is absolutely unusual for our nature. There is no situation where bio-organisms on Earth could be exposed to this kind of light and develop unresponsiveness to that during evolution. Because of that, we believe that the most important for laser effects is not the wavelength but the monochromatic nature, especially with narrow spectral band.

If we will excuse ourselves from the discussion on differences in light absorption and energy of photons (the important aspect of optimisation in laser therapy) and will focus on the induction of adaptive reaction: the more "odd" light we are exposed to, the more response we can expect. If the light's bandwidth increases, the effector loses power to induce adaptive reaction (even if this light still is considered monochromatic, at some degree, it may be not so unique evolutionary as the light with less band-width).

In other words, extreme monochromatic light (such as laser light) exposure was not experienced evolutionary. As such, it is a stimulus that is unique to the experience of the organism. The more unique the light, the more the organism is required to resort to adaptive mechanisms, to resolve the stimulus. For this reason, laser light is considered a unique adaptogen, generating adaptive reactions. The less band-width of the light, the more unique the light is to the experience of organism resulting in greater efficiency of laser therapy."

In the book "The science of low-power laser", Karu pinpoints some typical features of laser therapy, based on extensive in vitro studies:

* Patient response to laser therapy depends upon their physiological status;
* Laser therapy effects are truly dosage and wavelength dependent;

* Biological responses may be maximised within certain "action spectra". A number of action spectra may apply for a particular biological response, and the response may be maximised at a specific wavelength within each action spectrum.
* The biological responses of cells to pulsed laser therapy can be different (but not necessarily better or worse) from responses to continuous wave, and there is a strong dependence on pulse repetition rate, pulse duration and duty cycle, as well as dosage and wavelength.
* Visible and infrared light affect biomodulation in different ways - visible light elicits photochemical changes, whilst infrared can only produce physical changes. However, the end result may - in some cases - be the same.
* The biological response to laser stimulation can be significantly different according to the sequence in which different wavelengths are applied, and even non-existent if two or more wavelengths are used simultaneously.

Further literature:
The stimulation of ATP synthesis [140, 149, 241, 257, 378, 590, 946, 1258]
DNA replication [21, 22, 33, 75, 121, 181, 220, 249, 251, 510, 587, 675, 754, 947, 948, 950].

11.4 Summary of mechanisms

In an effort to summarise the mechanisms to some degree, in the manner we believe we understand them, and in accordance with other researchers we have contacted, we have created the block diagramme shown below. There is, of course, a lot more published about the details in the different stages of the diagramme, but including all these beyond the scope of this book.

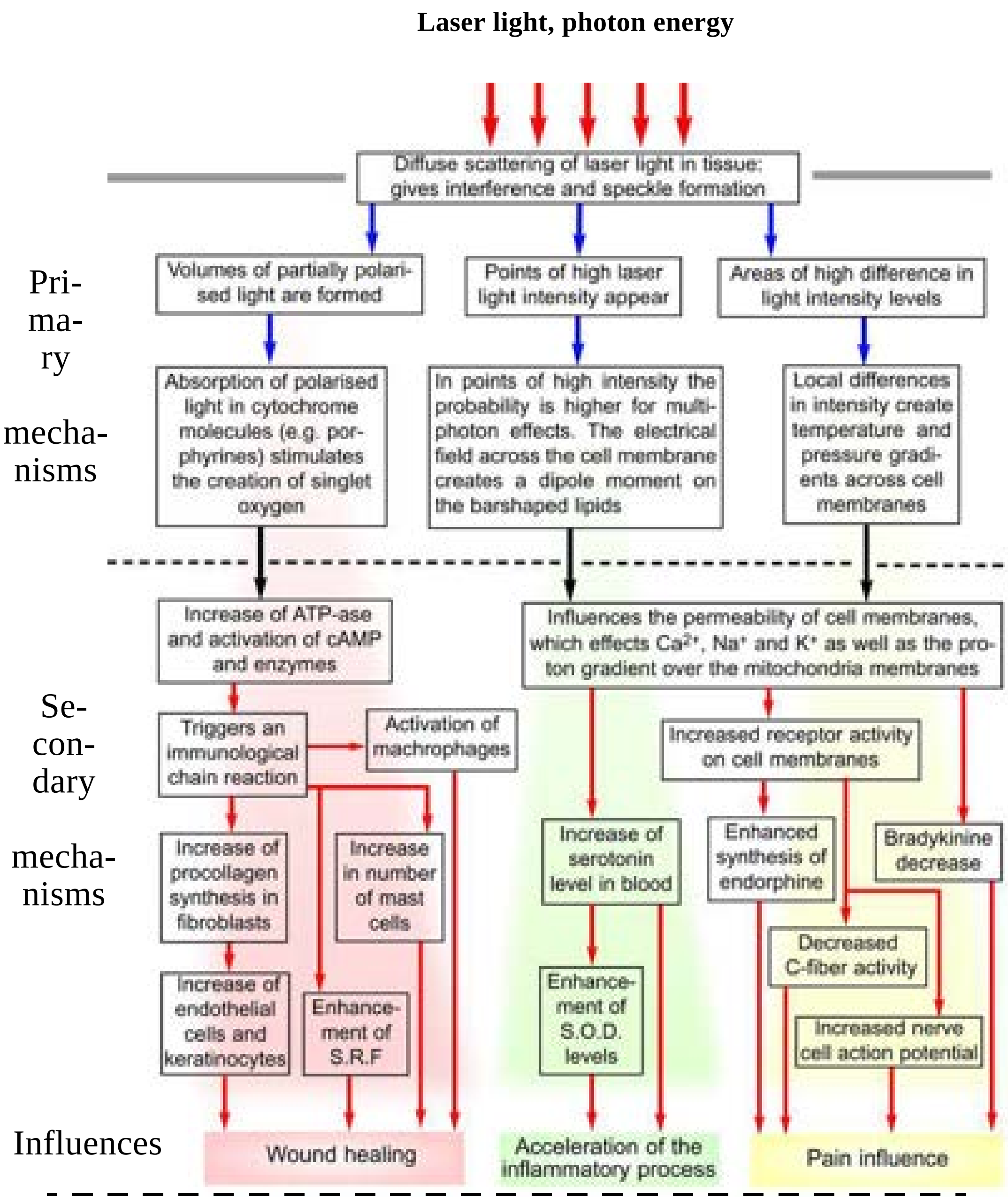


Figure 11.8 The mechanism of laser therapy

11.5 Diagnostics with therapetic lasers

In Chapter 7 we have mentioned that horses are more sensive to laser light than humans. High local power density - and superpulsing - brings about a reaction (sometimes including a pain reaction) when the probe enters the vicinity of an injury or problem area. This is particularly true of GaAs lasers and at high pulse-train frequencies. It can therefore be used to locate an injury.

Another possibility of using a laser therapy instrument to locate a problem is to use a focused GaAlAs-laser with a sufficiently high output. If 100 - 500 mW is focused or concentrated on a surface in the order of 1 mm^2, most patients will feel some kind of sensation when this "light needle" hits a place connected to a problem. This can be used as a diagnostic aid.

In dentistry, laser has been used to make a differential diagnosis in cases of pulpitis of uncertain origin. By irradiating over the apex of the suspected teeth, microcirculation will increase, intra-pulpal pressure will rise and the "guilty" tooth will react with a pain attack. The longer the duration of the attack, the more compromised is the pulp.

Majlesi [2372] has shown that red laser light can be used as a diagnostic device. By irradiating through oral tissues, the change of the penetration properties of oedemas and pathological tissue will make them observable and their area determined.

11.6 Photodynamic Therapy - PDT

A method for detecting and destroying cancer tumours, is photodynamic therapy. It is often performed in two steps: detection and destruction. Detection is based on the following. HPD (hematoporphyrin derivate = a selectively retained photosensitive dye, at a dose of 10 mg/kg), or Photofrin, photosan etc, labelled with an antibody specific to the kind of tumour in question, is injected in the patient intravenously 24 hours prior to light irradiation. By irradiating the patient with green light and looking at the irradiated area through red bandpass filters, fluorescence can be seen. Fluorescence will occur at areas with higher concentrations of the dye, indicating the presence of a tumour. By irradiating the tumour area with laser light with a wavelength around 630 nm, the dye will split, releasing toxic agents in the tumour area, possibly killing the tumour. It has been established [24, 25] that the depth of laser light penetration is sufficient to obtain a biological response (necrosis) as far down as 10 mm in the tissue.

In 1903, Ryberg Finsen was awarded the Nobel Prize for his invention of light therapy for skin tuberculosis (lupus vulgaris). The mechanism of action has not been shown; thus, Möller et al [1510] wanted to elucidate the mechanism of Finsen's light therapy. They measured radiation that could be transmitted through his lens systems and absorption of the stain solution filters in the lamps, and related the obtained results to the possible biological effects on Mycobacterium tuberculosis. Judged from transmission characteristics all tested lens systems were glass lenses (absorbing wavelength < 340 nm). The tested filters likewise absorbed wavelengths < 340 nm. The methylene blue solution used to absorb heat, blocked out wavelengths below 340 nm and between 550 and 700 nm. Furthermore, fluorescence of M. tuberculosis indicated the presence of porphyrins and HPLC analysis of sonicated M. marinum showed that coproporphyrin III was present, which highly justified that porphyrins were present in M. tuberculosis. Production of singlet oxygen through radiation of porphyrins with light of e.g. 400 nm seems to be a most plausible explanation why Finsen's therapy worked in spite of the lack of shortwave ultraviolet radiation, which Finsen believed was the most effective radiation for treating skin tuberculosis. Finsen was therefore a PDT pioneer without knowing it.

Literature: [24, 25, 825]

11.7 Other medical uses of lasers

The critics of laser therapy have repeatedly claimed that coherence disappears when laser light is scattered in tissue. If this were correct, optical coherence tomography [862] would not work.

A useful application of laser technique is the Laser Doppler Velocimeter that can be used to measure arterial, venous and lymph microcirculation. Speckle Interferometry can be used to measure intracellular movements.

Laser spectroscopy can be used for quantitative analysis of e.g. frozen skin biopsies for calcium, arsenic and gold. This technique has also found its application in forensic medicine. With the Laser Doppler Spectrometer, spermokhinezymetry can be performed.

Laser microscopy exists in many different forms, such as Laser Microscopic Masonic Analyser (LAMMA) and Laser Fluorescent Microscopy.

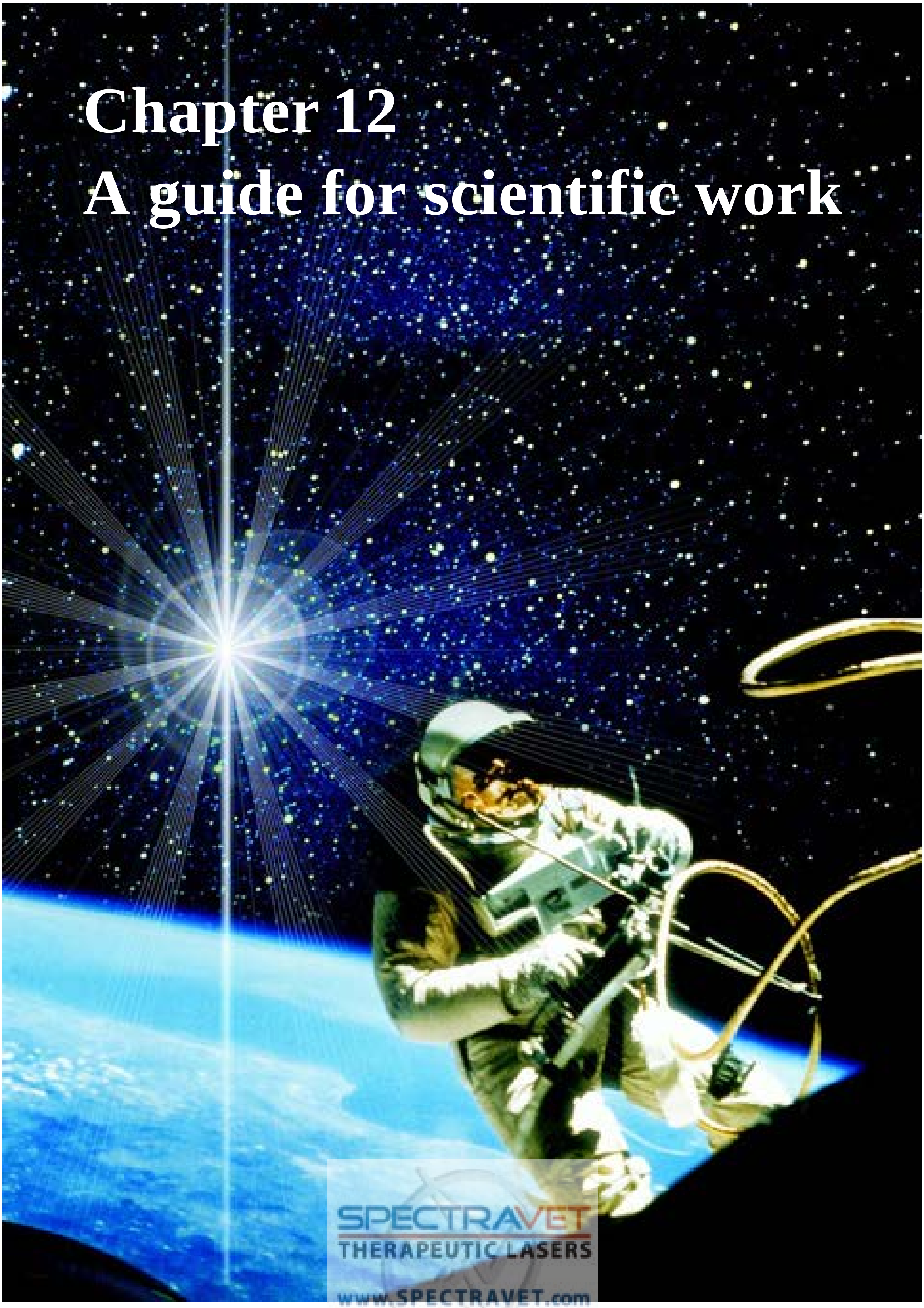
Laser cytofluorometry utilises the argon laser for scanning single stained cells and has achieved utilisation in mass examination programs for Pap-smear determinations. The same technique is used in a cell sorting system that is now important in monoclonal antibody determination in hybridoma technology.

Lasers can also be used in laser particle size measurement techniques, and laser nephelometry for determination of immunoglobulin classes and autoantibodies such as rheumatoid factors.

Examples of other techniques are transillumination by lasers (diaphanography), laser retinoscopy and holography

Laser-based methods have also been used to study air pollution involving carcinogens in occupational exposures and for the detection of narcotic drugs.

Chapter 12
A guide for scientific work



Designing a clinical trial is part science, part art. You need a sense of what works and the commitment to stick to it. The acceptance of a new method of medical treatment or medication must be based on good scientific research. In chapter 13 “The laser therapy literature” on page 379 in this book we will look at the laser therapy literature. We have found that many of the published articles are of low scientific value. However, this is not typical only of the positive studies. In the following chapter we suggest some guidelines for scientific work with laser therapy. Basically, laser therapy should be subject to the same standards of evaluation as other physical methods but must be combined with a knowledge of the special parameters of this method. Without this it will not become the valuable therapeutic tool in medicine that it has the potential to become. It is not uncommon to find a trial that is methodologically sound but not reproducible on the basis of the information supplied.

If you are going to perform a study and want to publish it, it is worth taking a look at how a study can be evaluated in a meta-analysis. Then you can allocate points to different criteria, such as the following, taken from the thesis by Lucas [1184].

A One point each if selection criteria are clearly described, restriction to a homogenous population with respect to diagnoses, duration of complaint, previous treatments and contra-indications for the laser treatment.

B Five points if randomisation procedure is described and is a procedure which excludes bias.

C Five points if smallest group is larger than 25 patients immediately following randomisation; ten points if larger than 50 patients and fifteen points if larger than 75 patients.

D Two points each if the study groups are comparable at baseline for (1) duration of complaint; (2) age; (3) baseline scores for outcomes measured; (4) recurrence status; (5) previous treatment of complaint.

E Five points if there are no dropouts after randomisation. Two points if there are dropouts, with the number of dropouts given for each study group. Three additional points if the reason for withdrawal after randomisation is given for each study group.

F Loss-to-follow up: 1 minus (the number of patients at the main moment of effect measurement / the number or patients at randomisation) x 100 %. One point if loss-to-follow up is less than 20% in each group. Four points if it is less than 10% in each group.

G Points are given to a description of the treatment. One point each for: (1) type of laser used; (2) wavelength and repetition rate [pulse repetition rate]; (3) duty cycle; (4) power; (5) irradiation [intensity]; (6) distance of probe to skin or contact; (7) mono-laser or multi-laser; (8) treatment time and pulse repetition rate; (9) probe position to skin - angular or perpendicular; (10) miscellaneous - plastic foil used for hygienic reasons, alcohol use, etc.

H Three points if a comparison is used with a study group receiving a placebo treatment only.

I Three points if a comparison is made between two or more existing interventions.

J One point if co-interventions are comparable between the groups; three points if co-interventions are standardised or avoided in the study design.

K One point if blinding of patients was attempted. Three additional points if the blinding proved to be successful.

L One point if blinding of therapists was attempted. Three additional points if the blinding proved to be successful.

M Points for assessed outcome measure: Two points for pain; four points for global measure of improvement (decreased wound surface area) and one point for adverse reactions.

N Points for every blindly assessed outcome measure: One point for pain; two points for global measure of improvement (decreased wound surface area), and one point for adverse reactions.

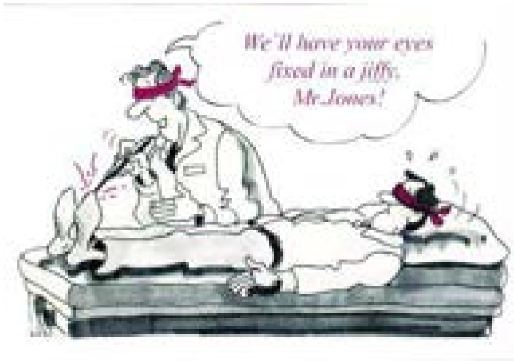
O Three points if the timing of effect measurement is identical for all study groups. Two additional points if final effect measurement was made at least three months after randomisation.

P Two points for intention-to-treat analysis. One point if data for most important outcomes measure on the most important moments of effect measurements are adequately presented (frequencies, mean, standard deviation). One additional point for an adequate analysis with adjustments for dropouts, loss-of-follow up, missing values, non-compliance and co-interventions if appropriate.

Q Two points for having adequate corrections for confounding variables.

As can be seen from this list, some 95% of the points concern methodology and 5% concern description of parameters, while no points concern the realism of parameter values. Hence, there are studies that receive a lot of points - i.e. are methodologically very well done - but are still more or less worthless because the laser parameters are badly chosen. For instance, if the dose chosen is so low that it can be regarded as "homeopathic", the study is bound for failure. To include such a study in a meta-analysis can lead to incorrect conclusions. An example:

Five studies based on sound methodology but using very low dosages, resulting in five negative studies with high scores. Another five studies, methodologically less sound but using realistic dosages, resulting in five studies showing positive effects but low scores. In this case a summing up of the average score leads to the conclusion that laser therapy has no significant effect.



Double blind study?

12.1 Methodology of a trial

After selecting a medical indication, consider the following points:

1 *Type of trial.* Do you want to make a pilot study, a single or double-blind study, a randomised or maybe a multi-centre study? A literature study or a meta-analysis? What resources do you have and how much time can you spend? Are there other studies published within your selected field?

2 *Preparations.* It is not unusual that the author(s) have not studied the literature well enough. Study articles - both positive and negative ones. Do not confine your literature search to Medline. Make independent evaluation of references.

3 *Selection of patients.* Remember that the effects of laser treatment on healthy tissue are much lower (if any) than on pathological or disturbed tissue.

4 *Blinding* In the case of treating people (contrary to treating cells and animals), attention must be paid to the blinding of the observer and the patients. Observer blinding has priority. Blinding procedures when visible lasers are used are difficult.

5 *Randomisation.* It is important that the randomisation occurs in such a way that a patient has an equal chance of being in the placebo group or the control group. Care must be taken to ensure that there is true randomisation rather than pseudo-randomisation. Therapists should be unaware of which group the patients have been randomised into.

6 *Cross-over study*. Sometimes it is necessary to use a reference group that gets no laser treatment, even in the case of suffering people (or animals). In this case a so-called crossover study is acceptable. This means that after the treatment sessions have been completed, only a short-time evaluation is done and the groups are then switched, so that the laser group gets placebo and vice versa. This method can also be used in blinded studies.

Much has been written about designing trials which are methodologically sound, and we will not further dwell on these matters. In order to make a trial reproducible, it is necessary to describe in considerable detail the parameters and mode of application of the laser, as outlined below.

12.2 Parameters

The parameters can be separated into three categories: Technical parameters that are related to the equipment used, treatment parameters that are related to the treatment situation, and medical parameters that are independent of the instrument used.

Technical parameters

1. Name of instrument (producer), production year.
2. Laser type and wavelength (e.g. 632.8 nm, HeNe laser)
3. Laser beam characteristics (polarised, divergent, collimated)
4. Number of laser sources (source distribution spatially)
5. Beam delivery system (fibre optics, hand held probe, scanner)
6. Pulsed or continuous emission (pulse repetition rate, type of pulsing and duty cycle)
7. Output power (peak power / average power / energy per pulse)
8. Power density (mW/cm²) at probe aperture (aperture size)
9. Calibration of the instrument (external, internal, meter type)

Treatment parameters

1. Treatment area (size and number of sites and/or number of treated points)
2. Dose: Energy density (described in detail) in J/cm² and/or J/point.
3. Total dose per treatment session and total dose for the entire course of treatment.
4. Intensity: Power density (at the treated surface) in mW/cm²

5 Rationale for chosen dosage

6 Treatment method (contact, pressure, distance illumination)

7 Treatment distance (spot size), type of movement, scanning

8 Sites of treatment (leg, knee, internal via fibre etc.)

9 Intended tissue target (synovia, cartilage, ganglion etc.) and its approximate distance from the skin surface.

10 Number of treatment sessions (is it the same for all patients?)

11 Frequency of treatment sessions (e.g. 2 per week for 3 weeks, then 1 per week)

Medical parameters

1 Description of the problem to be treated (history of disease)

2 Patients (number, age, sex)

3 Exclusion criteria (pregnancy, high blood pressure, epilepsy etc)

4 Inclusion criteria (how is the diagnosis defined?)

5 Condition of patients (acute, chronic, diabetics, other diseases)

6 Pre- parallel- or post-medication

7 Treated with other methods before (acupuncture, ultrasound, pharmaceuticals)

8 Dropout rate

9 Follow up (short- and long term)

12.2.1 Closer description of the technical parameters

Many of these parameters have been described previously and are well known to workers in the field. Some are less well described, however, and it is essential to understand them in order to know how a laser is best used in a particular trial.

1) Name of instrument (producer)

In many studies, where many parameters are lacking, it can be helpful to know the name (and producer) of the laser instrument. This makes it at least possible to get some information afterwards. It may also be useful to know the year of manufacture.

2) Laser type and wavelength

Traditionally a certain wavelength has been typical of a certain laser type, but with the development of semiconductor laser, groups of possible wavelengths for a certain laser type have appeared. The GaAlAs laser can be mentioned as an example; it can have more or less any wavelength in the region 730 to 890 nm. Tuneable lasers are also becoming more frequent. Even a HeNe laser does not necessarily have a wavelength of 632.8 nm (possible wavelengths for the HeNe laser are 543, 594 and 612 nm, although the 632.8 nm wavelength can give the highest output power).

Furthermore, two laser types can have the same wavelength but still give different biological results due to different coherence lengths. An InGaAlP-laser, for instance, can have the same wavelength as a HeNe-laser (632.8 nm). But a HeNe laser has a higher degree of coherence and a narrower bandwidth. (See chapter 1.5.1 “The Helium-Neon laser (HeNe)” on page 40 and chapter 11.1.2 “Comparisons between coherent and non-coherent light” on page 697.

The wavelength of the laser is an essential parameter. A certain wavelength may hence be more appropriate for a certain condition than other wavelengths. The wavelength should be given in nanometres or in micrometers. It is not sufficient just to describe the laser as "visible" or "infrared", though this can be added.

3) Laser beam characteristics

A laser beam is not just a laser beam. Typical characteristics are polarised or non-polarised light, divergent light, collimated or even focused light. Furthermore, the distribution of intensity within a beam of light can be very different from one laser to another. A semiconductor laser often has a fan-shaped beam.

4) Number of sources

It is not uncommon to have more than one laser source in a single instrument. A multi-probe has more than one light source. In this case, it is important to describe the situation carefully - how many sources, their spatial distribution and orientation and sometimes also different wavelengths. Always describe the outline of the diodes of a multi-probe by means of a photo or a drawing of the end of the laser probe - a picture says more than a thousand words!

N.B! Sometimes light emitting diodes (LEDs) are used as the active source/ sources together with laser diodes. It is of importance to describe this and to specify the wavelength, bandwidth, power and power density of each source. If LEDs are used as light indicators only, this should be specified.

5) Beam delivery system

Laser systems can look very different and, depending on the beam delivery system, the distribution of the light on the surface of the tissue and inside the tissue can vary considerably. The light can be transported by fibre optics (which usually eliminates polarisation), or it may come from a hand-held probe. It may be defocused to cover a larger area, or a focused beam may be moved across a determined surface using a scanner.

6) Pulsed or continuous emission

It is important to specify whether a laser is pulsed or not, as well as the method of pulsing. One reason is that it has been shown that different pulse frequencies give different biological responses, even when all other parameters are kept constant. Furthermore, there is a connection between penetration depth, power density and output power (peak and average output power).

However, there are many ways to pulse light (often the term "modulate" is used). This is described in: chapter 1.2.10 "Continuous and pulsed lasers" on page 16, chapter 1.2.12 "Average power output" on page 17 and Figure 1.7 "Different types of pulsing" on page 18. It is, of course, important to specify not only whether the light is pulsed or not, but also the duty cycle.

The most important parameter for a pulsed laser is the pulse repetition rate. This means the number of laser pulses per second and is measured in Hz. In some instruments, programmes control the pulse repetition rate so that at first one pulse repetition rate is used, and after some seconds the pulse repetition rate is changed. There are even examples of devices where the pulse repetition rate is gradually changed from low to high and back again. In the case of pulsing with pulse trains, it is necessary to specify exactly how the pulsing is done.

In the literature there are many examples showing that different pulse frequencies give different biological effects - (See chapter 3.3.1.13 "Pulse repetition rate" on page 78.) However, although research clearly shows that pulsing is of importance, there is very little knowledge about the clinical implication of a specific pulse repetition rate. And chopping of a continuous laser and true pulsing of a GaAs laser is probably not the same, even if the pulse repetition rate happens to be the same. The author should explain the reason for the choice of the pulsing mode.

7) Output power

The output power of a laser should be stated in watts or milliwatts per source. If the laser is pulsed, the situation becomes a bit more complicated. Then the following parameters must be clearly described:

- A Pulse repetition rate. One or several frequencies used?
- B Type of pulsing (chopping/switching, super-pulsing, modulation, e.g. pulse trains)
- C Duty cycle
- D Peak power
- E Pulse shape, pulse energy.
- F Average output power

There is also the following relation between average power and energy per pulse: average power = energy per pulse multiplied by the pulse repetition rate.

8) Power density at probe aperture

Power density at the probe aperture is not always important, because it is the power density in the actual problem volume that is the essential parameter. However, this is usually not known in detail and normally we chose a surface dose that is sufficiently high to obtain at least a reasonable dose at the depth of the problem to be treated. However, in order to make it possible to repeat a study, power density at the probe aperture is essential to know. Also, when some parameters are missing in a published study, this can be helpful to know. Power density is stated in mW/cm². It is also important to specify the area and shape of the aperture.

The most common treatment technique is to put a hand-held laser probe in contact with the skin or mucosa under which there is a problem to treat. In this case, the treated area is equal to the aperture size. If the aperture is small (5 mm diameter or less) the treated area can be regarded as a point and we can regard the power distribution across the treated area as a constant (in reality it is practically never constant, but with small treated areas it will not make any difference in the three-dimensional power distribution deep in tissue if the power density across the aperture is constant or not).

9) Calibration of the instrument

The output power of an instrument is often not the same as stated in the brochure. It is recognised that, as a laser diode heats up during use, its power tends to fall off unless the machine has an appropriate cooling device. The power of the laser should be measured, preferably by an independent source, before the beginning of the trial as well as at appropriate intervals within the trial and on completion of the trial, in order to determine that the laser power has remained constant throughout. It also happens that a laser diode or some electronic part breaks, leading to loss of most or all of the energy - in the worst case, maybe the whole trial is thus invalidated.

The power meter (or equivalent) should be specified (type of detector, wavelength sensitivity, make and producer). Some instruments have a built-in power meter, which may often be inaccurate. The user of an instrument needs to know if the laser source loses power over time and correct measurements are essential in scientific work.

12.2.2 Closer description of the treatment parameters

Among these parameters we find the two most essential ones: the energy density (dose) and the power density (intensity). These parameters are more closely described in chapter 1.2.13 “Power density” on page 17, chapter 3.3.1.4 “Power density” on page 69, chapter 3.3.1.5 “Energy density” on page 70 and chapter 10 - “The difficult dose and intensity” on page 311.

The combination and permutation of laser therapy variables for the treatment of different conditions is practically infinite and it can be very difficult to make decisions about what is an optimal dose for a particular pathology when the primary evidence is equivocal.

1) Treatment area

It is of course important to clearly specify the treatment area - if it is one area or several, if it includes areas over deep or shallow problems, as well as acupuncture and trigger points.

2) Dose: Energy density

In the absence of clearly defined protocols in the current literature, decisions about dosage need to come from clinical experience, case series and reports as well as from secondary sources of information such as books and manufacturers' manuals. Energy density of penetrating radiation falls off exponentially in the tissues - much higher doses at skin surface are needed to achieve the desired dose at deeper sites. Too low doses are certainly one of the reasons why many studies are reported as having negative outcomes. However, when treating over a vein or artery with low or no probe pressure, a marked fraction of the light affects the blood cells. This is of importance for systemic effects and general effects on the immune defence.

3) Dose per treatment and total dose

There are many methods of treatment and the description of treatments is essential. The description should include dose per treatment session, whether different doses are given to different areas, such as open wound area and wound edges (acupuncture or trigger points included) as well as the total dose for the whole series of treatment for each patient.

4) Intensity: Power density

The power density of the machine is a function of the power of the laser and the spot size of the area being treated. When in contact with the skin, the spot size will be the area under the probe tip. It is a measure of the potential thermal effects of the laser beam. Very often the power density at skin surface is determined by the aperture of the laser probe (the aperture is the area of the beam as it leaves the probe. When treating in contact, it is also the area of light penetration into the skin/tissue). For small apertures it is suggested that the power density be given in watts or milliwatts/point and for larger areas (<0.5 cm^2) in watts or milliwatts/cm^2.

5) Treatment method

A description of whether the laser is to be used in a scanning mode or in contact with the surface of the skin must be given. Also, it should be specified whether pressure is applied and if the probe area is flat or if the aperture(s) protrude(s), (which will give a higher local pressure, resulting in a larger blood-free volume under the contact area). Doses will vary according to which technique is used. In some cases, manufacturers might be able to indicate the appropriate distance from the skin surface used to achieve a particular dosage, as calculation of the dose is dependent on the particular characteristics of the machine. Some machines will calculate doses and energy densities depending on the technique used.

6) Treatment distance (spot size), type of movement, scanning

In some studies, the light from a laser aperture is spread out to cover the whole area to be treated (e.g. a leg ulcer). This results in a low power density. An alternative is to use a narrow beam and scan it over the surface - by hand or mechanically. This will give a higher power density and a better result. Whatever the method, it should be described in detail.

7) Sites of treatment

The anatomical entity that is treated should be explicitly described. This will differ depending on the condition or site being treated as well as the site of the pathology. A schematic picture would be desirable.

Anatomical sites should be described as well as sites of muscle insertions or ligaments. For example, in the treatment of lateral epicondylitis, the lateral epicondyle itself would be treated. But tender/trigger points in the extensor muscles of the forearm and their insertions may also be treated, as well as tender points in the neck relating to the myotome of the affected muscles. The position of the arm/leg will affect the distance to the patholgy in several conditions.

Where possible, a quantitative estimate of the depth of a site being treated should be performed, by ultrasound, CT scan or MRI, to help assess whether or not an appropriate dose has been applied to that area.

Acupuncture points should be described, using the WHO nomenclature for acupuncture points. It is also appropriate to describe the rationale for the point selection. Trigger points should be described according to the muscle in which they are located, a diagram being used where possible, and the rationale for their selection should be explained.

If the light is brought in by means of fibre optics or endoscopes, this should be described in detail. Output power should be measured at the aperture of the transfer system.

It is only when an explicit description of the treated sites is given that the study will be reproducible. It will then be possible to gauge whether or not the laser light has been able to reach the target tissue and an appropriate dose applied.

8) Number of treatment sessions

The total number of treatment sessions given in the course of treatment needs to be stated. Three or four sessions for laser acupuncture may be totally inadequate when a course of ten is regarded as usual.

It is also of interest to state if all patients receive treatment on the same number of occasions and whether all sessions are equal. Maybe a smaller dose is given per session as the surface of an ulcer decreases.

The total number of joules per treatment session should also be stated. If 10 contact points are treated at a rate of 1 joule/point, the total dose will be 10 joules per session. This may have relevance in terms of the condition treated as well as potential side effects. This may not need to be explicitly stated if it can be calculated from the number of points treated and the number of joules/point.

9) Frequency of treatment sessions

The intervals between sessions should be stated. Treatment once a week may be inappropriate for an acute condition but may be appropriate for a chronic condition. The pathology will determine the frequency of treatment. It is rather common to start a treatment series with two or three sessions per week and after some time go down to one treatment per week - this should be described. In the clinical situation, the intervals can be related to the patient's response, but in a scientific set-up the schedule must be rigid.

12.2.3 Closer description of the medical parameters

1) Description of the problem to be treated

It is important that the problem to be treated is well defined and that the treatment situation is as equal as possible for all the patients. In other words, we must have a correct diagnosis. One of the most important issues is to find out the history of disease for each patient. Also, it may be of interest how the diagnosis was reached - the tools used; X-rays, ultrasound scanning, thermal mapping, etc.

2) Patients (number, age, sex)

In the description we need to state parameters as number, age and sex. But things like skin type may also be of interest, as dark skin absorbs light much more than white skin.

3) Exclusion criteria

Typical exclusion criteria may be pregnancy, high blood pressure, epilepsy, etc. - also extremes (e.g. when treating ulcers, too large and too small ones can be excluded).

4) Inclusion criteria

In selecting the patient population to be treated within the trial, appropriate inclusion and exclusion factors should be used to obtain as homogeneous a group as possible. The diagnosis, e.g. tendinitis or myofascial pain, should be as clear as possible. The particular pathology of the patient being treated should, if possible, conform to standard diagnostic criteria such as those of the International Society for Pain or other appropriate international bodies.

5) Condition of patient

Diabetes or other diseases may influence the reaction to laser therapy treatment. Acute and chronic conditions should be differentiated. The dose of laser may need to be adjusted according to the type of pathology.

6) Pre-, parallel- or post-medication

Sometimes it is of interest to compare the effects of laser therapy with effects of medication. If parallel medication is prescribed, one group with medication only, one with laser only and one with a combination of laser and medication could be considered. Synergistic effects can be expected in many cases. A drug intake diary will be a valuable indirect clue to the effect of the laser therapy.

7) Treated with other methods before

Many times the patients have tried many other treatment modalities like physiotherapy, acupuncture, ultrasound, electro-stimulation and pharmaceuticals. This information is of interest, since a favourable outcome of laser therapy would indicate the severity of the condition to be overcome.

8) Drop-out rate

This information is of importance since it will give a clue on patients' compliance and researchers' control of the protocol.

9) Follow up

While the effect of laser therapy may be immediate for some problems, it may also take a long time to surface in other conditions. It may have a long lasting effect or be of short duration only. Therefore, short-time as well as long-time follow up is valuable.

10) Outcome measures

Visual Analogue Scale and other subjective outcome measures are useful, but to obtain more objective outcome measures methods such as thermography, blood analysis, microdialysis, MRI, etc., are recommended.

11) Statistical Analysis

A statistical evaluation of the study is necessary and it is advisable to consult an expert before the final design of the study is determined. Student's t-test, Mann Whitney U-test, Chi-square test are examples of methods used and they should be selected according to the type of study outlined.

12) Economy

In order to be able to follow the specifications above, good research funding is necessary. This is seldom the case. Laser manufacturers of today are not too profitable and the outcome of a study cannot be patented, like a pill. The above list can therefore be seen as the list given to Santa Claus before Christmas - you must expect to receive less. The main thing is to be aware of "the ideal situation" and to explain why limitations have been made.

12.3 Gallium-aluminium and all that

The first commercially promoted biostimulative laser was a gas laser - the HeliumNeon laser, wavelength 632.8 nm. A bit ironically the next one was a GaAs laser, the 904 nm Gallium-Arsenide laser. One gas laser and one GaAs laser. Opportunities for confusion. But the GaAs laser, in spite of its semantic similarity to the HeNe gas laser was not based on any gas, but on a diode. And all the forthcoming ones too. Even the 635 nm red laser is these days a diode laser. It is based on a diode consisting of indium, gallium, aluminium and phosphide and called InGaAlP. The ones above 770 nm are generally based upon a diode consisting of gallium-aluminium-arsenide - the GaAlAs laser. All are diodes. So is the GaAs 904 nm laser, but it is different because it is always pulsed. But to make things more complicated, it is possible to produce a 904 nm GaAlAs diode, which then would not be (super)pulsed.

A bit confusing? Yes, and quite unnecessarily so. In research papers you can often read something like "the laser used was a Gallium-Aluminium-Arsenide diode laser of 808 nm". Simply too much information! Just presenting the wavelength is quite sufficient, because this is what counts. And frequently authors get it wrong and call the red lasers GaAlAs, when they actually are InGaAlP ("indium lasers"). An on top of this, some manufacturers use the term AsGa and AsGaAl. They are free to do so, because there is no international standard and the scientific journals do not seem to care. But it certainly adds to the overall confusion. So throw the "gallium-aluminium" out of the window and just write "an 808 nm laser". Only in exceptional cases the composition of the crystal is needed to be described, for instance if the 904 nm laser actually is a GaAlAs laser and not a GaAs laser. That indeed makes a difference. And if someone would invent a gas laser of 808 nm, that would also have to be reported, because a gas laser has different speckle characteristics than a diode laser.

While on the subject - there are very few 808 nm lasers, although these are by far the most commonly used biostimulative lasers. The actual wavelength varies about +- 10 nm. If you want one with 808 nm and nothing else, it is expensive! The ones with a variation in the same box of diodes are less expensive and therefore added to 99% of the therapeutic lasers. Not that it matters a lot, but a 790 nm laser and an 808 nm laser could actually both be working on 799 nm! And then this: when used over a longer period the diode not only loses power as the temperature goes up, the wavelength may shift too.

All these details do not matter very much in the clinical setting. But if you are contemplating starting as scientific study, think about it!

12.4 Recommendations of WALT - The World Association for Laser Therapy

The World Association for Laser Therapy (WALT) has published recommendations to guide scientists and researchers. These can be found on the WALT website http://waltza.co.za/ and are:

Consensus agreement on the design and conduct of clinical studies with low level laser therapy and light therapy for musculoskeletal pain and disorders.

Standard for the design and conduct of systematic reviews with low level laser therapy for musculoskeletal pain and disorders.

Laser dosage table for musculoskeletal disorders using 904 nm pulse lasers.

Laser dosage table for musculoskeletal disorders using 780 - 860 nm lasers.

The recommendations of the World Association for Laser Therapy can be found here:

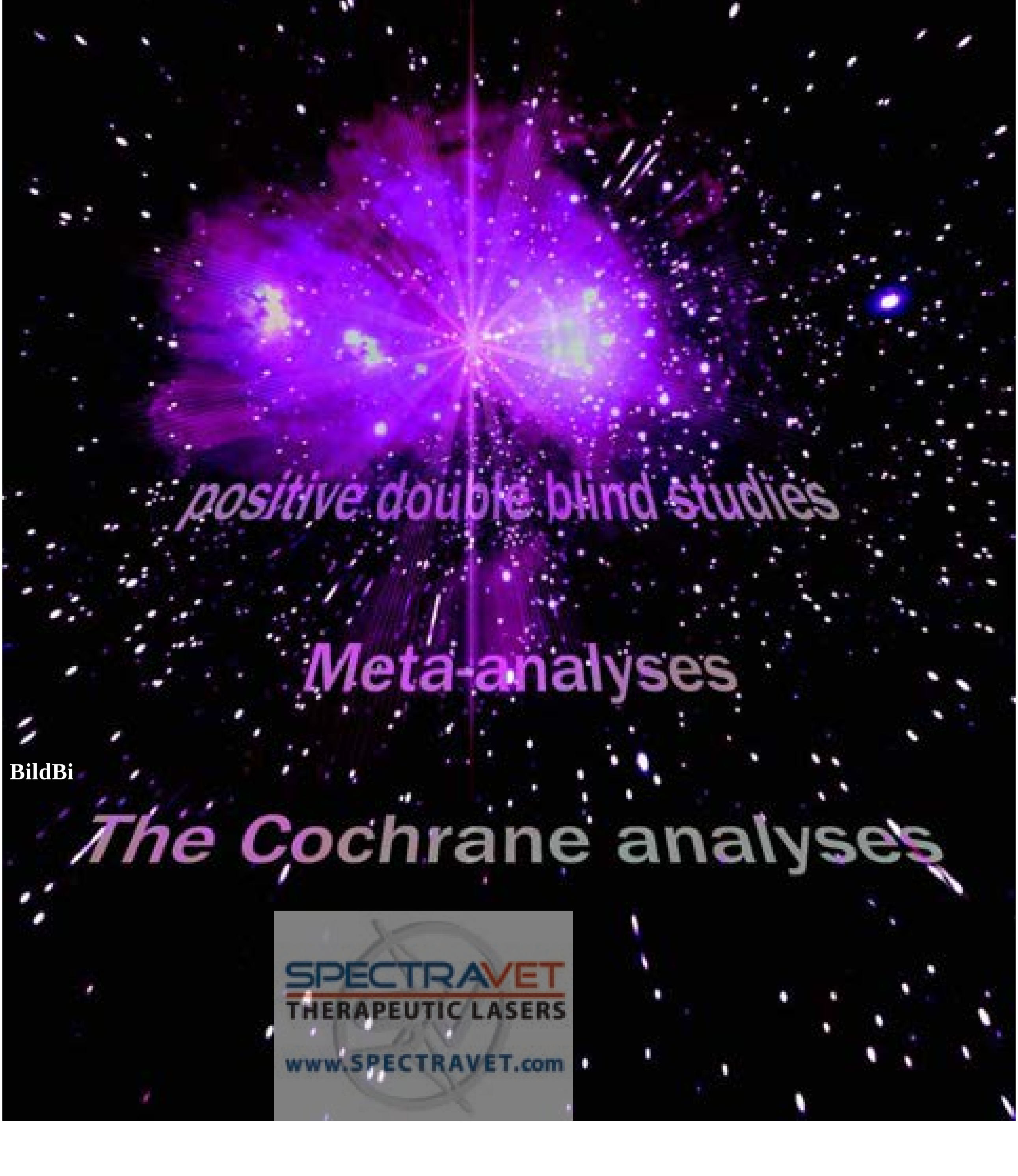
http://waltza.co.za/documentation-links/recommendations/dosage-recommendations/

The dosage commendations are based upon the scientific studies where positive results have been reported. The time for each point varies between 20-600 seconds, which could suggest that “anything goes”. However, it is only a reflection of the fact that many lasers were very low powered in the 90ies. But a minimum time of 20 seconds remains a reasonable recommendation.

Conclusion

One of the reasons for the lack of general acceptance of laser therapy among medical doctors and dentists is the overall quality of research. Lack of quality control has produced negative results in some studies and criticism of many of the positive studies. Ironically enough, the major failure in many laser therapy studies has been lack of attention to the therapeutic tool itself. By improving the design as well as the reporting of all the variables used in trials, we believe that laser therapy will become as well a recognised entity as laser surgery.

Chapter 13
The laser phototherapy literature



BildBi

13.1 The laser phototherapy literature

From a strict scientific point of view, LPT is not an evidence based therapy, except for a few indications. In order to be considered such therapy, rigorous requirements need to be fulfilled. In some fields these requirements are indeed fulfilled, for example the use of LPT as a therapy for mucositis. But the beauty of the therapy is standing in the way for a general acceptance. The beauty is that LTP is a useful treatment modality for so many indications. But this also connotes that some indications have but a few acceptable studies to lean on and the quality of these are not sufficient for reaching an evidence based level. This is not unique for LPT; many traditional therapies are accepted out of tradition, although the level of evidence is poor. Therapies for endodontic therapy [2148] and TMD [2301] are just a few of these. Indeed, the majority of therapies subjected to the rigorous Cochrane requirements fail to reach the highest level of evidence.

Research published in quality journals is indexed on PubMed and this is the most common source for searching for information about the scientific standards. For a moment disregarding the problems with trusting the abstracts on PubMed, the number of studies in this gigantic data base is a good yardstick. Today, there are some 3.700 papers on LPT registered on PubMed. Seems to be an impressing figure, but it is actually not. More traditional therapies may have 100.000 papers, but LPT is not playing in that division - yet. To make a couple of comparisons, we can compare with acupuncture and massage therapy. Acupuncture has some 20.000 hits and massage therapy some 11.000. But then, these therapies have been around for decades and massage therapy has references to papers way back in 1967 and onwards. LPT had hardly entered PubMed in the year 2001 (total of 85 listings), and today the number of papers published annually for LPT and massage therapy is about the same. So LPT is catching up. In the PEDro data base for physiotherapy, there are about 200 randomised clinical studies listed and althogether there are about 400 RCT:s. But again, for a diversity of indications. In spite of the lack of a strict evidence based acceptance, LPT is moving into acceptance in many areas. One example is the evaluation of strategies to publish neck pain [2326] where the authors state that "For whiplash-associated disorders, there is evidence that educational videos, mobilization, and exercises appear more beneficial than usual care or physical modalities. For other neck pain, the evidence suggests that manual and supervised exercise interventions, low-level laser therapy, and perhaps acupuncture are more effective than no treatment, sham, or alternative interventions; however, none of the active treatments was clearly superior to any other in either the short- or long-term." The evaluation of the Swedish Council on Health Technology Assessment (2014) is also on a positive note [2525].

For those wishing to make a reasonable evaluation of the clinical effect of LPT, without being able of finding an evidence based level of documentation, it is recommended to make a collected evaluation of the papers on pain, oedema and inflammation. After all, most pathologies contain these three conditions to a varying degree. And certainly containing cells in a low redox situation and with low ATP production. The conclusion becomes indirect but will in most cases lead to a positive evaluation.

Some problems

In order to improve the acceptance of LPT, the quality of studies needs to be improved and indeed the reviewers of LPT papers have to improve. It is not unusual to find a paper where everything is fine, except the laser part. Reviewers have been experts in their areas but not in LPT, and thus overlooked flaw in design and laser parameters. A too common feature is the lack of complete laser parameters. And unless all parameters are accounted for, the study cannot be duplicated to control its statements. A control study then is likely to become a different study. A too common mistake is to state the dose (J/cm^2) only and not the energy (J) or vice versa. And readers of this book have already noted that a high value for J/cm^2 can be achieved with just about any energy, simply by choosing a very thin or a very wide laser aperture. So comparing "doses" can lead to pitfalls. It is not uncommon to read the discussion part of studies where apples and oranges are compared. Too often, authors seem to believe that J and J/cm^2 are the same thing. Further, old and less relevant papers are often quoted in order to produce a good list of references.

In order to reach an evidence based level, several RCTs with the same design and conclusion must be available. With the problems above in mind, this is hard to find. And further to that, different authors have different laser protocols, treatment strategies and evaluation protocols. This means that it is difficult to find two verifying studies, even if there are dozens of papers in the area.

Now back to PubMed. Here we find the abstract of the papers. If we want to read the full paper, it has to be obtained elsewhere and very often at a price. Thus, a majority of scientifically oriented persons look at PubMed, read the abstracts and draw their conclusions. However, the abstracts often fail to give a complete account of the laser parameters. These may or may not be found in the full paper, but if not in the abstract, the value of the paper cannot be estimated. Another *cul de sac*. If you are interested in setting up a LPT trial, please consult the guidelines of the World Association for Laser Therapy, available on www.waltza.com.za.

The negative studies

LPT cannot work for everything, and especially if the laser parameters are outside of the therapeutic range. A part of the available literature contains negative results. The authors of this book have analysed a lot of these studies in order to find out if it is a "true" negative study or if there is something wrong with the paper. In previous editions of this book we have devoted an entire chapter to these evaluations. Readers may check www.laser.nu or www.laserannals.com to read about this in greater details. It is obvious that there are many negative papers being referred to by people who have not read them or understood them, and thus disseminating them as a city tale. This situation is certainly not unique to LPT, but needs to be underlined. Here, it is fair to state that a lot of the positive studies are candidates for criticism as well.

The Cochrane collaboration

The Cochrane system is one of the most rigorous scientific systems there is. Old and new therapies are continuously evaluated by skilled collaborator teams. Although these evaluations every now and then are met with controversies, Cochrane is considered the Number One and is highly respected, and for good reasons. It is therefore problematic when such an esteemed system evaluates LPT and shows signs of incompetence. The first evaluations were on venous ulcers [2367], osteoarthritis [1024] and rheumatoid arthritis [1023]. All published in the year 2000, and could not find many studies of any quality. The papers consequently report that LPT for these indications has no scientific documentation. This was, at that time, quite correct. However, the conclusion was based upon a poor understanding of laser phototherapy. Studies using incoherent light were included as laser studies, papers having very little or no reporting on the laser parameters where included and also, unknowingly, the evaluation of venous ulcers was mainly based upon two papers published by a researcher who was later on found to be fraudulent. And further to that, the evaluators put all the studies "into the same basket" and draw their conclusions, disregarding the variations in laser parameters and even the absence of such. One of the main evaluators has later on continued to publish in the same fashion [1528]. The Cochrane OA group has further to that been accused of bias [1507]. Other Cochrane evaluations have followed and the rather negative inclination of these has had a better base, such as lumbar pain [1787] and tuberculosis [1283].

Other experts

When performing a literature review, it is important that the participants are qualified in science and its methods, and unbiased. Several evaluations have been fulfilling these requirements. Unfortunately, just one thing was lacking: knowledge about the very method the group was about to evaluate. The Cochrane collaboration has already been mentioned. Yet another is The Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, Chicago, USA [2368]. The evaluation is prepared for Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The latter is of course a very important decision-maker in healthcare. The Blue Cross evaluation follows the Cochrane style: incorrect inclusion of studies, no evaluation of dosage windows, no understanding of what is laser and what is LED. The conclusion at the end is still inevitable:

there is no scientific evidence for the use of pressure and crural ulcers. So what is the problem? The problem is that the conclusion is based upon an incorrect evaluation of the included studies and next time, when there is more evidence, this may show.

Another example follows:
Effectiveness of low level laser therapy in treating various conditions. A rapid review. By WorkSafeBC Evidence-Based Practice Group, British Columbia, Canada.
http://www.worksafebc.com/health_care_providers/Assets/PDF/low_level_laser_therapy.pdf

The aim of a literature review was to check if there was any scientific documentation for chiropractic use of laser phototherapy. Literature search was done up till 2008. The outcome was very negative. Here is why: Of the 38 references, 15 were later than the year 2000. The majority of qualified clinical studies and reviews have been published during the past decade.

One literature review quoted is from 1995
The only reference on rheumatoid arthritis is a Russian abstract using blood irradiation
3 references are on combined LED/Laser therapy
2 references are in vitro studies
2 references are congress abstracts
1 is on macular degeneration
2 are on postmastectomy complications, not finding the relevant Carati study.
1 is on leukemia
1 is on the growth of bacteria
1 is on orthodontics
1 is a comment in a journal
No study is from Photomedicine and Laser Surgery

Now, the questions are:
Are these studies relevant to chiropractic treatment?
Is the selection of references reflecting the present availability of scientific evidence?
Is the search for literature thorough?
Will this review meet the aim of the work?
Will chiropractors be better informed by reading this review?

The answer to all these questions is NO

Cost benefit
The first aim of medical research should be to find successful methods to treat disease. However, there are also important economic aspects. Not only for the patent holder to get their invested money back and with a profit.

There are also other interested parties - politicians. For good reasons, politicians and medical decision makers are interested in offering good health services, but also to cut costs. Therefore, every therapy has to prove that it is cost effective. So far very few cost -benefit LPT studies have been reported. One study [2246] found that using LPT for mucositis cut costs by 30%. This is just the beginning for a therapy likely to save billions, if used according to the available knowledge. A patient with a venous ulcer on average costs Swedish tax payers about 4.000 USD per year. Suppose costs could be cut by 30%, and millions are saved for other purposes. Costs for hospitalisation, pharmaceuticals and sick leave could be reduced by 30% and more in several pathologies, especially if used in the initial phase and not waiting until LPT is used as a last resort.

The funding of research

Every researcher needs funding and quite often this funding is not available from a university, government funds or private funds. Cooperation with the industry is quite usual and often needed. Industry funding is not without problems; this is only too well known. A research group [1421, 1798] summarises that non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors (coxibs), reduce short-term pain associated with knee osteoarthritis only slightly better than placebo, and long-term use of these agents should be avoided. Up for analysis were 23 placebo-controlled trials involving 10,845 patients, 7767 of whom received NSAID therapy and 3078 placebo therapy. All in all 21 of the NSAID-studies were funded by the pharmaceutical industry, and the results of 13 of these studies were inflated by patient selection bias as previous NSAID-users were excluded if they had not previously responded favourably to NSAID. In the remaining 10 unbiased NSAID-trials, the difference from placebo was only 5.9 mm on a 100 mm pain scale. This is far less than established data on differences that are considered minimally perceptible (9 mm) or clinically relevant (12 mm) for knee osteoarthritis patients. In addition, none of the trials found any effects beyond 13 weeks. As can be seen, 21 out of 23 were funded by the industry and several of these were biased and all of them actually demonstrated a poor long term outcome. Still, NSAIDs remain the most common therapy for knee osteoarthritis.

The Laser Phototherapy industry is far from rich. A lot of money is needed to perform an RCT of any quality, and the majority of manufacturers are not profitable enough to sponsor such research. The best they can do is to offer a laser machine and technical support. And if the study is successful, any competitor can use the information to promote his own business. No patents possible. Having this in mind, almost 400 annual studies on PubMed is not too bad.

Measures to be taken
In order to improve the quality of LPT research, scientific journals ought to require a proper set of laser parameters for any paper and to have these parameters included in the abstract. Today, not even the specialised laser journals have this requirement. Journals further need to look for competent reviewers in the field of LPT before publishing papers. Research groups are recommended to cooperate with technical experts and to study the scientific recommendation of the World Association for Laser Therapy. The laser equipment should be independently measured and the parameters applied should be motivated, not just picked at random. References to other studies should include the parameters of these, if available, and comparisons of apples and oranges should be avoided in the discussion.

Summing up
LPT research needs to expand and improve, no doubt. However, there are several misunderstandings circulating, due to negative but incorrect studies. The lack of side effects ought to make LPT an attractive option in a time where the side effects of pharmaceuticals have reached an alarming level and the havocking use of antibiotics is fighting back.

13.2 The importance of reporting all laser parameters - even in the abstract

It is a regrettable fact that the reporting of laser parameters has not yet reached a satisfactory level in scientific journals. These parameters must always be reported, or should the paper be returned for improvement, or discarded. The parameters must also be included in the abstract. Indeed, in several papers the proper reporting is found in the manuscript but not in the abstract. But the abstract goes in an unchanged version to PubMed - and most people confine themselves to reading the PubMed abstracts. The original papers are expensive to buy, if not available through a university library.
Below are the first ten PubMed papers on LLLT from a random day in July 2012. Reviews and Meta analyses were excluded. Let us see what is reported about the laser parameters!

They received transcutaneous LLLT irradiation at the lesion site. The LLLT parameters were: wavelengths - 660 or 780 nm; energy densities - 10, 60 or 120 J/cm²; power - 40 mW; spot - 4 mm².
Not bad at all, but the energy is not reported and since the time per point is not reported, it cannot be calculated.

This study evaluated the effect of LLLT (GaAlAs, 780 nm, 20 J/cm², 40 mW)
The lasing medium such as GaAlAs is of no interest, wavelength tells anyway. Applied energy, spot size and time per spot missing.

A 5×200-mW 810-nm cluster array was used to deliver 25 W/cm^2 to the skin.
With cluster probes, the spot size and the geometrical configuration need to be reported. A total of 1 W over one cm^2? Reporting is inadequate.

Transcutaneous 808 nm, 450 mW, (13.5 or 54 J) continuous wave (cw) mode or 650 nm, 35 mW, (1.1 or 4.4 J), cw LI or sham LI, was applied for 30 or 120 sec to a single point overlying the midpoint of rat sciatic nerve.
Spot size and J/cm^2 missing.

…was performed followed by 25 mW/cm^2 LLLT at 650 nm for 10 min/day.
Not very informative

820 nm; continuous wave; output power: 50 mW; focal spot: 0.0314 cm^2; exposure duration: 5 sec; power density: 1.59 W/cm^2; energy dose: 0.25 J; energy density: 7.96 J/cm^2 for each shot.
Wow!

….investigated the effects of LLLT with a diode laser (808 nm) device on the healing.
Everything missing except for the wavelength.

…before and after treatment with low-level laser therapy (LLLT).
The least informative of them all.

Group 1 was the control group, group 2 received 830 nm laser radiation, and group 3 was submitted to 670 nm laser radiation (power density = 0.5 mW/cm^2). The animals underwent laser therapy with 36 J/cm^2 energy density (total energy = 2.52 J and 72 sec per session) immediately after surgery and on the 4 subsequent day.
Power of lasers and spot size missing. Were the parameters of the two wavelengths really identical?

…10 sessions of LLLT (830 nm, output power of 50 mW, and fluence of 707 J/cm^2.
Energy, time and spot size missing

So why are all these parameters necessary? One obvious reason is that it must be clear what was actually performed. The other one is that with all parameters given, a qualified reader will be able to make a control calculation of the reported parameters. Too often (in fact, always) the discussion part in LLLT papers refers to studies with a great variation of parameters and without stating these differences. So the discussion will compare apples and oranges.

So, here is the checking list for your next study. Report these parameters in the manuscript and in the abstract:

1. Wavelength
2. Output power in mW (as independently measured!)
3. For GaAs laser: average output in mW
4. Spot size
5. Energy per point (J)
6. Energy density (J/cm²)
7. Power density (mW/cm²)
8. Time per point, in seconds

And before you start, check these guidelines too: http://waltza.co.za/documentation-links/recommendations/scientific-recommendations.

Complicated and difficult? Yes, it's science!

13.3 Diclofenac, dexamethasone or laser phototherapy?

In the May 2013 edition of Photomedicine and Laser Surgery, the editorial written by Tiina Karu has the title: *Is it time to consider photobiomodulation as a drug equivalent?* Let us have a look and see what the literature has to say about two very popular drugs:

NSAIDs (non steroidal anti-inflammatory drugs) are the best sold pharmaceuticals ever. The short term effects on pain and inflammation are obvious and very valuable. The long term effects, however, have been questioned and this is especially valid considering the many side effects of NSAIDs. Millions of patients are on long term medication with NSAIDs, and even lifelong. Indeed, many persons die from their medication. So an alternative option is required. I believe it is already available: laser phototherapy! First, let us have a look at the strength of the scientific evidence for NSAIDs as such, and long term use of these in particular:

The previously mentioned Meta-analysis by Bjordal [1] on the effect of NSAIDs on knee osteoarthritis pain appears to become important for the recognition and future development of LPT. Let us read the abstract again: The research group summarises that nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors (coxibs), reduce short-term pain associated with knee osteoarthritis only slightly better than placebo, and long-term use of these agents should be avoided. Up for analysis were 23 placebo-controlled trials involving 10,845 patients, 7767 of whom received NSAID therapy and 3078 placebo therapy. All in all 21 of the NSAID-studies were funded by the pharmaceutical industry, and the results of 13 of these studies were inflated by patient selection bias as previous NSAID-users were excluded if they had not previously responded favourably to NSAID. Such an exclusion criterion for non-responders has never been seen in any controlled trial of LPT or other non-pharmacological therapies of osteoarthritis. In the remaining 10 unbiased NSAID-trials, the difference from placebo was only 5.9 mm on a 100 mm pain scale. This is far less than established data on differences that are considered minimally perceptible (9 mm) or clinically relevant (12 mm) for knee osteoarthritis patients. In addition, none of the trials found any effects beyond 13 weeks. This bleak support for long term use of NSAIDs is an excellent support for non-pharmaceutical methods, such as LPT.

Diclofenac is one of the best-selling NSAIDs. Several investigators have compared the effect of LPT and diclofenac:

The aim of a study by Marcos [2] was to evaluate the short-term effects of LPT or sodium diclofenac treatments on biochemical markers and biomechanical properties of inflamed Achilles tendons. Wistar rats Achilles tendons (n=6/group) were injected with saline (control) or collagenase at peritendinous area of Achilles tendons. After 1 h animals were treated with two different doses of LPT (810 nm, 1 and 3 J) at the sites of the injections, or with intramuscular sodium diclofenac. Regarding biochemical analyses, LPT significantly decreased COX-2, TNF-alpha, MMP-3, MMP-9, and MMP-13 gene expression, as well as PGE_2 production when compared to collagenase group. Interestingly, diclofenac treatment only decreased PGE_2 levels. Biomechanical properties were preserved in the laser-treated groups when compared to collagenase and diclofenac groups.

Ramos [3] investigated the effects of LPT (810 nm) in rat-induced skeletal muscle strain. Male rats were anaesthetised with halothane prior to the induction of muscle strain. Previous studies have determined that a force equal to 130% of the body weight corresponds to approximately 80% of the ultimate rupture force of the muscle tendon unit. In all animals, the right leg received a controlled strain injury while the left leg served as control. A small weight corresponding to 150 % of the total body weight was attached to the right leg in an appropriate apparatus and left to induce muscle strain twice for 20 minutes with 3 minute intervals. Walking index, C-reactive protein, creatine kinase, vascular extravasation and histological analysis of the tibial muscle were performed after 6, 12 and 24 hours of lesion induction. LPT in an energy dependent manner markedly or even completely reduced the Walking Index, leading to a better quality of movement. C-reactive protein production was completely inhibited by laser treatment, even more than observed with Sodium diclofenac inhibition (positive control). Creative Kinase activity was also significantly reduced by laser irradiations. In conclusion, LPT operating in 810 nm markedly reduced inflammation and muscle damage after experimental muscle strain, leading to a highly significant enhancement of walking activity.

The aim of the study by de Almeida [4] was to analyse the effects of sodium diclofenac (topical application), cryotherapy, and LPT on pro-inflammatory cytokine levels after a controlled model of muscle injury. For such, we performed a single trauma in tibialis anterior muscle of rats. After 1 h, animals were treated with sodium diclofenac (11.6 mg/g of solution), cryotherapy (20 min), or LPT (904 nm; superpulsed; 700 Hz; 60 mW mean output power; 1.67 W/cm^2; 1, 3, 6 or 9 J; 17, 50, 100 or 150 s). Assessment of interleukin-1 and interleukin-6 (IL-1 and IL-6) and tumour necrosis factor-alpha levels was performed at 6 h after trauma employing enzyme-linked immunosorbent assay method. LPT with 1 J dose significantly decreased IL-1, IL-6, and TNF-alpha levels compared to non-treated injured group as well as diclofenac and cryotherapy groups. On the other hand, treatment with diclofenac and cryotherapy does not decrease pro-inflammatory cytokine levels compared to the non-treated injured group. Therefore, the authors conlude that 904 nm LPT with 1 J dose has better effects than topical application of diclofenac or cryotherapy in acute inflammatory phase after muscle trauma.

The purpose of a study by Albertini [5] was to investigate the effect of LPT on the acute inflammatory process. Male rats were used. Paw oedema was induced by a sub-plantar injection of carrageenan, the paw volume was measured before and one, two, three and four hours after the injection, using a hydroplethysmometer. To investigate the action mechanism of the GaAlAs laser on inflammatory oedema, parallel studies were performed using adrenalectomised rats or rats treated with sodium diclofenac. Different laser irradiation protocols were employed for specific energy densities (EDs), exposure times and repetition rates. The rats were irradiated with laser for 80 s each hour. The EDs that produced an anti-inflammatory effect were 1 and 2.5 J/cm^2, reducing the oedema by 27% and 45.4%, respectively. The ED of 2.5 J/cm^2 produced anti-inflammatory effects similar to those produced by the cyclooxigenase inhibitor sodium diclofenac at a dose of 1 mg/kg. In adrenal-ectomised animals, the laser irradiation failed to inhibit the oedema. These results suggest that LPT possibly exerts its anti-inflammatory effects by stimulating the release of adrenal corticosteroid hormones.

The aim of a work by Meneguzzo [6] was to investigate the effects of infrared 810 nm on the acute inflammatory process by the irradiation of lymph nodes, using the classical model of carrageenan-induced rat paw oedema. Thirty mice were randomly divided into five groups. The inflammatory induction was performed in all groups by a sub-plantar injection of carrageenan (1 mg/paw). The paw volume was measured before and 1, 2, 3, 4 and 6 hours after the injection using a plethysmometer. Myeloperoxidase (MPO) activity was analysed as a specific marker of neutrophil accumulation at the inflammatory site. The control group did not receive any treatment (GC); GD group received sodium diclofenac (1mg/kg) 30 minutes before the carrageenan injection; GP group received laser irradiation directly on the paw (1 Joule, 100 mW, 10 sec) 1 and 2 hours after the carrageenan injection;

GLY group received laser irradiation (1 Joule, 100 mW, 10 sec) on the inguinal lymph nodes; GP+LY group received laser irradiation on both paw and lymph nodes 1 and 2 hours after the carrageenan injection. MPO activity was similar in the sodium diclofenac as well as in the GP and GLY groups, but significantly lower than the GC and GP + LY groups. Paw oedema was significantly inhibited in GP and GD groups when compared to the other groups. Interestingly, the GP+LY groups presented the biggest oedema, even bigger than in the control group. LPT showed an anti-inflammatory effect when the irradiation was performed on the site of lesion or at the correlated lymph nodes, but showed a pro-inflammatory effect when both paw and lymph nodes were irradiated during the acute inflammatory process.

The aim of a study by Barretto [23] was to investigate the analgesic and anti-inflammatory activity of LPT on the nociceptive behavioural as well as histomorphological aspects induced by injection of formalin and carrageenan into the rat temporomandibular joint. The 2.5% formalin injection (FRG group) induced behavioural responses characterised by rubbing the orofacial region and flinching the head quickly, which were quantified for 45 min. The pre-treatment with systemic administration of diclofenac sodium-DFN group (10mg/kg i.p.) or irradiation with infrared LPT (LST group, 780 nm, 70 mW, 30s, 2.1 J, 52.5 J/cm^2), significantly reduced the formalin-induced nociceptive responses. The 1% carrageenan injection (CRG group) induced inflammatory responses over the time-course of the study (24h, and 3 and 7days) characterised by the presence of intense inflammatory infiltrate rich in neutrophils, scanty areas of liquefactive necrosis and intense interstitial oedema, extensive haemorrhagic areas, and enlargement of the joint space on the region. The DFN and LST groups showed an intensity of inflammatory response that was significantly lower than in CRG group over the time-course of the study, especially in the LST group, which showed exuberant granulation tissue with intense vascularization, and deposition of newly formed collagen fibres (3 and 7days).

The aim of a study by de Almeida [7] was to analyse the effects of sodium diclofenac (topical application) and LPT on morphological aspects and gene expression of biochemical inflammatory markers. The researchers performed a single trauma in tibialis anterior muscle of rats. After 1 h, animals were treated with sodium diclofenac (11.6 mg g(-1) of solution) or LPT (810 nm; continuous mode; 100 mW; 1, 3 or 9 J; 10, 30 or 90 s). Histological analysis and quantification of gene expression (real-time polymerase chain reaction-RT-PCR) of cyclooxygenase 1 and 2 (COX-1 and COX-2) and tumour necrosis factor-alpha (TNF-alpha) were performed at 6, 12 and 24 h after trauma. LPT with all doses improved morphological aspects of muscle tissue, showing better results than injury and diclofenac groups. All LPT doses also decreased COX-2 compared to injury group at all-time points and to diclofenac group at 24 h after trauma. In addition, LPT decreased TNF-alpha compared both to injury and diclofenac groups at all-time points. LPT mainly with dose of 9 J is better than topical application of diclofenac in acute inflammation after muscle trauma.

Yet another study by Marcos [8] investigated if a safer treatment such as LPT could reduce tendinitis inflammation, and whether a possible pathway could be through inhibition of either of the two-cyclooxygenase (COX) isoforms in inflammation. Wistar rats (six animals per group) were injected with saline (control) or collagenase in their Achilles tendons. Then treated with three different doses of IR LPT (810 nm; 100 mW; 10 s, 30 s and 60 s; 3.57 W/cm^2; 1 J, 3 J, 6 J) at the sites of the injections, or intramuscular diclofenac, a nonselective COX inhibitor/NSAID. It was found that LPT dose of 3 J significantly reduced inflammation through less COX-2-derived gene expression and PGE_2 production, and less oedema formation compared to non-irradiated controls. Diclofenac controls exhibited significantly lower PGE_2 cytokine levels at 6 h than collagenase control, but COX isoform 1-derived gene expression and cytokine PGE_2 levels were not affected by treatments. As LPT seems to act on inflammation through a selective inhibition of the COX-2 isoform in collagenase-induced tendinitis, LPT may have potential to become a new and safer non-drug alternative to coxibs.

The aim of the study by de Paiva Carvalho [9] was to evaluate the effect of single and combined therapies (LPT, topical application of diclofenac and intramuscular diclofenac) on functional and biochemical aspects in an experimental model of controlled muscle strain in rats. Muscle strain was induced by overloading tibialis anterior muscle of rats. Injured groups received either no treatment, or a single treatment with topical or intramuscular diclofenac (TD and ID), or LPT (3 J, 810 nm, 100 mW) 1 h after injury. Walking track analysis was the functional outcome and biochemical analyses included mRNA expression of COX-1 and COX-2 and blood levels of prostaglandin E_2 (PGE_2). All treatments significantly decreased COX-1 and COX-2 gene expression compared with injury group. However, LPT showed better effects than TD and ID regarding PGE_2 levels and walking track analysis. The author concludes that LPT has more efficacy than topical and intramuscular diclofenac in treatment of muscle strain injury in acute stage.

Crystalopathies are inflammatory pathologies caused by cellular reactions to the deposition of crystals in the joints. The anti-inflammatory effect of He-Ne laser and that of the nonsteroidal anti-inflammatory drugs (NSAIDs) diclofenac, meloxicam, celecoxib, and rofecoxib was studied in acute and chronic arthritis produced by hydroxyapatite and calcium pyrophosphate in rats. The presence of the markers fibrinogen, L-citrulline, nitric oxide, and nitrotyrosine was determined. In the study by Rubio [10] crystals were injected into the posterior limb joints of the rats. A dose of 8 J/cm^2 of energy from a HeNe laser was applied for 3 d in some groups and for 5 d in other groups. The levels of some of the biomarkers were determined by spectrophotometry, and that of nitrotyrosine was determined by ELISA. In arthritic rats, the fibrinogen, L-citrulline, nitric oxide, and nitrotyrosine levels increased in comparison to controls and to the laser-treated arthritic groups. When comparing fibrinogen from arthritic rats with disease induced by hydroxyapatite with undiseased and arthritic rats treated with NSAIDs, the He-Ne laser decreased levels to values similar to those seen in controls. Inflammatory and oxidative stress markers in experimental crystalopathy are positively modified by photobiostimulation.

Although the above studies indicate that LPT is as effective, or more effective as diclofenac, a potentiation of the effect of diclofenac by adding LPT is suggested in the following study:

The aim of the study by Markovic [11] was twofold: (1) to evaluate the postoperative analgesic efficacy, comparing long-acting and intermediate-acting local anaesthetics; and 2 to compare the use of laser irradiation and the non-steroid anti-inflammatory drug diclofenac, which are claimed to be among the most successful aids in postoperative pain control. A twofold study of 102 patients of both sexes undergoing surgical extraction of LTM was conducted. In the first part of the study, 12 patients with bilaterally impacted lower molars were treated in a double-blind crossover fashion; local anaesthesia was achieved with 0.5% bupivacaine plain or 2% lidocaine with 1:80.000 epinephrine. In the second part of the study, 90 patients undergoing lower molar surgical extraction with local anaesthesia received postoperative laser irradiation (30 patients) and a preoperative single dose of 100 mg diclofenac (30 patients), or only regular postoperative recommendations (30 patients). The results of the first part of the study showed a strikingly better postoperative analgesic effect of bupivacaine than lidocaine/epinephrine (11 out of 12; 4 out of 12, respectively, patients without postoperative pain). In the second part of the study, LPT irradiation significantly reduced postoperative pain intensity in patients premedicated with diclofenac, compared with the controls. Provided that basic principles of surgical practice have been achieved, the use of long-acting local anaesthetics and LPT irradiation enables the best postoperative analgesic effect and the most comfortable postoperative course after surgical extraction of lower molars.

Dexamethasone is a corticosteroid, thus not an NSAID, but the issue of replacing pharmaceuticals with long term negative effects with a treatment with no side effect is urgent here as well.

A rabbit model of endophthalmitis was established by Ma [12] to evaluate the antiinflammatory effect of LPT as an adjunct to treatment for Staphylococcus epidermidis endophthalmitis. Rabbits were randomly divided into three groups to receive intravitreal injections into their left eye: group A received 0.5 mg vancomycin (100 mcl), group B received 0.5 mg vancomycin + 0.2 mg dexamethasone (100 mcl), and group C received 0.5 mg vancomycin (100 mcl) and laser irradiation (10 mW, 632 nm) focused on the pupil.

Slit lamp examination and B-mode ultrasonography were conducted to evaluate the symptoms of endophthalmitis. Polymorphonuclear cells and tumour necrosis factor alpha (TNF-alpha) in aqueous fluid were measured at 0 h, and 1, 2, 3, 7 and 15 days. A histology test was conducted at 15 days. B-mode ultrasonography and histology revealed that groups B and C had less inflammation than group A at 15 days. Groups B and C had fewer polymorphonuclear cells and lower levels of TNF-alpha in aqueous fluid than group A at 2, 3 and 7 days. There was no significant difference between groups B and C. There was no significant difference between groups A, B and C at 15 days. As an adjunct to vancomycin therapy to treat S. epidermidis endophthalmitis, LPT has an antiinflammatory effect similar to that of dexamethasone.

Castano [13] tested LPT on rats that had zymosan injected into their knee joints to induce inflammatory arthritis. The author compared illumination regimens consisting of a high and low fluence (3 and 30 J/cm^2), delivered at high and low irradiance (5 and 50 mW/cm^2) using 810 nm daily for five days, with the positive control of conventional corticosteroid (dexamethasone) therapy. Illumination with a 810 nm laser was highly effective (almost as good as dexamethasone) at reducing swelling, and a longer illumination time (10 or 100 minutes compared to 1 minute) was more important in determining effectiveness than either the total fluence delivered or the irradiance. LPT induced reduction of joint swelling correlated with reduction in the inflammatory marker serum prostaglandin E_2 (PGE_2).

Reis [14] investigated the role of extracellular matrix elements and cells during the wound healing phases following the use of LPT and anti-inflammatory drugs. Thirty-two rats were submitted to a wound inflicted by a 6-mm-diameter punch. The animals were divided into four groups: sham treated, those treated with the GaAlAs laser (4 J/cm^2, 9 mW, 670 nm), those treated with dexamethasone (2 mg/kg), and those treated with both LPT and dexamethasone. After three and five days, the cutaneous wounds were assessed by histopathology using polarised light and ultrastructural assessments by transmission electron microscopy. Changes seen in polymorphonuclear inflammatory cells, oedema, mononuclear cells, and collagen fibre deposition were semi-quantitatively evaluated. The laser-treated group demonstrated an increased collagen content and a better arrangement of the extracellular matrix. Fibroblasts in these tissues increased in number and were more synthetically active. In the dexamethasone group, the collagen was shown to be non-homogenous and disorganised, with a scarcity of fibroblasts. In the group treated with both types of therapy, fibroblasts were more common and they exhibited vigorous rough endoplasmic reticulum, but they had less collagen production compared to those seen in the laser group. Thus, LPT alone accelerated post-surgical tissue repair and reduced oedema and the polymorphonuclear infiltrate, even in the presence of dexamethasone.

In a study by Jajarm [15] thirty patients with erosive-atrophic OLP were randomly allocated into two groups. The experimental group consisted of patients treated with the 630 nm laser. The control group consisted of patients who used dexamethasone mouth wash. Response rate was defined based on changes in the appearance score and pain score (VAS) of the lesions before and after each treatment. Appearance score, pain score, and lesion severity was reduced in both groups. No significant differences were found between the treatment groups regarding the response rate and relapse. The study demonstrated that LPT was as effective as topical corticosteroid therapy without any adverse effects and it may be considered as an alternative treatment for erosive-atrophic OLP in the future.

The aim of a study by Aimbire [16] was to investigate if LPT can modulate formation of haemorrhagic lesions induced by immune complex, since there is a lack of information on LPT effects in haemorrhagic injuries of high perfusion organs, and the relative efficacy of LPT compared to anti-inflammatory drugs. A controlled animal study was undertaken with 49 rats, randomly divided into seven groups. Bovine serum albumin i.v. was injected through the trachea to induce an immune complex lung injury. The study compared the effect of irradiation by a 650 nm laser with doses of 2.6 J/cm^2 to celecoxib, dexamethasone, and control groups for haemorrhagic index (HI) and myeloperoxide activity (MPO) at 24 h after injury. The HI for the control group was 4.0. Celecoxib, laser, and dexamethasone all induced significantly lower HI than in the control animals at 2.5, 1.8 and 1.5, respectively. Dexamethasone, but not celecoxib, induced a slightly, but significantly lower HI than laser. MPO activity was significantly decreased at 1.6 in groups receiving celecoxib at 0.87, dexamethasone at 0.50, and laser at 0.7 when compared to the control group, but there were no significant differences between any of the active treatments. In conclusion, LPT at a dose of 2.6 J/cm^2 induces a reduction of HI levels and MPO activity in haemorrhagic injury, which is not significantly different from that obtained by celecoxib. Dexamethasone is slightly more effective than LPT in reducing HI, but not MPO activity.

In an effort to clarify the molecular based mechanism of the anti-inflammatory effects of laser irradiation, Abiko [17] used a rheumatoid arthritis (RA) rat model with human rheumatoid synoviocytes (MH-7) challenged with IL-1, treated with laser or dexamethasone (DEX), monitored by gene expressions and analysed by the signal pathway database. RA rats were generated by the immunisation of type-II collagen, after which foot paws and knee joints became significantly swollen. The animals were laser treated and the swelling rates measured. MH-7 was challenged with IL-1ß and gene expression levels monitored, using the Affymetrix Gene Chip system, and the signal pathway database analysed using the Ingenuity Pathway Analysis (IPA) tool. LPT significantly reduced swellings in the rats' foot paws and knee joints and made it possible for them to walk on their hind legs. LPT altered many gene expressions of cytokines, chemokines, growth factors and signal transduction factors in IL-ß induced MH-7. IPA revealed that LPT as well as DEX kept the MH7A at a normal state to suppress mRNA levels of IL-8, IL-1ß, CXC1, NFkB1 and FGF13, which were enhanced by IL-1ß treatment. However, certain gene expression of inflammatory factors were reduced by LPT, but were enhanced by DEX. LPT reduced inflammatory factors through altering signal pathways by gene expression levels. Interestingly, LPT altered useful targeted gene expressions, whereas DEX randomly altered many gene expressions, including the unwanted genes for anti-inflammation. Dexomethasone is a steroid known for having a long range of serious side effects. Thus, genome based gene expression monitored by the Gene Chip system together with a signal pathway based database provide unprecedented access to elucidate the mechanism of the biostimulatory effects of LPT.

It has been suggested that LPT acts on pulmonary inflammation. Thus, Mafra de Lima [18] investigated in a work if LPT (650 nm, 2.5 mW, 31.2 mW/cm^2, 1.3 J/cm^2, spot size of 0.08 cm^2 and irradiation time of 42s) can attenuate oedema, neutrophil recruitment and inflammatory mediators in acute lung inflammation. Thirty-five male Wistar rats (n = 7 per group) were distributed in the following experimental groups: control, laser, LPS, LPS+laser and dexamethasone+LPS. Airway inflammation was measured 4h post-LPS challenge. Pulmonary microvascular leakage was used for measuring pulmonary oedema. Bronchoalveolar lavage fluid (BALF) cellularity and myeloperoxidase (MPO) were used for measuring neutrophil recruitment and activation. RT-PCR was performed in lung tissue to assess mRNA expression of tumour necrosis factor-alpha (TNF-alpha), interleukin-1ß (IL-1ß), interleukin (IL-10), cytokine-induced neutrophil chemoattractant-1 (CINC-1), macrophage inflammatory protein-2 (MIP-2) and intercellular adhesion molecule-1 (ICAM-1). Protein levels in both BALF and lung were determined by ELISA. LPT inhibited pulmonary oedema and endothelial cytoskeleton damage, as well as neutrophil influx and activation. Similarly, LPT reduced the TNF-alpha and IL-1ß, in lung and BALF. LPT prevented lung ICAM-1 up-regulation. The rise of CINC-1 and MIP-2 protein levels in both lung and BALF, and the lung mRNA expressions for IL-10, were unaffected. Data suggest that the LPT effect is due to the inhibition of ICAM-1 via the inhibition of TNF-alpha and IL-1ß.

Steroids are frequently used to treat inflammation. Some studies report a reduced effect of LPT in the presence of steroids, while others have found positive results of LPT even in the presence of steroids. However, steroids are known to delay wound healing through a reduction of leukocyte migration and a suppression of interleukins, while LPT is known to stimulate wound healing. In a study by Pessoa [19], 48 rats were used, and after the execution of a wound on the dorsal region of each animal, they were divided into four groups (n=12), receiving the following treatments: G1 (control), wounds and animals received no treatment; G2, wounds were treated with laser; G3, animals received an intraperitoneal injection of sodium phosphate of dexamethasone, dosage 2 mg/kg of body weight; G4, animals received steroids and wounds were treated with laser. The laser emission device used was a 904 nm unit, in a contact mode, with 2.75 mW gated with 2.900 Hz during 120 sec. After a period of 3, 7 and 14 days, the animals were sacrificed. The results showed that the wounds treated with steroid had a delay in healing, while laser accelerated the wound healing process. Additionally, wounds treated with laser in the animals also treated with steroids, presented a differentiated healing process with a larger collagen deposition as well as a decrease in both the inflammatory infiltrated and in the delay on the wound healing process. Laser accelerated healing, delayed by the steroids, acting as a biostimulative coadjutant agent, balancing the undesirable effects of the steroids on the tissue's healing process. The effect of LPT is almost as potent as dexamethasone but, again, without side effects.

In a study by Lara [20], 44 rats were treated with fluorouracil and, in order to mimic the clinical effect of chronic irritation, the palatal mucosa was irritated by superficial scratching with an 18-gauge needle. When all of the rats presented oral ulcers of mucositis, they were randomly allocated to one of three groups: group I was treated with laser (GaAlAs), group II was treated with topical dexamethasone, and group III was not treated. Excisional biopsies of the palatal mucosa were then performed, and the rats were killed. Tissue sections were stained with haematoxylin and eosin for morphological analyses, and with toluidine blue for mast-cell counts. Group I specimens showed higher prevalence of ulcers, bacterial biofilm, necrosis and vascularisation, while group II specimens showed higher prevalence of granulation tissue formation. There were no significant statistical differences in the numbers of mast cells and epithelial thickness between groups. For the present model of mucositis, rats with palatal mucositis treated with laser showed characteristics compatible with the ulcerative phase of oral mucositis, and rats treated with topical dexamethasone showed characteristics compatible with the healing phase of mucositis. Topical dexamethasone was more efficient in the treatment of rats' oral mucositis than the laser.

It has been suggested that LPT and dexamethasone (DEX) in combination do not bring about any advantages. But the following study suggests that LPT works even in an environment with DEX.

The stud by Marchionni [21] aimed to assess the effect of LPT associated with and without dexamethasone on inflammation and wound healing in cutaneous surgical wounds. Limited studies are directed at the possible interference of laser photobiomodulation on the formation of myofibroblasts, associated with an antiinflammatory drug. Standard skin wounds were performed on 80 Wistar rats, distributed into four groups: no treatment (sham group), laser only (670 nm, 9 mW, 0.031 W/cm^2, 4 J/cm^2, single dose after surgery), dexamethasone only (2 mg/kg 1 h before surgery), and laser with dexamethasone. Tissue was examined histologically to evaluate oedema, presence of polymorphonuclear, mononuclear cells, and collagen. The analysis of myofibroblasts was assessed by immunohistochemistry and transmission electron microscopy. The intensity was rated semiquantitatively. The results showed that laser and dexamethasone acted in a similar pattern to reduce acute inflammation. Collagen synthesis and myofibroblasts were more intense in the laser group, whereas animals treated with dexamethasone showed lower results for these variables. In a combination of therapies, the synthesis of collagen and actin and desmin-positive cells was less than laser group. Laser was effective in reducing swelling and polymorphonuclear cells and accelerated tissue repair, even in the presence of dexamethasone.

The aim of a study by Garcia [22] was to compare LPT as adjuvant treatment for induced periodontitis with scaling and root planing (SRP) in dexamethasone-treated rats. One-hundred twenty rats were divided into groups: D group (n = 60), treated with dexamethasone; ND group (n = 60) treated with saline solution. In both groups, periodontal disease was induced by ligature at the left first mandibular molar. After 7 days, the ligature was removed and all animals were subjected to SRP and were divided according to the following treatments: SRP, irrigation with saline solution (SS); SRP + LPT, SS and laser irradiation (660 nm; 24 J; 0.428 W/cm^2). Ten animals in each treatment were killed after 7 days, 15 days and 30 days. The radiographic and histometric values were statistically analysed. In all groups radiographic and histometric analysis showed less bone loss in animals treated with SRP + LPT in all experimental periods. SRP + LPT was an effective adjuvant conventional treatment for periodontitis in rats treated with dexamethasone.

From the above papers it is clear that LPT has an effect similar to that of dexamethasone. Possibly not as strong as dexamethasone, but without the side effects. Thus, a promising alternative, especially for long term use.

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13.4 Another pithole in LPT research

The quality of LPT research papers varies and there are several reasons. A much too common reason is that the researchers do not have anyone of the team with a basic knowledge on physics and laser phototherapy itself. It is not uncommon to find that authors do not understand the difference between joules and joules per cm^2. This leads them to choosing suboptimal or quite ineffective parameters. Yet another is to have a manufacturer as the sole advisor. Here follows an example of wasted time. That is bad in itself and for those not knowledgeable enough to interpret the study, one gets the impression that LPT does not work. It does - but only if parameters are within the therapeutic window.

A total of 33 adult subjects were enrolled in the study by Goldman [1]. The data from three additional subjects were not included in the analysis. One subject yielded unreliable audiometric and speech understanding data, speech scores could not be obtained from one subject with a profound hearing loss, and calibration problems compromised data from the third subject. Data from the remaining 30 subjects were included in the analyses. An Erchonia EHL laser was used to provide the laser stimulation. The device was a portable unit that consisted of a hand-held probe and a main body. The probe contained two laser diodes. One diode produced light in the green part of the visible light spectrum (532 nm), and the other diode produced light in the red part of the visible light spectrum (635 nm). Both diodes produced energy levels of 7.5 mW. The laser beams from both diodes were dispersed through lenses to create parallel line-generated beams, rather than spots. The 532 nm light was constant, and the 635 nm light was pulsed, with frequencies of 15 and 33Hz. The pulsing alternated between frequencies every 30 seconds. A second device served as the placebo. No statistically significant effect of LPT on auditory function was found, as assessed by pure-tone audiometry, speech understanding, and TEOAEs. Additionally, no individual subjects showed any clinically significant change.

In the above study the cochlea is reported to be one of the targets of the irradiation, although seven areas of the head were irradiated. The negative outcome of the study is therefore obvious, in that few, if any, photons reached this area or any area of the brain. The combined energy of the two lasers was 15 mW and the power density was considerably decreased by using a line generated beam in non-contact. With an irradiation time of 225 seconds, the total energy was 3.4 J. Given the large area of irradiation, this energy is insufficient even at the surface and at a homeopathic level beneath the bony areas. Light in the red spectrum has primarily been used to treat superficial conditions, due to its lower penetration through tissues. Infrared light has therefore been preferred to reach deeper areas, such as the cochlea. Kolárová et al. [2] used CCD camera technique to establish the penetration of 50 mW, 632.8 nm and 21 mW, 675 nm. In the thickest skin sample (19 mm with epidermis + dermis + subcutaneous fat from regio abdominalis) approximately 0.3% of the HeNe and 2.1% of the diode laser light penetrated. So the power of the 7.5 mW red laser light would have reached a level of 0.2 mW after passing through the skin, and still not being inside the bone. The penetration of the 532 nm wavelength is three times lower.

Regarding the pulsing used, there is no information about what it is supposed to do and what the chosen pulse repetition rates would do, other than reducing the energy per time. In the review on the possible effects of pulsing in LPT, Hashmi et al. [3] conclude: "It was impossible to draw any meaningful correlation between pulse frequency and pathological condition, due to the wide-ranging and disparate data. As for other pulse parameters, these were in general poorly and inconsistently reported."

The above is, regrettably an example of a very qualified team of scientists using parameters that are bound to fail. One positive aspect of this study is that it actually confirms the need of knowing the reasonable parameters.

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13.5 Database of Abstracts of Reviews of Effects (DARE)

The Database of Abstracts of Reviews of Effects (DARE) contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services. Reviews are quality assessed for inclusion making DARE a key resource for busy decision-makers in both healthcare policy and practice. DARE complements the CDSR by identifying and including systematic reviews that have not been carried out by The Cochrane Collaboration.

A critical commentary on the reliability of the evidence is provided for reviews of key relevance to the UK NHS. The records for these reviews contain a summary of the review and a critical commentary about the overall quality and reliability of the findings. For bibliographic records where a commentary has not yet been prepared, users can submit a request via the CRD website: priority is given to UK NHS, public health, and social care services. The commentaries are written and independently checked by researchers with in-depth knowledge and experience of systematic review methods.

DARE contains details of all Cochrane Reviews, Protocols for Cochrane Reviews, and other publications based on Cochrane Reviews. Details of Campbell Reviews are included where the interventions evaluated impact directly on health or have the potential to impact on health.

DARE is produced by the NIHR Centre for Reviews and Dissemination (CRD) at the University of York, UK.

Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews of LPT.

Ottawa Panel evidence-based clinical practice guidelines for electrotherapy and thermotherapy interventions in the management of rheumatoid arthritis in adults. Review published: 2004.

Conclusion: The Ottawa Panel recommends the use of low-level laser therapy, therapeutic ultrasound, thermotherapy, electrical stimulation, and transcutaneous electrical nerve stimulation for the management of rheumatoid arthritis.

Low level laser treatment of tendinopathy: a systematic review with meta-analysis. Review published: 2010.

Conclusion: LLLT can potentially be effective in treating tendinopathy when recommended dosages are used. The 12 positive studies provide strong evidence that positive outcomes are associated with the use of current dosage recommendations for the treatment of tendinopathy.

Therapeutic effects of low-level laser on lateral epicondylitis from differential interventions of Chinese-Western medicine: systematic review. Review published: 2010.

Conclusions: We suggest that using LLLT on tender points or MTrPs of LE could effectively improve therapeutic effects.

A systematic review with procedural assessments and meta-analysis of low level laser therapy in lateral elbow tendinopathy (tennis elbow). Review published: 2008.
Conclusion: LLLT administered with optimal doses of 904 nm and possibly 632 nm wavelengths directly to the lateral elbow tendon insertions, seem to offer short-term pain relief and less disability in LET, both alone and in conjunction with an exercise regimen. This finding contradicts the conclusions of previous reviews which failed to assess treatment procedures, wavelengths and optimal doses.

Effectiveness of low-level laser therapy for lateral elbow tendinopathy. Review published: 2005.
Conclusions: LLLT need not be ruled out for LET as it is a dose-response modality, and the optimal treatment dose has obviously not yet have been discovered. Further research with well-designed RCTs is needed to establish the absolute and relative effectiveness of this intervention for LET.

Systematic review of the literature of low-level laser therapy (LLLT) in the management of neck pain. Review published: 2005.

Conclusions: This review provides limited evidence from one RCT for the use of infrared laser for the treatment of acute neck pain (n=71) and chronic neck pain from four RCTs (n=202). Larger studies are required to confirm the positive findings and determine the most effective laser parameters, sites and modes of application.

13.6 The wound healing contradiction

Improved wound healing was one of the first discoveries when low level laser was tested in medicine. Since then, a multitude of cell studies and animal studies have been carried out and published. The overall result is that dosages within the "therapeutic window" have an impressing effect on wound healing, and in particular for the healing of chronic wounds. Nevertheless, its use in traditional medicine is more of an exception than a rule. And why? Probably because the clinical studies are so few. This is rather surprising. With the vast number of cell and animal studies as support, one could presume that there would be an interest in clinical studies. But these are few and small. Is it because other methods are working well? No! In Sweden alone, with a population of 9 million inhabitants, more than 40.000 persons are suffering from chronic wounds. The average cost per patient and year is estimated to be around 3.000 euro. That adds up to 120 million euro! Are new methods needed? Are big national savings around the corner?

Clinicians using LPT for wound healing know very well that it has an impressing effect, if applied within the therapeutic window. What is typical of a chronic wound is exactly that it is chronic. But with LPT these wounds start to heal. Typically, the pain disappears after a few sessions. Often, what looks like a worsening of the situation appears, but this is just the phase when the chronic wound turns into an acute wound. And different from the chronic wound - the acute wound has an ability to start a healing process.

Here are some illustrative figures:

Data from the 2011 National Diabetes Fact Sheet (released Jan. 26, 2011).
Total prevalence of diabetes.
Total: 25.8 million children and adults in the United States - 8.3% of the population - have diabetes.
Diagnosed: 18.8 million people
Undiagnosed: 7.0 million people
Prediabetes: 79 million people
New cases: 1.9 million new cases of diabetes are diagnosed in people aged 20 years and older in 2010.

So here is the contradiction: (1) Chronic wounds are chronic in their nature, and the number of chronic wounds is steadily increasing. From a strict economic point of view, Health Care authorities and insurance companies could save a lot of money by introducing new and better methods (not forgetting the individual suffering). (2) Cell and animal studies are strongly pointing at the value of introducing LPT. But to finally convince the medical authorities, more and better clinical studies are needed. But no one seems to be interested. Catch 22!

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5) Clinical studies
- Hopkins J T, McLoda T A, Seegmiller J G, Baxter G D. Low-Level Laser Therapy Facilitates Superficial Wound Healing in Humans: A Triple-Blind, Sham-Controlled Study. J Athl Train. 2004; 39 (3): 223-229.

13.7 Wikipedia

The web based encyclopaedia Wikipedia is these days the most common encyclopaedia of them all. The major advantages are the quick access to the information and the constant updating of the texts. The information available differs in the various language versions. So does the contents from day to day in some cases. When it comes to "Low Level Laser Therapy", we have followed the development in the English and Swedish versions for several years. Sadly, the information provided has seldom been correct, often biased and sometimes unqualified. On one occasion, the name of a certain company was mentioned frequently, and the source was rather obvious. There are specialised companies offering to produce corporation-adapted information on Wikipedia. As an example of incorrect information, here is a comment to the text accessed on October 24th, 2013. The presentation appears to be written by a competent person, but a closer scrutiny says differently. The two references to "dentistry" refer to an Er:YAG paper and a 2006 review, hardly mentioning LLLT. One reference points at an article on Quackwatch, published in 2009. This very negative article presents "Low Level Laser Therapy" as a placebo therapy. However, the majority of the text is an attack on an LED company and offers no clue to the understanding of LPT. Thus, these two authors seem to have no insight in the subject. Wikipedia will remain an unreliable advisor for some years when it comes to the subject LPT.

13.8 Poor documentation – compared to what?

It is sometimes claimed that LPT has a rather poor scientific documentation. While this may be a valid point to some extent, it is surprisingly common for generally used treatment modalities to have a poor documentation without being questioned. It is interesting to compare the widely used ultrasound modality with LPT. In the book “Clinical electrotherapy – your guide to optimal treatment”, Bjordal [1187] has compared the documentation found in the randomised studies on LPT and ultrasound in physiotherapy.

	LPT	**Ultrasound**
Strong evidence of effect	Tendinopathy Osteoarthritis	None

Table 13.1 LPT vs. ultrasound

Moderate evidence of effect	Myofascial trigger point syndrome	None
Weak evidence of effect	Rheumatoid arthritis Soft tissue injuries	Tendinopathy Soft tissue injuries Wounds

Table 13.1 LPT vs. ultrasound

13.9 LPT equipment and the future

The traditional laser equipment is a probe with one single diode. It is used by a therapist holding it in his hand and using it on selected points on the patient. This procedure has advantages in that it creates a contact between therapist and patient and the therapist can find tender points and anatomical landmarks by inspection and palpation. It will continue to dominate but needs to be followed by other methods. Having a trained person sitting there holding a probe in his hand (and charging you for it) can be a waste of time. Laser treatment is seldom a quick-fix, so it often requires follow up treatments. Once the diagnosis is set and the initial treatment has started, other less therapist-required equipment is helpful and time saving. A painful shoulder or an arthritis knee could at advantage be additionally treated with a laser/LED containing bandage or strap. Just put in place by the therapist - or possibly by the patient at home between professional sessions. For the dentist, a laser/LED containing impression tray-style equipment could be inserted into the patient's mouth after periodontal surgery and held in place by the patient by biting together during 5-10 minutes. Some dental surgical diode lasers now have a small LPT array as an option to the surgical periodontal treatment. These are initially intended for tooth bleaching but can also be used for LPT with some difficuly.

Already, there is novel thinking on the market, but still being the exception. There is a "mini-solarium" laser available, LED-containing "blankets", multi diode arrays, double laser "pens" to be used simultaneously, laser combes, laser "showers", headphone style lasers for tinnitus therapy and hand held lasers allowing for variations of power output, making them more versatile. And home care lasers. These are of particular interest. Not only for the patient to use between sessions, but to own and keep for personal use. It may be a person with recurrent herpes attacks, a young individual with acne or a person with arthritis. In the latter case it is a life-long home treatment, but it can replace a lot of pills and their severe side effects. Ideally these should be bought from a professional therapist after diagnosis and initial therapy, possibly with regular check-ups. In fact, conditions like HSV-1, angular chielitis and similar superficial ones can successfully be treated with a red 5 mW laser pointer! Not ideal, but it works.

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13.13 Information for your patient

Pain problems? Therapeutic laser could be good for you.

Something about laser
Laser is a source of light, a lamp, if you like. Lasers produce visible or invisible light. However, the characteristics of laser light are unique when comparing them to other sources of light. Already in 1966 there was published research showing that certain forms of laser light could influence pain and wound healing in humans as well as in animals. The most commonly used term for this kind of treatment is Laser Phototherapy (LPT). These therapeutic lasers do not burn and the light is perfectly safe in the hands of a competent therapist.

Medical laser applications
Lasers can be used in many ways. Strong lasers can burn and cut and there are other weak lasers which can heal and relieve pain. The latter lasers are often referred to as "therapeutic lasers". Their power is much lower than those of the surgical lasers and their effects on us are completely different. Their light can penetrate deep into our bodies and stimulate the natural functions of our cells. 50 years of clinical use and research show that laser light of the correct wavelength and intensity has a positive influence on many conditions, among them wound healing and pain.

What is taking place?
Most of us have some time seen that a portion of the light is passing through the fingers if a traditional torch light is held in front of the hand. On its way through the hand, the light meets our cells, but do not affect them much. The laser light also penetrates through the hand but interacts strongly with the cells. The biological mechanisms are complex, but it is fair to say that the light increases the energy production of the cells, thereby improving the capacity of the cell to return to work. This goes for a cell in a poor condition. Other cells tend to ignore the light, they are healthy enough.

How is the treatment performed?
The light is emitted from a handheld probe, kept near or in contact with your skin. The light is generally applied in the area of the problem, but distant points are in some instances also used. The therapist will know which wavelength and which energy is best suited for the condition in question.

Which conditions can be treated?
Many conditions have a component of pain and inflammation. LPT can reduce pain and inflammation, thereby speeding up the process of recovery. Chronic and acute conditions are treated differently, but the principle is the

same. Chronic conditions require many sessions over a prolonged period of time whereas acute conditions heal faster and require fewer sessions. Age is of little importance, but the applied energy is adapted to things like body weight, type of tissue, skin colouration and depth of location.

Does it hurt?

No, not at all. Sometimes there may be a small sensation of warmth, especially if you have a dark complexion or irradiation is performed over a tattoo. Treatment is often, on the contrary experienced as pleasant and relaxing. One thing to remember, though, is that there may be a brief initial pain period when chronic conditions are treated. This may appear soon after treatment or within 24 hours but is always transient. You can say that the chronic condition has been turned into an acute condition, which shows that the laser has broken the chronic stage and is initiating the healing process. Patients with long-standing chronic pain conditions may also experience an immediate but transient tiredness. This is due to the accumulated lack of rest, caused by the pain. And when pain is reduced, the obvious lack of sleep may overwhelm the patient. Both the described reactions are good signs.

How many sessions?

Persons are different and so is their medical condition. Therefore, it is seldom possible to promise any immediate effect, even if looking quite probable. The number of sessions needed must be chosen according to the evolution of the healing process and in the light of the correctness of the initial diagnosis.

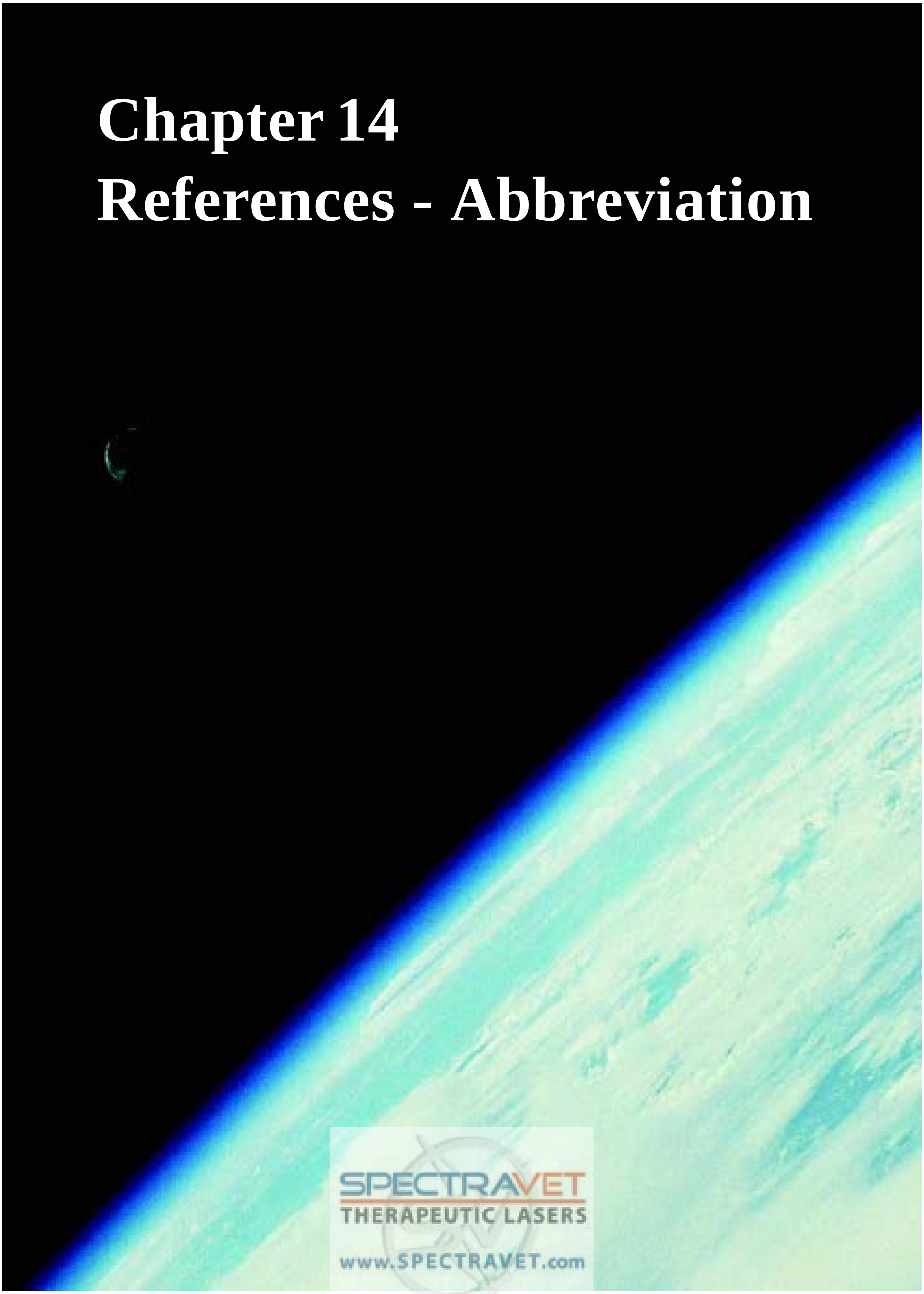
Are there any risks?

The great advantage with LPT is that there are no risks! No one has ever been harmed by a therapeutic laser used by a qualified user. But in general, strong light sources means ocular hazard. Therefore you should never look straight into the aperture of a laser. This is a general rule, but fortunately therapeutic lasers have never caused any eye damages. And the use of proper eye protection will even make you feel perfectly safe.

What about cancer?

Therapeutic lasers cannot cause cancer. Even if a person has cancer and is unaware of it, the laser light will not worsen the cancer. Several of the side effects of cancer treatments are actually counteracted by LPT. However, for legal and security reasons, known cancerous areas are only to be treated by specialists.

Chapter 14
References - Abbreviation



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14.2 Abbreviations

Abbreviations used in this book are explained but not everywhere you meet them in the text. The following is a list of some of these abbreviations.

ASA	Acetylsalicylic Acid
ATP	Adenosine Triphosphate
BMP	Bone Morphogenetic Protein

CL	Chemiluminescence
CO_2	Carbon Dioxide
CTS	Carpal Tunnel Syndrome
CW	Continuous Wave
DNA	Deoxyribonucleic Acid
ED	Energy Density
EDL	Emitted Defocused Laser-Light
EMG	Electromyogram
ENT	Ear-Nose-Throat
Er:YAG	Erbium Yttrium-Aluminium-Garnet
FCS	Fetal Calf Serum
FDA	Food and Drug Administration
GaAlAs	Gallium Aluminium Arsenide
GaAs	Gallium Arsenide
Gy	Gray
HeNe	Helium Neon
Ho:YAG	Holmium Yttrium-Aluminium-Garnet
HSV	Herpes Simplex Virus
IL	Interleukin
InGaAlP	Indium Gallium Aluminium Phosphide
IR	Infra Red
IRB	Institutional Review Board
KTP	Potassium (Kalium) Titanyle Phosphide
LED	Light Emitting Diode
MRI	Magnetic Resonance Imaging
Nd:YAG	Neodymium Yttrium-Aluminium-Garnet
NMRI	Nuclear Magnetic Resonance Imaging
NO	Nitric Oxide
NSAID	Non-Steriodal Anti-Inflammatory Drug
OA	Osteoarthritis

PD	Power Density
PDT	Photodynamic Therapy
PGE	Prostaglandine E
PHN	Postherpetic Neuralgia
RA	Rheumatic Arthritis
RNA	Ribonucleic Acid
ROM	Range Of Movement
SEM	Sweep Electron Microscopy
SOD	Super Oxide Dismutase
SPIE	The International Society for Optical Engineering
TBO	Tolouidine Blue
TMD	Temporo Mandibular Disorders
TMJ	Temporomandibular joint
TMR	Transmyocardial Revascularisation
VAS	Visual Analogue Scale
YAG	Yttrium Aluminium Garnet

Find a laser therapist

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Alphabetic index

M

N

O

P

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