ARE ALL THE NEGATIVE STUDIES REALLY NEGATIVE?

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This article presents an analysis of a number of frequently cited studies on the effects of low level laser therapy (LLLT). In many of these studies, the analysis uncovered one or more reasons for the negative findings reported, the most common being the use of extremely low doses. Other reasons included faulty inclusion criteria, inaccurate control group definition, ineffective methods of therapy, inadequate attention to systemic effects and tissue condition, and low incident power density. A weakness often encountered in these studies is their failure to provide sufficient data on laser parameters. Since negatively inclined studies such as these are often quoted as "proof" of the ineffectiveness of LLLT, it is important that they be subjected to a proper critical analysis. 1,400 articles were reviewed for this analysis, the emphasis being on double-blind studies. Of the 135 localized double-blind studies, 85 reported positive findings. Though important, the critical examination of scientific literature is decidedly unglamorous. It involves hours and days of searching through a wide variety of different sources, and by no means all information is yet available on-line. There are numerous pitfalls, too, especially for those who opt to read abstracts only - criticism of sources is impossible unless an article can be studied in its entirety. Basing an opinion from abstracts obtained from online services such as Medline is risky. In addition, only a very small number of the early LLLT research reports are available from the major databases. In the following analysis of the available literature, we have chosen to analyze those studies unable to demonstrate the effectiveness of LLLT. Although priority was given to double-blind studies, non-double-blind studies were also included in certain typical cases. Certain studies were also included merely on the grounds that they are among the most frequently cited. The 1,400 articles reviewed for this analysis are now being stored in computerized form.

Key words: meta analysis, LLLT, double blind study, treatment parameters

Introduction

'Rumor per urbem currit'

A recognizable pattern is often distinguishable in the bibliographies accompanying scientific reports. The manner in which these patterns arise goes something like this: Researcher A is the man or woman behind some pioneering achievement and is therefore extensively quoted by researcher B, as well as by C, D, E and several others. Researcher K, however, is content to read what E has written about A and B, while researcher Z treats the work of A and B as a simple historical reference point previously described by researcher P. And, like a rumour, word spreads: everyone knows about A, B and C, but no-one has actually read their published work. Although generally known, therefore, older

studies are not always relevant and it may sometimes be rewarding to go back and review them in detail. Often, especially in the light of new findings, the impression given is quite unlike that suggested in later, second-hand reports.

Positive from negative

Having traditionally concentrated on studies positive to LLLT, over the last few years we found ourselves becoming more and more interested in those studies with a negative spin: provided they have been properly carried out, they may be able to show us the parameters that do not appear to work. Naturally, negative reports must always be taken seriously, but the fact that a given study has been unable to demonstrate the effectiveness of LLLT does not necessarily mean that the method studied is incapable per se of producing results within

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the indication in question. All that it shows is that the parameters selected for the study were not sufficiently effective. Therefore, it is illogical to conclude that LLLT is ineffective simply because no effect was reported in that particular study. A number of studies reporting negative results are marred by such startling illogicality.

Negative from negative

LLLT is a relatively young science that has only just emerged from its Sturm und Drang period, and it might perhaps be unfair to criticize the earlier negative studies. Many medical researchers then had – and indeed still have – a rather diffuse knowledge of physics, and qualified books on the physics of laser therapy were long in appearing. In many cases, the only information available to researchers on doses, methods of treatment and suitable indications came from the manufacturers or agents, while over-optimistic, ignorant salesmen often laid traps that would ensnare both themselves and the researchers.

Many studies will come in for criticism in the following paragraphs, although the researchers involved need not always take this to heart. As often as not they pioneered new territory, seeking either to retain an open mind towards the examination of new methods or reacting to what they perceived as a lack of objectivity. The purpose of our criticism is described in the Abstract – we wish to draw the reader's attention to the fact that many negative studies are poorly structured and are therefore largely irrelevant, even though they constantly feature in bibliographies and reading lists and are cited as "evidence" that LLLT does not work. Few people appear to have actually read them. As we see it, it is high time they were weeded out so that they can no longer function as traveller's tales in the future.

Important parameters

A. Wavelength

That biological effect is significantly related to the wavelength of the light emitted by the laser has been demonstrated in numerous studies. Today, the wavelengths most commonly used for therapeutic purposes are 633 nm (HeNe lasers), 635 nm, 650 nm, 660 nm, 670 nm (InGaAlP lasers), 780 nm, 820 nm, 830 nm (GaAlAs lasers), 904 nm (GaAs lasers), and 10600 nm (CO₂ lasers). Except for GaAs and CO₂ lasers, all these lasers usually produce a continuous beam but may also be pulsed.

B. Dose

Apart from the incident power density, one of the most important parameters in LLLT is always the dose, often referred to as "fluence". By dose (D) is meant the energy (E) of the light directed at a given unit of area (A) during

a given session of therapy. The area is calculated using the formula $A = \pi r^2$ where π is the constant 3.142 and r is the radius (not the diameter) of the irradiated spot expressed in cm. The energy is measured in J (joules), the area in cm², and, consequently, the dose in J/cm². Mathematically, this may be expressed as follows:

$$D = \frac{E}{A} \text{ J/cm}^2$$

Assuming that the power (P) output of the laser probe remains constant during treatment, the energy (E) of the light will be equal to the power multiplied by the time (t) during which the light is emitted. The dose may then be calculated as follows:

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

Sometimes, however, the power output is not constant, such as when the laser is pulsed or switched, which may be achieved in several ways. Switching is where the laser is a continuous wave (C/W) system, the output of which is simply turned on and off, whereas pulsing involves the production of a high peak power over a very short pulse width with a very long interpulse interval, which gives an average output power very similar to a C/W system.

The preferred method of switching a HeNe or other C/W laser is to use some form of mechanical switching device or shutter, such as a rotating pierced disc, the useful proportion of the time during which light is emitted by the laser normally being fixed at a given value (duty cycle), most often 50%. In other words, light is permitted to pass through the disc for 50% of the total operating time (and is blocked for the remaining 50%). This enables use of the concept of mean power (P_m) and maximum power. In the example given here, the mean power is 50% of the maximum power. If the laser is switched at mean power, the above formula will apply, giving:

$$D = \frac{P_m \times t}{A} \text{ J/cm}^2$$

GaAs lasers are always true pulsed lasers, the duration of each pulse being extremely short, and in these lasers the maximum or peak power is always much, much greater than the mean power. This type of pulsing is often referred to as 'super-pulsing', or more correctly, a quasi-continuous wave. In GaAs lasers, the duration of the pulse is normally in the region of 100-200 ns (nanoseconds) and the maximum power is typically 1 - 20 W (watts). Assuming, for example, that the duration of the pulse is 150 ns and that the maximum power is 10 W, each pulse emitted by the laser will have an energy of 1.5 μJ (microjoules).

If the laser emits 100 such pulses per second (a pulse frequency of 100 Hz), its mean power output will

be 0.15 mW (milliwatts). A pulse frequency of 1000 Hz gives a mean output of 1.5 mW, etc. In other words, the mean power output varies with the number of pulses emitted per second.

By applying these relationships, it is often possible to obtain doses or other parameters not explicitly stated in the article under review.

C. Power density

Power density, indicating the degree of concentration of the power (in watts) incident on the target tissue (P_i) per unit area (A), has also increasingly proved to play a major role. It is measured in watts per square centimetre (W/cm^2). And is calculated using the formula

$$PD = \frac{P_i}{A} \text{ W / cm}^2$$

If, for example, a circular area having a diameter of 5 mm (approx. 0.2 cm^2) is illuminated with a laser operating at a power output of 100 mW, the biological effects are quite different from those produced by illuminating a circular area of 5 cm diameter (approx. 20 cm^2) with the same laser. In the first case, the power density is 100 times greater than the second ($509 \text{ mW}/\text{cm}^2$ compared with $5.09 \text{ mW}/\text{cm}^2$). Some studies have concluded that the power density may be of even greater significance than the dose. This parameter is very seldom indicated in the articles we have studied. It must also be remembered that the power density varies over the area illuminated: lasers with a Gaussian distribution beam, for example, will have the highest power density at the centre of the beam.

Typical laser therapy instrumentation

Whenever possible, we also reviewed the brochure or brochures describing the instruments used for the study. The power output of the first commercial therapeutic lasers was very low. HeNe instruments often achieved an output of 1 - 2 mW at the laser tube, while the losses sustained in the optical fibres were frequently 50% or more. Furthermore, the laser was not applied in continuous mode, usually being switched to produce a duty cycle of about 50%, thereby reducing the power/mean output power sent to the tissue by another half.

Brochures describing GaAs lasers often only specify the peak pulse power, whereas the mean output power, which is of the greatest significance for LLLT, is often not given at all.

In the following data we were often obliged to make a number of assumptions, since it was only very seldom that all the parameters were indicated in the studies. For example, unless otherwise stated, we have assumed that the fibre incurred a 50% loss; if the light was switched we assumed a 50% duty cycle, and, unless otherwise indicated, we assumed that the mW val-

ues quoted envisage power output at the laser rather than at the distal end of the fibre, in those systems using a flexible fibre optic delivery system. For GaAs lasers, we sometimes had to make several assumptions at once, since here there are more parameters to be taken into account and they were often incompletely reported.

During the eighties, considerable discrepancies between actual outputs and those stated in manufacturers' brochures were not unusual. Only a handful of authors stated whether they themselves measured actual output at the tissue or whether they merely relied on the figure quoted in the brochure. Clearly, we must expect the 'dark figure' to be quite large here.

Dose development

A number of early positive reports on the clinical effects of very weak HeNe lasers suggested that there was cause for some optimism - and scepticism, too. Among them are Walker (1983)⁽¹⁾ (calculated at approx. 0.005 J per point) and Snyder-Mackler (1988)^(2,3) (calculated at approx. 0.01 J per point), reporting on the effect of very weak HeNe lasers.

It must be remembered that Mester had been working with doses of around 1 J as far back as the very late sixties. Later, in an article published in 1971⁽⁴⁾ he recommended a dose of $1.5 \text{ J}/\text{cm}^2$ as conducive to wound healing. The HeNe laser he used had an output of 25 mW at the laser. For a long time Mester's papers attracted little attention in the West, since they were published in relatively unknown journals. Later, in 1981, Kana⁽⁵⁾ published a study on the healing of open skin wounds in which he presented an analysis of the biological effect of 4, 10 and 20 J therapy. The instrument he used was an HeNe laser producing an output of 25 mW from the laser tube. Mester's and Kana's experience of doses suitable for wound healing still hold good today. Although HeNe lasers with a power output of 25 mW were extremely expensive at the time, it cannot be held that information on suitable doses was not then available. It should be noted, too, that from many reports in the literature the treatment of pain requires larger doses than does the healing of open wounds. It seems that a large proportion of the negative studies concentrated mainly on testing the reliability of studies such as references 1, 2 and 3 without regard to existing knowledge of reasonable doses.

Pitfalls

Low output power

In the following examples of negative reports on LLLT action we review some of the studies in which low dose can plainly be identified as the most significant negative factor. We have also listed the parameters that we consider should always be specified in studies of this nature. It is not unusual for an author to criticize previous stud-

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Table 1: Parameters and data from the paper by Waylonis and colleagues.⁽⁶⁾

Chronic Myofascial Pain: Management by Low-Output Helium-Neon Laser Therapy			
Laser type:	HeNe-laser (633 nm)	Output:	Not specified
Beam type:	Not specified	Frequency:	Not specified
Dose:	Not specified	Power density:	Not specified
Treatment distance:	Not specified	Laser model:	Dynatron (model 1120) with fiberoptic delivery
Treated area:	Total of 12 acupuncture points	Treatment time:	15 sec per point
No of patients:	62	No of treatments:	2 x 5 (6 weeks in between)
	Time between treatments:		Not specified

This study is frequently quoted. No dose is specified. However, other sources state that the tube output of the HeNe laser (Dynatron 1120) is less than 1 mW. Assuming that losses in the fiberoptic set-up reduce this to 0.5 mW, and given an irradiation time per point of 15 seconds, the dose will be $0.5 \text{ mW} \times 15 \text{ sec} = 0.0075 \text{ J}$. Since a normal dose today is 0.5 - 2 J per acupuncture point and 1 - 4 J per trigger point, it is hardly surprising that no significant effect was observed. And since the instrument used can be frequency modulated (switched), the dose and the effect may actually have been reduced still further. The study is said to have been double-blind, although there is no description of how this was achieved. This would, in fact, have been valuable information, since double-blind studies are normally quite difficult to carry out with HeNe lasers - they use red, visible light that is immediately distinguishable from conventional red light by its characteristic laser speckles.

Table 2: Summary of paper by Jensen and colleagues.⁽⁷⁾

Is Infrared laser effective in painful arthroses of the knee?			
Laser type:	GaAs-laser (904 nm)	Output:	0.3 mW (average power)
Beam type:	True pulsed, 200 ns PW	Frequency:	190-250 Hz
Dose:	Not specified	Power density:	Not specified
Treatment distance:	Not specified	Laser model:	Space Laser IR CEB
Treated area:	All together 4 points per knee	Treatment time:	180 sec per point
No of patients:	29	No of treatments:	5
	Time between treatments:		1 day

Although the incident energy is not explicitly stated, approximate figures may be calculated from other data. The power output is given as 0.3 mW, although in Space's instruments (as in many other GaAs lasers), the output is directly proportional to the pulse frequency. At 1000 Hz, these Space instruments usually produce an output of 1 mW. The pulse frequency interval is stated as being 195 - 250 Hz. On the basis of the power output stated, the dose may be estimated as $0.0003 \text{ W} \times 3 \times 60 \text{ sec} = 0.054 \text{ J}$. Four points were treated on each knee, giving a total incident energy per session of 0.2 J. This dose is totally inadequate for a part of the body as large as the knee. This was a double-blind cross-over study.

ies for inadequate specification of parameters, then himself to be found guilty of the same sort of omission.

In the following examples (Tables 1 - 10), the parameters in each paper are summarized in tabular form. It should be noted that the power output is here to be understood as either continuous wave, mean output in frequency modulated C/W or the average output power in true pulsed systems, since this is the figure required in order to calculate the incident dose.

The above list could be made much longer. For example, Krikorian⁽¹⁵⁾ used a HeNe laser and a dose of 0.05 J/cm^2 to study wound healing in rats. Zarkovic⁽¹⁶⁾ used a GaAs laser and a dose of 0.0004 J/cm^2 to study

pain perception in mice. Using a HeNe laser and a dose of 0.004 J/cm^2 , Jarvis⁽¹⁷⁾ could (naturally) find no evidence of stimulation of thermoreceptors in humans.

It is interesting to quote the abstract of the negative study by Siebert⁽⁴⁰⁾ and then compare it to the analysis of the same study from Baxter.⁽³⁵⁾

Siebert : "The efficacy of "athermic" lasers (HeNe/GaAs) in the treatment of tendinopathies was investigated in a randomized double-blind study. On 10 consecutive days, 64 patients (32 therapy, 32 placebo) were treated for 15 minutes each with a switched-on or switched-off laser under otherwise identical conditions. The extent of movement in involved

Table 3: Summary of paper by Basford and colleagues.⁽⁹⁾

Low-energy Helium Neon laser treatment of thumb osteoarthritis			
Laser type:	HeNe laser (633 nm)	Output:	0.9 mW
Beam type:	Continuous wave	Pulse frequency:	N/A
Dose:	Not specified	Power density:	Not specified
Treatment distance:	Not specified	Laser model:	Dynatronics (model not specified) via fiberoptic delivery
Treated area:	4 different points around 3 joints (All together 12 points)	Treatment time:	15 sec per point
No of patients:	81	No of treatments:	9
Time between treatments:		2-3 days	

The dose will here be $15 \text{ sec} \times 0.45 \text{ W} = 0.007 \text{ J}$ per point. No obvious effect can be expected from such a low dose. This was a single-blind study.

Table 4: Summary of paper by Taube and colleagues.⁽¹⁰⁾

Helium-neon laser therapy in the prevention of postoperative swelling and pain after wisdom tooth extraction			
Laser type:	HeNe-laser (633 nm)	Output:	8 mW (tube)
Beam type:	Frequency modulated C/W	Frequency:	50 Hz
Dose:	Not specified	Power density:	Not specified
Treatment distance:	Not specified	Laser model:	Biotronical Laser MC-8
Treated area:	Not specified	Treatment time:	120 sec before suturing and day 2
No of patients:	17	No of treatments:	2
Time between treatment:		24 hrs	

Given a 50% fibre loss and a 50% pulsing loss, the total dose will be $2 \text{ mW} \times 120 \text{ sec} \times 2 = 0.48 \text{ J}$. This is a very low dose for such major surgery.

Table 5: Summary of paper by Lundeberg and colleagues.⁽¹¹⁾

Effect of laser versus placebo in tennis elbow			
Laser type (1):	HeNe-laser (633 nm)	Output:	1.56 mW
Beam type:	Continuous Wave	Frequency:	N/A
Laser type (2):	GaAs-laser (904)	Output:	0.07 mW
Pulsing:	True pulsed	Pulse frequency:	73 Hz
Dose:	0.09 J/point (HeNe); 0.004 J/point (GaAs)	Power density:	Not specified
Treatment distance:	1 mm	Laser model:	Model was not specified nor if fiberoptics were used
Treated area:	10 different acupuncture points through a 1 mm transparent plastic disc	Treatment time:	60 sec per point
No of patients:	82	No of treatments:	10 per point
Time between treatment:		2 treatments per week	

The doses are so low that significant effects can hardly be expected.

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Table 6: Summary of paper by Masse J-F and colleagues.⁽¹²⁾

Effectiveness of soft laser treatment in periodontal surgery			
Laser type (1):	HeNe-laser (633 nm)	Output:	0.27 mW
Beam type:	Continuous wave	Frequency:	N/A
Laser type (2):	GaAs-laser (904 nm)	Output:	0.8 mW
Pulsing:	True pulsed. PW 200 ns	Pulse frequency:	47.5-3040
Dose:	Not specified	Power density:	Not specified
Treatment distance:	1 mm	Laser model:	Stomalaser with independent measurement of output power
Treated area:	Not specified	Treatment time:	2 min 30 sec
No of patients:	28	No of treatments:	1
Time between treatment:		?	

In this report, the authors studied the effect of combined HeNe/GaAs therapy on bilateral free autogenous gingival grafts and, commendably, performed independent measurement of the output specified by the manufacturer. The HeNe output, specified as 4 mW, proved actually to be 2 mW and a mere 0.27 mW after sustaining heavy losses in the fiberoptic rig. The maximum output of the GaAs laser, given as 2 watts, was found to be only 0.8 watts. The size of the area treated is not specified, but assuming it was 1 cm², the total dose would be 0.0022 J/cm² GaAs plus 0.04 J/cm² HeNe, that is, a total of 0.0422 J/cm².

Table 7: Summary of paper by Smith and colleagues.⁽¹³⁾

The effect of low-energy laser on skin-flap survival in the rat and porcine animal model			
Laser type:	HeNe-laser (633 nm)	Output:	2.75 mW
Beam type:	Continuous wave	Frequency:	N/A
Dose:	Not specified	Power density:	310 mW/cm ² at probe tip
Treatment distance:	1 mm	Laser model:	Biostim 2000
Treated area:	Four dorsally based skin flaps with distal demarcation of necrosis	Treatment time:	30 sec/cm ²
No of patients:	82	No of treatments:	5
Time between treatment:		Treatment every day	

This study specifies just about everything but the dose, although this may be calculated as being 0.0825 J/cm² per day. Five sessions of treatment were given before the skin flaps were prepared, five afterwards. Therapeutic treatment carried out before surgical invasion of healthy tissue is probably of little value. The total dose per flap will therefore be 5 x 0.0825 J/cm² = 0.4125 J/cm². This dose is quite low. The control procedure may also be called into question since symmetrical flaps were prepared on the right and left sides of the animal and only one side was irradiated. This procedure ignores the systemic effects of laser treatment (see below).

Table 8: Summary of paper by Klein and colleagues.⁽¹⁴⁾

Low-energy laser treatment and exercise for chronic low back pain: double-blind study			
Laser type:	GaAs (904 nm)	Output:	10 diodes of each 0.4 mW
Beam type:	True pulsed	Frequency:	1000 Hz
Dose:	Stated: 1.3 J/cm ² per point. Calculated: 0.1 J/cm ²	Power density:	Not specified
Treatment distance:	Not specified	Laser model:	Omniprobe
Treated area:	Not specified	Treatment time:	4 min per point
No of patients:	20	No of treatments:	12
Time between treatment:		Three times per week	

The authors state that a GaAs laser was used to produce a dose per point of 1.3 J/cm², the indication being the heterogeneous diagnosis of "low back pain". However, analysis of the parameters shows that the dose was in fact only 0.1 J/cm² (Pm = 2 W x 10-19 sec x 1000 Hz = 0.4 mW; t = 240 sec) and that the total dose was 5 J. In our experience, this recalcitrant indication calls for 2 - 4 J/cm².

Table 9: Summary of paper by Seichert and colleagues.⁽⁸⁾

Wirkung einer Infrarot-Laser-Therapie bei weichteilrheumatischen Beschwerden			
Laser type (1):	GaAs laser (904 nm)	Output:	1.2 mW
Beam type:	True pulsed. 200 ns pulse width	Frequency:	1200 Hz
Laser type (2):	HeNe-laser (633 nm)	Output:	6.5 mW
Beam type:	Continuous wave	Frequency:	N/A
Dose:	Not specified	Power density:	Not specified
Treatment distance:	15 cm	Laser model:	Space Laser MIX 5
Treated area:	Circular area 6 cm diameter = 28 cm ²	Treatment time:	10 min (600 sec)
No of patients:	18	No of treatments:	5
Time between treatment:		Once per day	

Although the author claims that his instrument is a GaAlAs laser, it is clear from the wavelength (as from the brand) that it is actually a GaAs laser. The dose is not explicitly stated, but, for the GaAs laser, can be set at $600 \times 0.0012 \times 5/28 = 0.128 \text{ J/cm}^2$. On top of this comes the NeHe dose, which is more or less the same (0.134 J/cm^2). See below for the purported double-blind procedure.

Table 10: Summary of paper by Mulcahy and colleagues.⁽⁴¹⁾

Low level laser therapy: a prospective double blind trial of its use in an orthopaedic population			
Laser type:	Not stated	Output:	35 mW
Beam type:	Not stated	Frequency:	Not stated
Dose:	1 J/cm ² 'of skin' [sic]	Power density:	Not stated
Treatment distance:	Not stated	Laser model:	Not stated
Treated area:	Not stated	Treatment time:	Not stated
No of patients:	20	No of treatments:	8
Time between treatment:		2-4 days	

Very little is known about the parameters, such as wavelength, pulsing/continuous and treatment technique. Even the laser type is not reported! The indications are plantar fasciitis, trochanteric bursitis, tendinitis, lateral epicondylitis, knee pain, cervical pain and lumbar pain. If applied in the contact pressure technique, 1 J/cm² may be a reasonable dose (even if slightly on the low side) for some of the indications but is most certainly subclinical for indications such as cervical pain and lumbago.

joints (neutral 0 method) and rating on a pain scale for pain at rest, movement pain, and pressure pain before treatment, after treatment, and 2 weeks after conclusion of therapy, as well as infrared thermography, served to check therapy. After the end of therapy, a significant reduction ($P = < 0.001$) of 50% was shown for resting pain as well as reductions of 30% for movement and 30% for pressure pain. This result was identical in the therapy group and in the placebo group. There was also no indication of a different result of therapy between the therapy and placebo groups with regard to the thermographic control and the extent of movement. The breakdown of the data in terms of age, sex, and duration of disease did not provide any indications of different results for placebo or therapy. It was striking that the patients who reported sensations during or after the treatment (irrespective of whether pleasant or unpleasant) had a greater reduction of pain than the patients without sensations. This laser therapy thus did

not show any effect above and beyond that in the untreated group".

Baxter's comments: "Despite being highly critical of the standard of previous laser research, these investigators employed a non-contact technique in their trial, irradiating the patients' skin from a distance of 10 cm. Given the beam divergence of clinical LLLT apparatus, the use of such a distance would appear to be inappropriate, producing minimal power and energy densities on the irradiated tissue. This, coupled with the apparent inaccuracies in calculation of dosage (by a factor of 10), casts serious doubts upon the reliability and validity of the reported findings."

Inclusion criteria

In a study by Hansen,⁽¹⁸⁾ 40 patients suffering from various "chronic orofacial pains" were tested. The pain had on average lasted 4.9 years (0.5 - 42 years). Twenty-eight patients suffered from "The burning mouth syndrome" (oral dysesthesia), five from toothache in one single tooth, three from tension headaches,

and so on. There were no objective pathological findings. X-ray examination had revealed nothing. In the headache group, acrylic splints had proved ineffective. A GaAs laser was used, and the initial dose of 2.4 J/cm^2 was increased to 4.8 J/cm^2 if no effect was observed initially. According to the literature (quoted in the study), the burning mouth syndrome is considered to be either multi-factorial, psychosomatic or purely psychogenic. It is therefore safe to assume that the tissue treated for this study was healthy in every respect. That no pain relief was obtained and that there was an absence of 5-HIAA in the patients' urine is therefore only to be expected.

Lack of proper control groups

Seichert⁽⁸⁾ (see above) used a combined GaAs/HeNe laser in a study of patients suffering from various rheumatic complaints. The probes housed five GaAs diodes producing an output of 1.2 mW per diode, while the HeNe laser produced an output of 6.5 mW. One group was given GaAs + HeNe, another HeNe with the GaAs diodes switched off (the placebo group). As both the "verum group" (0.258 J/cm^2) and the "placebo group" (0.134 J/cm^2) were actually both treated by laser, there is in fact no control group here. The comparison made is not between laser and placebo but between a combination GaAs + HeNe laser and a HeNe laser.

Therapeutic technique

While Moustsen⁽¹⁹⁾ did not find any effect of LLLT in sinusitis, Neuman⁽²⁰⁾ found an objective effect of 70% in allergic rhinitis. Both studies are double blind. The difference in success on mucosal inflammation is found in the treatment technique. Moustsen, using 830 nm, irradiated four skin points close to the nose, 3 J per point. Neuman used 660 nm, 8 J directly on the nasal mucosa. The effects of the latter study were confirmed through tomography and endoscopic inspection. Interestingly enough, the placebo group improved 24% subjectively but only 3% objectively, while the ratio in the laser group was 72/70. Although Neuman applied lower doses than Moustsen, the actual dose at target was higher by far through the direct mucosal irradiation technique used. Treatment of sinusitis requires irradiation intraorally over the cavity borders and dosages 3-4 times higher than for direct irradiation of the mucosa, to compensate for absorption.

We believe that the difference in the results arrived at by these two studies is attributable to the difference in the approach to therapy - much of the energy of the laser light is absorbed by skin and bone - although it may partly be the case that 660 nm is a more effective wavelength under those particular conditions.

Systemic effects

The systemic effect of therapeutic laser light has been described by many researchers, such as Braverman⁽²¹⁾,

Rochkind⁽²²⁾, Airaksinen⁽²³⁾, Inoue⁽²⁴⁾ and Schindl⁽²⁵⁾. Essentially, a systemic effect is one such that treatment of a given complaint at one site will also tend to affect a similar complaint elsewhere. It is therefore important to observe caution in interpreting the result of studies in which parts of the test person's/animal's body has been treated by laser and another part of the same body has been used as a control, especially in small animal studies.

Tissue condition

Persson⁽²⁶⁾ observed no effect on angiogenesis in a study of experimental human gingivitis. Although this finding is confirmed in a study by Kusakari⁽²⁷⁾, this author does report LLLT as causing an increased flow of blood, which was not studied in Persson's work. Both studies, however, are marred by the fact that healthy humans/animals were used as test subjects. Gingivitis was, for example, induced in young, completely healthy individuals whose immune system was in excellent order. A study by Kozlov⁽²⁸⁾ reported that LLLT had a moderate effect on slight periodontitis, a good effect on more manifest periodontitis, and little effect on advanced periodontitis. The immunological condition of the tissue and of the individual is a significant factor in the effectiveness of LLLT, and a "genuine" clinical condition cannot be achieved in a study based on healthy volunteers. This may explain the discrepancy sometimes noted between clinical work and scientific tests.

The significance of the condition of the tissue can clearly be seen in an experiment by Steinlechner⁽²⁹⁾ in which keratinocytes, present in 1% and 5% solutions of fetal calf serum, were irradiated with laser light. The cells in the less nutritious solution were stimulated most. The same observation has been made by Yamamoto⁽³⁷⁾, irradiating human fibroblasts. There is reason to believe that the outcome of many *in vitro* studies has been just as influenced by the nutrient conditions of the cells as by the laser parameters.

Power density

According to a study by van Breughel,⁽³⁰⁾ power density appears to be more important than total dose in wound healing. Lundeborg⁽³¹⁾ used a 6 mW HeNe laser to treat venous leg ulcers. 4 J/cm^2 was said to be given to the ulcers. Ulcer size ranged from 3-32 cm^2 . The treatment technique is not stated. Regardless of technique, it would take between 36 minutes and 6 hours to achieve the stated dose, per wound and session. Using a sweep technique with a focused beam, the power density would be around 0.15 W/cm^2 . If a defocused beam was used to cover the entire wound (32 cm^2), energy density would be around 0.0002 W/cm^2 , which is lower than the energy density of the normal illumination in an dental operator or surgical operating theatre, which is very low. A dose miscalculation is probable but the authors of the study have been reluctant to reveal

the parameters used. In the absence of such parameters, this study cannot be properly evaluated, but very low power density is a probable reason for negative results. In another study on venous ulcers by Malm and Lundeborg,⁽³⁸⁾ a GaAs laser was employed. 4 mW was used for 10 minutes on ulcers ranging from 4 to 52 cm², regardless of ulcer size. The 4 cm² wound would thus receive 0.6 J/cm² and the largest wound 0.046 J/cm², not the 1.96 J/cm² as stated by the authors. Energy density as well as dose for larger wounds are thus low. Treatment technique was not indicated. "The laser was held perpendicular to the surface of the wound". This is not a sufficient description of the treatment method. There is a great difference between following the outer border of the wound (active healing area) and spreading the beam over the open wound area. It is also important to describe fully the beam pattern and the shape of the invisible GaAs beam. The distance between diode and wound is not indicated.

Mixed parameters

A study by Hall⁽³²⁾ is confidently entitled "Low level laser therapy is ineffective in the management of rheumatoid arthritic finger joints". Such a title suggests that all reasonable parameters (wavelengths, doses, pulsing, etc.) have been checked and are kept properly under control. One of the probes used is a so-called cluster probe having a 15 mW GaAlAs laser diode surrounded by 30 noncoherent light-emitting diodes of three different wavelengths. Which wavelength was effective, which was ineffective, and did any particular wavelength have a detrimental effect on the overall result? Indeed, were two or more of the wavelengths possibly antagonistic rather than synergistic?

Blending coherent and non-coherent light while giving therapy with light of different wavelengths may possibly result in some clinical improvement but may also result in less improvement than if the therapy had been more exactly controlled. Tiina Karu, for example, has showed that in cell cultures first irradiated with laser light and showing a clearly demonstrable biological effect, the effect is reduced practically to zero if the cells are then irradiated with broad-band (non-monochromatic, incoherent) light.⁽³⁶⁾ The main objection to mixed parameters is that they do not result in unequivocal new knowledge.

The influence of ambient light

The influence of ambient light is not a clinical problem *in vivo*. In the laboratory, however, it may influence the outcome of a study. As mentioned above Karu⁽³⁶⁾ has shown that the effect of laser light may be partly or completely washed out by broadband light. In a study by Lundeborg⁽³⁹⁾ the effect of HeNe and GaAs laser on the generation of signals in a sensory receptor was studied. The stretch receptor of *Astacus fluviatilis* (crayfish) was mounted over a glass platform. HeNe 1.56 mW

and GaAs 0.07 mW, 73 Hz was used, dose not indicated. Dissecting the stretch receptor and mounting it was carried out under the light microscope, using a very bright broadband light source. This disturbing factor must be taken into account when evaluating similar trials.

Meta-analyses

Two meta-analyses^(33, 34) of the clinical effects of LLLT have been performed. In one, various studies were graded by points on the basis of a number of quality criteria. By this means, a negative study may achieve a high grade even if one of the parameters - though it may be essential to the result of the study - is entirely wrong. In Beckerman's study,⁽³³⁾ for example, Basford's study⁽⁹⁾ has been given the highest score (18 out of a possible 25) in spite of the fact that the dose used is not actually therapeutic. A comparison might be made with a chain: it is no use having 19 perfectly sound links if the 20th is open. The chosen method is important. Bjordal⁽⁴²⁾, using a systematic review system, found a higher validity for the same studies as Gam.

Conclusion

In studying the therapeutic effects of laser light, there are many pitfalls along the way, and many are the researchers who have fallen therein. Unfortunately, their work is still cited as evidence that LLLT does not work. In fact, many of these older studies should be disregarded in future discussions on this subject, since they are clearly irrelevant. Meta-analyses, too, may also prove meaningless unless pitfalls of this type can be avoided. In our analysis we have criticized a number of well-known negative studies, and it would be right to insist that a number of positive studies should be subjected to critical scrutiny as well. Positive studies have, however, been the subject of critical comment for many years, whereas only Baxter⁽³⁵⁾ and Bjordal⁽⁴²⁾ have hitherto made a detailed analysis of the parameters of negative studies.

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