LIGHT AND LIFE: A REVIEW OF LOW REACTIVE-LEVEL LASER THERAPY, FOLLOWING 13 YEARS' EXPERIENCE IN OVER 12 000 PATIENTS

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Laser therapy, or preferably, Low reactive-Level Laser Therapy (LLLT) is now being recognized as a valid medical tool, with the theories advanced from clinical experiences and double-blind trials being backed up by research data. From its beginnings with Professor Endre Mester's experiments and clinical trials at the end of the 1960's, LLLT has steadily increased in applications to include an increasing number of medical specialties. The historical background of LLLT is given. The author examines the physical basics of LLLT, and demonstrates the differences between photoactivative laser therapy and photodestructive laser surgery. The α-effect phenomenon of simultaneous LLLT which was reported by early workers in conventional high-powered laser surgery is examined, and the development of pure LLLT is discussed. Wavelength-dependency is discussed, and the importance of methodology is demonstrated. The author discusses the importance of the use of correct terminology in writing or discussing LLLT, and the necessity for accurate and consistent reporting of LLLT therapeutic parameters. Some possible pathways of LLLT are examined. Examples are given showing a wide range of practical multispecialty clinical applications of LLLT, gained from the successful diode laser and combined laser therapy of pure and combined LLLT in over 12 000 patients over the past 13 years. Simultaneous LLLT, concomitant with laser surgery, is not included in these figures.

KEY WORDS Pure LLLT Simultaneous LLLT Bioactivation α-effect Laser therapy

Introduction

'And God said, Let there be light: and there was light' (*Genesis*, 1.1). Sunlight is the first natural light all living things know, mankind, and the animal and plant kingdoms, whether as individual cells, or as systemic and independently functioning organisms. Sunlight presents an interesting dichotomy. The light of the sun is simultaneously capable of creating lifeless deserts, and sustaining a wide variety of living things, including man. In other words, sunlight is at the same time photodestructive, and photoactivative, having a 'bad face' and a 'good face', respectively, as shown schematically in Figure 1. There are a combination of factors which decide in which sector sunlight works, which can be summarized as the amount and type of light that actually reaches the target organism, and is absorbed by it. In photobiological terms that incident light can be quantified in terms of power and energy, and qualified in terms of wavelength: the power density (incident power in watts divided by the area in square centimetres upon which it is incident), and the energy density, a function of the power density multiplied by the time of exposure in seconds, measured in joules per square centimetre. Depending on the wavelength of the incident light and the optical characteristics of the tissue, above a certain power density a photodestructive reaction will certainly occur in the target tissue. Below that threshold, the level of reaction is nondestructive, but instead the energy is absorbed directly by the organism, activating the organism in a primary reaction at the cellular and subcellular level to achieve a different level of activity. The secondary reaction at first is local, in the area of the primary absorption, but gradually gives rise to a systemic effect.

The medical laser outshines the sun, as far as the incident energy levels are concerned, by many orders of magnitude. Laser is a controllable source of incident energy, and can produce either photodestructive or photoactivative reactions in the target organism: both may also occur simultaneously. Photodestruction (with or without photoactivation) is what happens in laser surgery, and photobioactivation in laser therapy. In this article, I would like

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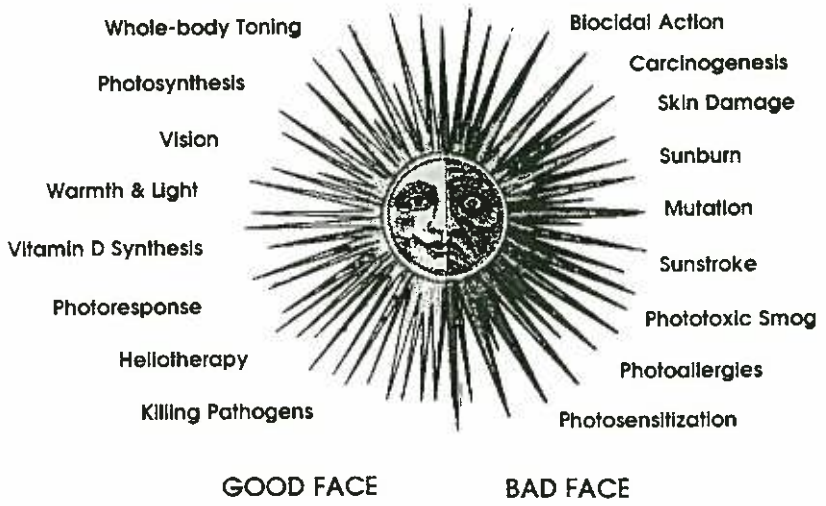


Figure 1. The two faces of the sun, contrasting the beneficial effects of sunlight with the detrimental ones

to compare and contrast both the surgical and therapeutic uses of laser energy, and then, having looked at some of the possible mechanisms and pathways of laser therapy which have been demonstrated in both controlled clinical settings and in the laboratory, give some examples of practical clinical applications of this new genre of photobiologically-based medicine.

Laser Surgery and Laser Therapy: HLLT and LLLT

The laser, first successfully developed in 1960 by Dr Theodore Maiman in California, U.S.A.[1] quickly found uses in the medical field, especially in ophthalmology and dermatology. The use of the laser in surgery has now spread to almost every medical specialty. When a surgical laser beam strikes target tissue, it is absorbed, causing a sharp rise in temperature. Depending on the degree of heat generated, tissue may be carbonized with burn-off, vapourized, coagulated, or the protein in the tissue may be degraded or denatured, as seen in the lower quadrant in Figure 2.[2] Because light travels at the same speed (3×10^{10} cm/s) in or out of tissue, these reactions take place almost simultaneously. They all have one thing in common: tissue structure is destroyed or permanently altered. Accordingly, as these effects are higher than the tissue damage threshold I class these effects as High reactive-Level Laser Treatment, or HLLT.

In addition to the photothermal destructive effects, the laser creates a variety of nonthermal effects: photoosmotic, photoionic, photoenzymatic, and photoimmunological, for example.[3] If these nonthermal effects also result in the irreversible alteration or destruction of tissue, even though they are not photothermal, then they also come into the category of HLLT.

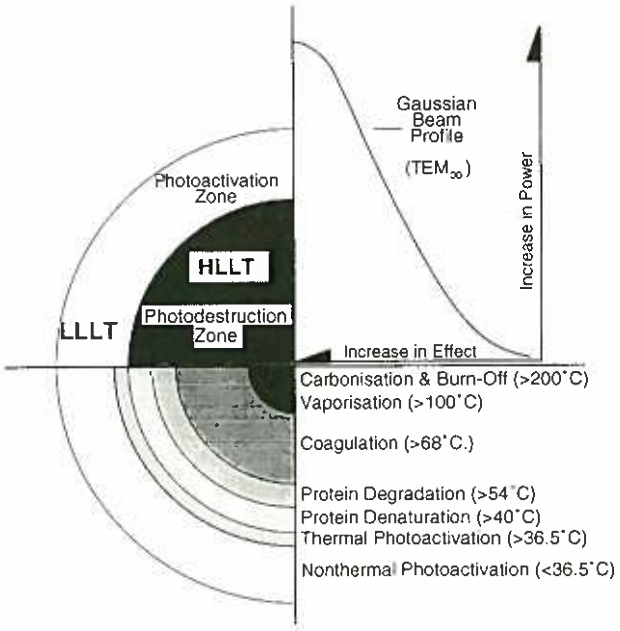


Figure 2. Composite schematic showing a typical bell-shaped TEM_{00} (Gaussian) beam distribution curve, and the beam imprint in target tissue. The greatest power density is at the centre of the beam, gradually diminishing towards the periphery, where the power densities are in the therapeutic range. Thus HLLT and LLLT effects can be found simultaneously in the laser/tissue reactions of a surgical laser beam, explaining the existence of the α-effect in simultaneous LLLT

Although the above effects are classed as photodestructive, they are extremely useful in laser surgery, and are what make the surgical laser in some instances superior to other conventional methodologies. The instantaneous conversion of light to heat, known as the radiant heat effect,[4] allows a high degree of colour selectivity in the treatment of abnormally coloured naevi, or birthmarks, for example. Figure 3 shows examples of how the photodestructive power of HLLT systems can be applied with varying degrees of cell and tissue

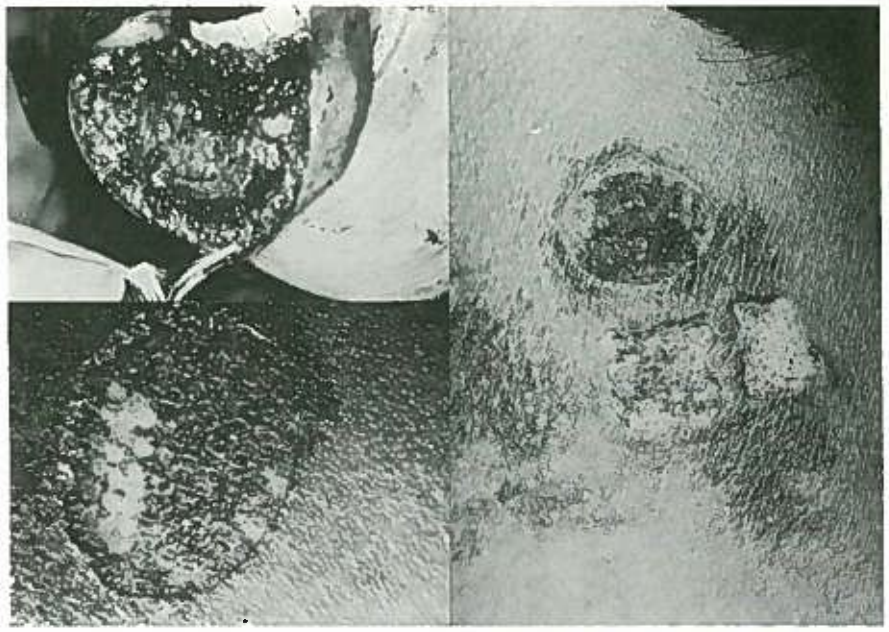


Figure 3. (Right, top treated area) Cell-selective radiant heat effects of the millisecond-pulsed ruby laser. Black change indicates selective haemocoagulation of superficial haemagioma simplex (HS) blood vessels, coupled with a laser-produced epithelial window (over 30 J). (Right, lower treated areas) Both these areas show argon laser treatment of HS. On the right, just after laser treatment, the white change of protein denaturation and thermal vasoconstriction can be seen. On the left, 10 min after laser treatment, cooling of the treated area has reversed the vasoconstriction, and normal colour can be seen to have returned in some parts of the treated area. (Lower left) White change following argon laser treatment of an HS lesion, with a ruby-laser created epithelial window (20 J). Longer irradiation time required means that secondary thermal damage occurs to areas contiguous with the target site caused by conducted heat. (Upper left) Intraoperative view following CO_2 laser excision of large cavernous haemangioma of the lower lip. Despite high bleeding tendency of this naevus type, a dry and clear operative field can be seen, with areas of bleeding controlled by haemocoagulation. This patient was treated on a same-day surgery basis

selectivity, while achieving other desired effects, such as shrinkage of a hypertrophic area, or intraoperative haemostasis.

From the beginning of the use of the laser in medicine and surgery, it has been noted in the literature that the laser had an additional effect, which I should like to call the α-effect, with users and patients reporting that there was for example less pain and inflammation following laser surgery compared with conventional methods. Figure 4 shows the condition of a haemangioma simplex lesion before laser treatment, which had been treated previously elsewhere with electrocoagulation. The abnormal colour of the lesion has not been completely removed, and in fact a large number of minute raised white hypertrophic scars indicate where the electrocoagulation system needle had been inserted. Figure 5 shows the same lesion after argon laser treatment in my 'zebra' method. Not only has the abnormal colour of the lesion gone, but the abnormal configuration caused by the electrocoagulation needle has also been removed, and there is no hypertrophic scarring after the argon laser treatment.

What was this α-component of laser surgery, which could, in the laser treatment of lesions, help prevent hypertrophic scarring; which could leave less postoperative pain than conventional methodology; which was claimed to assist wound healing, in some cases? One of the most popular laser beam modes is known as the Gaussian mode,[2] represented in a transverse cross-section of a laser beam by a bell-shaped curve, showing the distribution of the power at its highest in the centre of the beam, and gradually decreasing towards the periphery, as seen also in Figure 2. From this figure, which also shows schematically a typical Gaussian beam print in target tissue, it can be deduced that the beam power density gradually decreases as it spreads through tissue. It follows naturally that, at the borders of the photothermally destructive zones, the beam does not stop, but continues on, now extremely weak. At first there will be an area showing a slight rise in temperature, not enough to cause any kind of change to the tissue structure, but enough to activate the tissue: this is the nondestructive photothermal activation zone. In the outermost zone, the tissue temperature is not affected at all, but the tissue cells still absorb the light energy, and are activated, reacting in different ways. Accordingly I refer to this zone as the nonthermal photoactivation zone. These two last zones show no alteration in tissue structure, and the reaction in the tissue is below the destructive threshold: accordingly, the reaction can be referred to as Low reactive-Level Laser Therapy, or LLLT. As this type of LLLT

Figure 4. Condition of HS lesion after electrocoagulation treatment, before HLLT. The abnormal colour of the lesion has not been removed, and the sites of the electrocoagulation system needle insertion are marked by small, white hypertrophic scars, giving a rough appearance to the treated lesion

occurs simultaneously with the other surgical laser photodestructive reactions, I would like to refer to it as *simultaneous LLLT*.

This simultaneous LLLT was recognized by researchers in the field, producing in particular much less postoperative pain than when the same procedure was carried out with a conventional scalpel. Power densities, and energy densities, of existing systems were then lowered to the point where no photothermal or nonphotothermal damage was caused to the irradiated tissue. Following on from that, specialized LLLT systems were developed and designed to produce these low incident power densities, at the optimum wavelengths, to be used only for laser therapy, as distinct to laser surgery. This type of LLLT I should like to refer to as *pure LLLT*, the main subject of this article.

Brief History of LLLT

The first real experimental applications of LLLT were reported in the latter half of the 1960's by the late Professor Endre Mester, in Budapest, Hungary: he followed these up with the first clinical reports of laser biostimulation, using low-powered ruby and argon lasers to heal non-healing or slow-to-heal ulcers published in English in 1969.[5] From then until his death in 1984 he produced a tremendous volume of clinical and experimental work, gradually favouring the HeNe laser as his laser of choice. In 1974, Heinrich Plogg of Fort Coulombe, Canada, presented his work on the use of the laser in needleless acupuncture and pain attenuation, following on from Mester's work.[6]

The first appearance in the literature of the clinical applications of the GaAlAs diode laser appeared in 1981, in a paper comparing the pain attenuation properties of the GaAlAs diode laser with the Nd:YAG, another popular LLLT system.[7] In July 1988, the International Laser Therapy Association (ILTA) was founded. The first meeting of the Japanese Laser Therapy Association, JaLTA, was held in July 1989. February 1990 saw the first meeting of the European chapter of the ILTA (ELTA) in Manchester, England, and of course 'Tropical Laser 90', the first full meeting of the ITLA, was successfully held in Okinawa, in October of the same year. Elsewhere, the Mexican Laser Therapy Association (MeLTA) has been officially recognized by the Mexican government, similarly in Korea, and Spain, North America, the U.K. and Australia are poised to follow suit. The Belgian and Italian Associations applied in September of 1992 to become associate organizations under the ITLA banner. The third JaLTA meeting was held in Tokyo in 1991, and the fourth JaLTA meeting was held in July of 1992 in The University of Hokkaido, under the Presidency of Professor Kemmotsu. September 1992 saw the second ILTA meeting in London, just 4 years after the formation of the ILTA. Other national and international societies have started to devote more time and dedicated sessions to ILTA and photoactivation,

Figure 5. Same lesion as seen in Figure 4 during argon laser treatment in the 'zebra' method. Areas treated by argon laser HLLT show good colour removal, a return to normal skin texture and colour, and no hypertrophic tendency, including the removal of the old hypertrophic scarring. The α-effect at work

quite correctly separating it from other areas such as photodynamic therapy, or PDT. The fifth JaLTA meeting will be held in Tokyo, in June of 1993.

In 1994, as readers will already have seen in *Laser Therapy*, an extremely important joint meeting of the ILTA and the International Society for Laser Applications in Medicine (ISLAM) is being planned to be held in Barcelona, Spain, under the presidency of Dr Mario Trelles, of the Instituto Medico, Vilafortuny. It is quite clear that laser therapy and photobioactivation have started to attain real recognition in the medicoscientific world.

Theory of LLLT

Absorption and Reaction

The cell is the basic building block of living tissue, but the cell is a complete living being in its own right: just like us, cells require food; they must breathe; they must replicate; and they react to external stimuli, including light. In order for there to be any reaction, there has to be absorption (first law of photobiology). The wavelength of the incident light must therefore have a specific receptor or receptors in the target cell. It has been pointed out that visible light and invisible infrared 'light' in LLLT have similar effects in pain attenuation, and this is very strange, because according to the rules of photobiology, because of the inherent photon energy levels, they should induce completely different reactions in target tissue: visible light should produce a photochemical reaction (higher photon energy level inducing photochemical reaction in the cell), whereas infrared energy should produce a photophysical reaction, (lower energy level producing rotational and vibrational reactions, influencing cell membranes).[8]

Tiina Karu proposed a model for low level laser radiation stimulation of a biological system (i.e. a cell) for visible red light, as shown in Figure 6.[9] In this model, the receptors are within the cell, primarily components of the respiratory chain within the mitochondria. This activates the mitochondria to release an increased dose of ATP into the cytoplasm, which starts a photomediated chain of events within the cell during which the membrane is influenced, which in turn causes even more amplification of the received signal, affecting the nucleus and leading to cell proliferation, or some other photoresponse.

In the case of the infrared laser, infrared energy is absorbed in the cell membrane. Kendric Smith thus proposed an adaptation of Karu's model,[10] in which the photoreception occurs at the membrane, initiating the photocascade at a later stage than with visible red light, but producing the same ultimate photoresponse (Figure 7). What Smith proposed has been shown by Sugawara and Shiroto in an experiment on pooled human neutrophils:[11] a specific 830 nm receptor was found to exist on the neutrophil membrane which when excited led to an increase in the phagocytic activity of the neutrophil. In an earlier paper,[12] the same researchers had shown increased chemotaxis following IR laser irradiation, compared with unirradiated controls.

The necessity of absorption for any photoreaction to occur is an accepted factor. *In vitro* studies have shown that cells isolated in culture or medium in monosheets or at most a few cell layers absorb and react to noncoherent but monochromatic light just as well as laser light, provided however there is polarization of the incident light.[13] However, in living tissue, the LLLT targets cells are in a dense, nonhomogeneous medium, surrounded by pigments which can themselves absorb incident light, and at depths ranging from a millimetre to several centimetres. In such a situation, the photon density which only laser energy can provide is necessary to ensure sufficient photons get through to the deeper

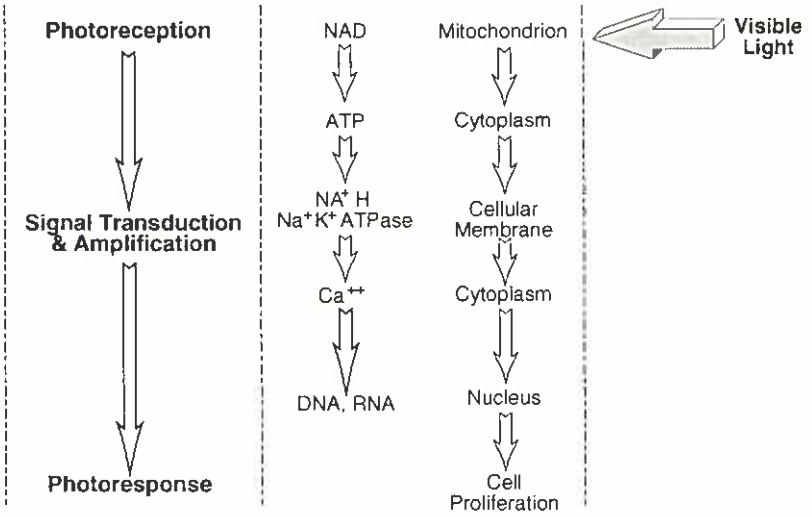


Figure 6. Model proposed by Karu for laser bioactivation with visible light at a cellular level.[9] On the left is the accepted photobiologic process of absorption (photoreception) followed by signal amplification, leading to the effect (photoresponse). Karu proposed that visible light was specifically absorbed by components of the mitochondrial respiratory chain, starting of the photocascade of events as shown, with the respective subcellular organelles involved and the photochemical events associated with their involvement

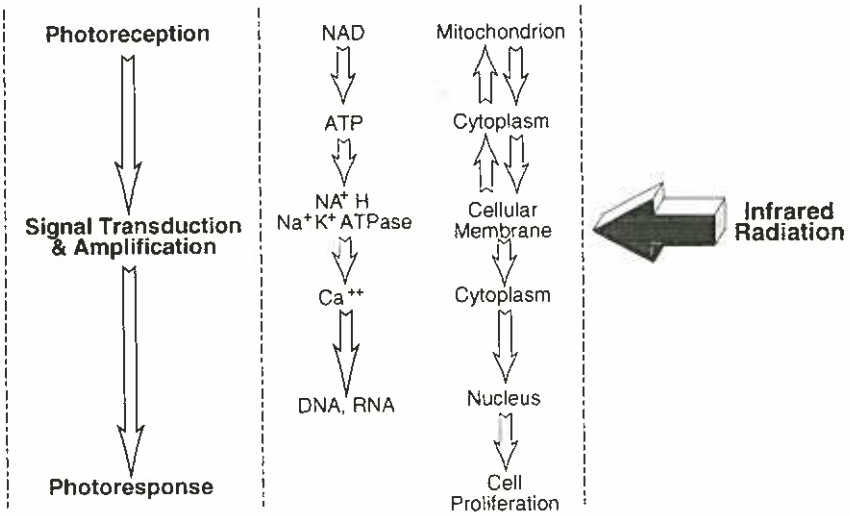


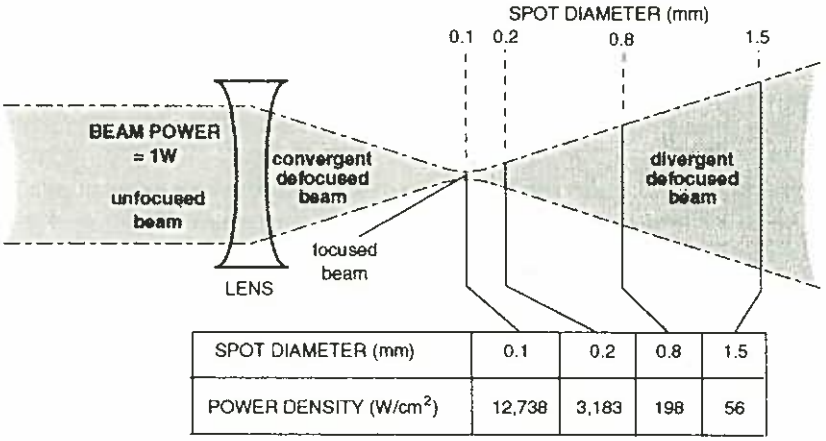
Figure 7. Model proposed by Smith for the effect in cells following irradiation with infrared light.[10] Infrared light has a photophysical effect, and its target is the cell membrane. The vibrational and rotational changes in the membrane molecules change membrane permeability, and enter the photocascade at a later stage than in Karu's model: this in turn affects the cytoplasm and the mitochondria, and the same chain of chemical events is initiated, as seen after visible light irradiation. This explains the occurrence of the same effects in pain therapy with both visible and infrared LLLT

target cells, and thus assure absorption in order to activate the photoreception–signal transduction/amplification–photoresponse cascade put forward by both Karu and Smith. In living target tissue, the important factors thus appear to be both coherence, and polarization, provided the polarization is either linear or right-handed.

Concept of Power and Energy Density

For laser surgeons, the most important single concept is that of *power density* (PD).[3] The PD of a laser is defined as the incident photon density of the laser beam at the target tissue, and can be arrived at by dividing the output power of the laser in watts (W) from the delivery device by the irradiated area on the tissue in square centimetres (cm^2). This gives the value of the PD in W/cm^2. It is by controlling the power density that a laser surgeon can cut, vapourize, coagulate or weld tissue. The appropriate PD's can also achieve photoactivation in LLLT.

Power density is controlled easiest by altering the spot size of the incident beam. Figure 8 shows a



SPOT DIAMETER (mm)	0.1	0.2	0.8	1.5
POWER DENSITY (W/cm^2)	12,738	3,183	198	56

Figure 8. A 1 W laser beam focused by a lens, showing the power densities at various points in the beam, ranging from potentially highly photodestructive effects to a mildly photothermal potential in the same beam, depending on the portion of the beam used in target tissue

1.0 W laser beam focused through a lens to a focal spot of 100 μm, or 0.1 mm. The portion of the beam before the lens is referred to as *unfocused*; at the focal waist it is *focused*; before the point of focus it is a *convergent defocused* beam, and beyond the focal point, a *divergent defocused* beam. Surgical lasers are usually used unfocused, focused, or divergent defocused. Thus by moving the laser delivery device back from the point of focus on tissue, an infinite variety of beam spots can be produced. The size of the beam dramatically affects the PD, much more than altering the output power. The PD is worked out according to the formula:

$$PD = \frac{\text{output power}}{\text{irradiated area}} (W/cm^2)$$

where the output power is the incident power at the tissue in W, and the irradiated area is expressed in square centimetres, arrived at by using the formula πr^2 where π is the constant 3.142, and r is the radius of the irradiated spot in cm.

At a 100 μm spot, by substituting the appropriate values the power density of the 1 W beam in W/cm^2 is:

$$PD = \frac{1}{3.142 \times 0.005^2} (W/cm^2)$$
$$\cong 12\,738\ W/cm^2$$

By simple focusing, a beam with an incident power of 1 W can develop a power density of over 12 000 W/cm^2. Doubling the spot size to 200 μm by defocusing the beam will not halve the PD, however. Using the same formula as above, the PD is 3183 W/cm^2, one quarter of the original value.

Considering Figure 8, it can be seen that the value of the PD for any given beam of constant power will vary as the inverse square of the area of the beam. Thus varying the spot size of a laser can give incision, vapourization for tissue debulking, coagulation for haemostasis, protein denaturation for tissue welding, and thermal or nonthermal photoactivation for laser therapy.

The other factor under user control is the exposure time. By multiplying the PD by the exposure time per shot in seconds, the energy density (ED) in joules per square centimetre (J/cm^2) can be found, according to the formula:

$$ED = \frac{\text{output power x exposure time}}{\text{irradiated area}} (J/cm^2)$$

The ED can be thought of as the *dose*, and is very important to the laser surgeon or therapist, although the power density remains the most important single user-controlled factor.

Wavelength

The power and energy densities are controllable by the user. The wavelength of the system is not. However, wavelength is extremely important, since the wavelength ultimately decides both the basic laser/tissue reaction and the penetration depth in the target tissue.[2,3] The author compared similar tissue effects in the mouse skin model with the Argon, Nd:YAG and CO_2 lasers, as assessed macroscopically by Evans blue exudation in the irradiated tissue, and microscopically with histological staining. With the CO_2 laser dose standardized at 1, to achieve a similar tissue effect a 10 times greater dose of argon laser was required, and 475 times longer for the Nd:YAG.[14] Visible light lasers interact preferentially with pigmented tissue. Blue-green light from the argon laser, for example, is very heavily absorbed in biologic pigments: in living tissue therefore the penetration rate is very low. Red light from the HeNe laser however is less well-absorbed in blood, which is also red, so the

penetration rate is much greater. The CO_2 laser wavelength of 10 600 nm is almost completely absorbed in water, so the penetration rate in biologic tissue is extremely small. Having said that, if the incident power densities are low enough, the beam will not instantly vapourize intra- and extracellular water, but will actually penetrate quite well. The Nd:YAG system is not really preferentially pigment-absorbed, but is taken up by protein generally, so the penetration rate in tissue is quite high. Highest of all is the diode laser, especially the GaAlAs laser at 830 nm, which is in the water-absorption tissue window of 820–840 nm. The choice of laser wavelength therefore determines the penetration depth even more than the power and energy densities. The wavelength could be looked at as the medicine, and the PD and ED as the dosage: unless the medicine is correct, there is no point in altering the doses! Figure 9 shows penetration data for the different laser wavelengths in diagrammatic form, based on CCD analysis of irradiation of *in vivo* tissues.[15]

Laser Therapy Terminology

Although covered in a paper in a previous issue of *Laser Therapy*,[16] I feel I must talk again about terminology. The literature is full of a variety of terms which are all hardware-, or laser system-based, as I have often said in previous Editorials. *Cool*, *cold*, *mid*, *low-energy*, and *low power*, are all terms in current use, and because they are based on the laser and not the reaction in tissue, I propose they are inaccurate. They are also factually inaccurate. Consider a surgical CO_2 laser delivering an incident power at the target tissue of 10 W. That is certainly not low-powered. However, when used at a spot size of 10 cm^2 (spot diameter of approximately 3.5 cm), the power density is only 1 W/cm^2. If the exposure time is 10 min, however, then the energy density is 600 J/cm^2: this in turn can not be called low energy, and is possibly capable of causing overexposure-related damage to the target tissue. If the same laser is used at 10 W with a spot size of 0.4 mm in diameter the PD becomes 7962 W/cm^2, certainly capable of causing thermal damage. If the exposure time however is 1 ms (0.001 s), then the energy density drops to just under 8 J/cm^2: definitely laser therapy levels.

From the above, the importance of careful choice of output power, spot size and irradiation exposure time is clear: however, their correct recording and complete reporting is also extremely important for other researchers or therapists to be able accurately to repeat the conditions. Since the therapist and the clinical investigator are more concerned with the reaction in the target tissue than the laser system being used, then I feel that the term Low reactive-Level Laser Therapy (LLLT) is the most accurate to describe the reactions following low therapeutic levels of laser radiation.

Concept of Photobioactivation

When driving a car, if the accelerator is pressed—an action—the engine of the car is fed more fuel, and the forward progress of the car is stimulated. On the other hand, when the brake is pressed—an action—the brakes are activated and the forward motion of the car is retarded. In both cases a system in the car is activated, but one results in acceleration and the other in retardation. The same can be said

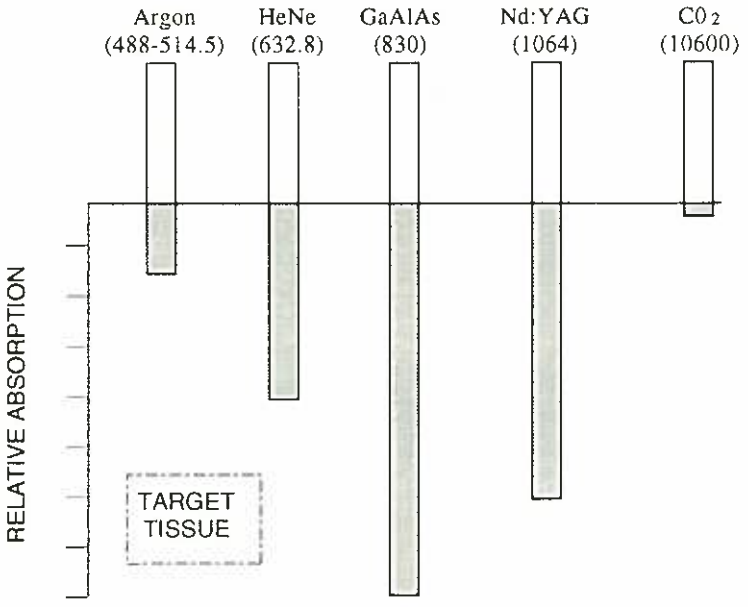


Figure 9. Penetration of different laser wavelengths for *in vivo* tissue from visible/infrared sensitive CCD video intensography data (after Nagasawa[15])

of LLLT, which as will be seen from the following section is used as both an accelerator and brake.[17] Mester's choice of terminology was *biostimulation*, and for what he was mainly using LLLT, namely acceleration of wound healing, stimulation is correctly applied: however LLLT is used to remove excess pigment and restore lack of pigment; to remove hypertrophic scars and to treat depressive scarring; to alleviate pain and to return feeling to numbed areas; and to control both hypertension and hypotension. In all the aforementioned cases, there is both acceleration and retardation, so I feel the term *photobioactivation* most accurately describes these balancing/normalizing functions. The application of LLLT in the accelerator/brake technique is most important to its correct use, and an understanding of the normalizing concept is essential for the laser therapist and LLLT researcher.

Photobioactivation follows as a result of an exogenous photostimulus, and therefore follows the Arndt–Schultz law, which states that weak stimuli will excite biological activity, moderate stimuli favour it, strong stimuli will halt increased activity, and very strong stimuli will retard or completely stop biological activity. Figure 10 shows Ohshiro's modified Arndt–Schultz curve.[18] The sharp rise in activity above normal is the bioactivation zone, and after the D point, the photodestructive zone commences. In order to ensure maximum activation, stimuli must be carefully controlled to keep the reaction on the B–C–D curve.

Practical Applications of LLLT

LLLT is currently applied in many specialties for many functions. It can be used to reduce or remove many types of acute and chronic pain, including such difficult cases as post herpetic neuralgia, frozen shoulder and tennis elbow.[19] LLLT can be used in soft tissue trauma such as sports injuries, to accelerate the resorption of oedema and reduce pain, turning a non-weightbearing injury into a weightbearing one: at the same time LLLT addresses the root cause of the pain, so that it is not just curing the symptoms.[20] Ischaemic grafts and flaps are one of the biggest problems for plastic and reconstructive surgeons. LLLT can increase the volume and flow rate of existing vasculature, and accelerate neovascularization, ensuring adequate blood supplies for grafts and flaps.[21] Bones have been shown to knit faster following LLLT, which brings an increased supply of the necessary mineral salts to the callus with the enhanced blood flow.[22,23] Hyper- and hypometabolic states can be abnormal, resulting in such lesions as naevus spilus and vitiligo. LLLT can be used to control the metabolic rate of the melanocyte, returning it to normal and thereby restoring normal pigment to the affected area:[24] this is an example of the balancing/normalizing effect of LLLT. LLLT can also be used to normalize an abnormal rate of collagen synthesis or lysis, in the treatment of hypertrophic and depressive scarring. LLLT has been shown in a controlled study to normalize blood pressure in both hypertensive and hypotensive patients.[25] In addition to the above examples, LLLT has present and possible applications in dentistry and oral surgery,[26] internal medicine, otorhinolaryngology, ophthalmology, and obstetrics:[27] More specialties will be able to use LLLT as other applications are researched, and a sound scientific body of data is amassed on the mechanisms and pathways.

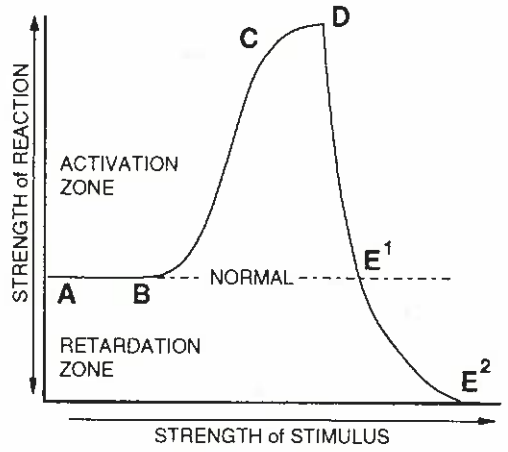


Figure 10. Ohshiro's Arndt–Schultz curve, showing activation by mild stimuli (BC, CD), arrest of activity by stronger stimuli (DE^1) and destruction by very strong stimuli (E^1E^2)

LLLT for Pain Attenuation

Although pain attenuation is one of the main applications for LLLT, it is now certainly not alone. As with many other discoveries, I happened on the use of laser for pain attenuation purely by accident. I was treating a young lady for a haemangioma simplex lesion on her upper sternum. During the pretreatment workup, it was noted that she had suffered very badly from postherpetic neuralgia (PHN) for several months, to the point of interfering severely with her social and work life. I carried out my usual test treatment for the haemangioma, using the argon laser in my zebra method. When she returned for assessment, she happily reported that the severe PHN discomfort had dramatically lessened.[28] At that time, over 14 years ago, other reports were appearing on the applicatiosn of laser in pain therapy, and Mester's continuing series of papers on the use of LLLT to heal non-healing vasculogenic ulcers were attracting international attention. I carried out my own investigations, and found that the 830 nm beam of the GaAlAs laser was particularly effective in many pain types, and since then I have developed and applied that system

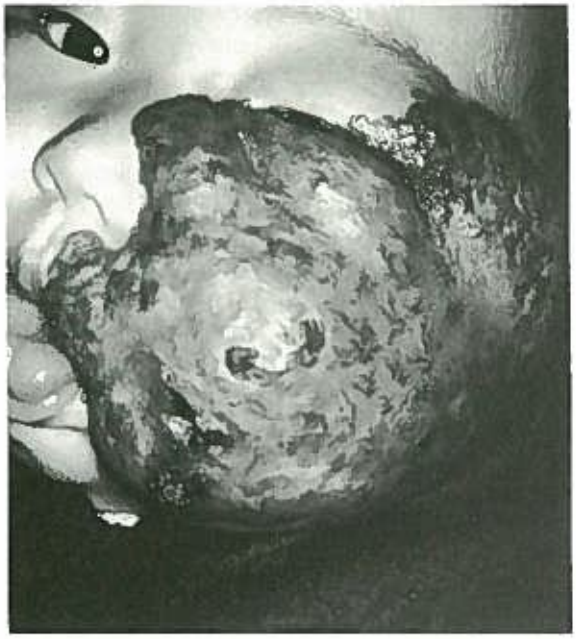


Figure 11. Large lobulated and growing strawberry haemangioma on left face of 5-month-old baby. Left eye is closed, and there is involvement of the left nasal ala. Spontaneous bleeding on lesion surface can be seen

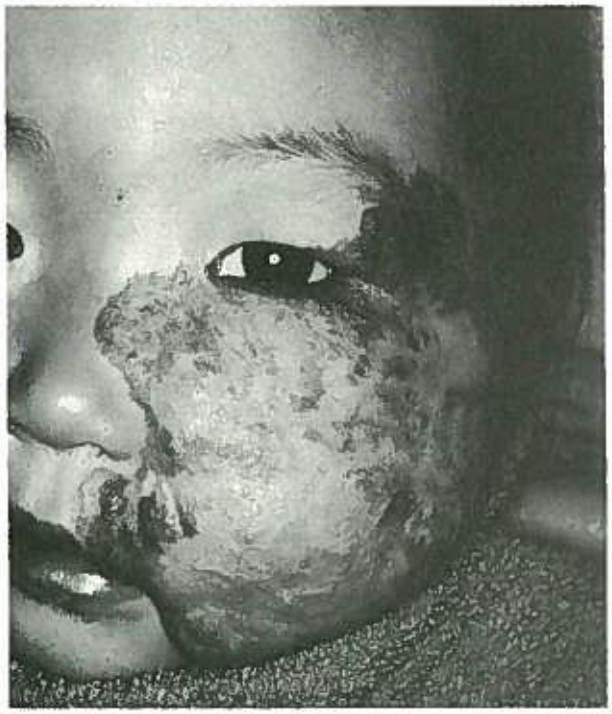


Figure 12. After 6 months' diode laser LLLT (see text for details): Left eye is open, with marked reduction in lesion bulk, and start of return to normal skin elasticity, texture and colour

for a large number of acute and chronic pain entities.

It is extremely difficult to capture successful pain alleviation photographically. Pain attenuation is mostly subjectively assessed by the patient: in the

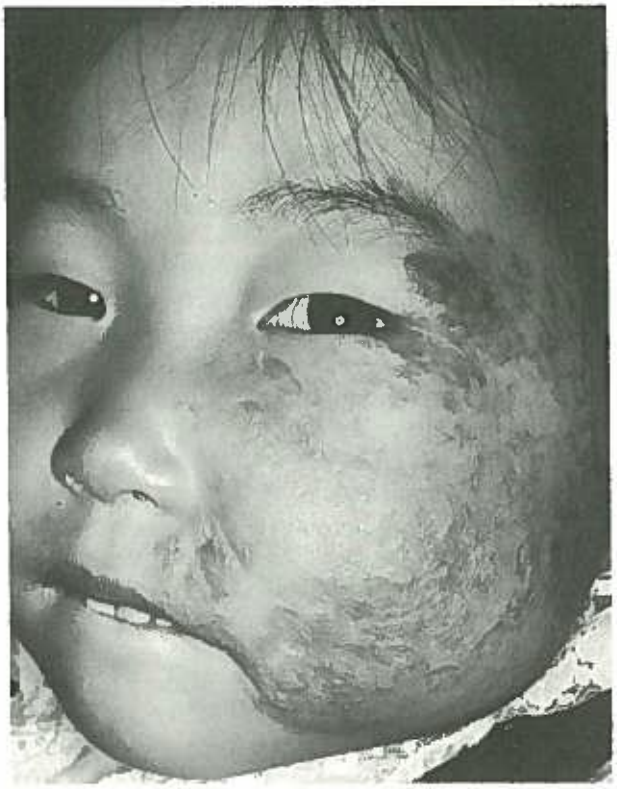


Figure 13. Same patient in Figures 11 and 12, 3 years after initial treatment

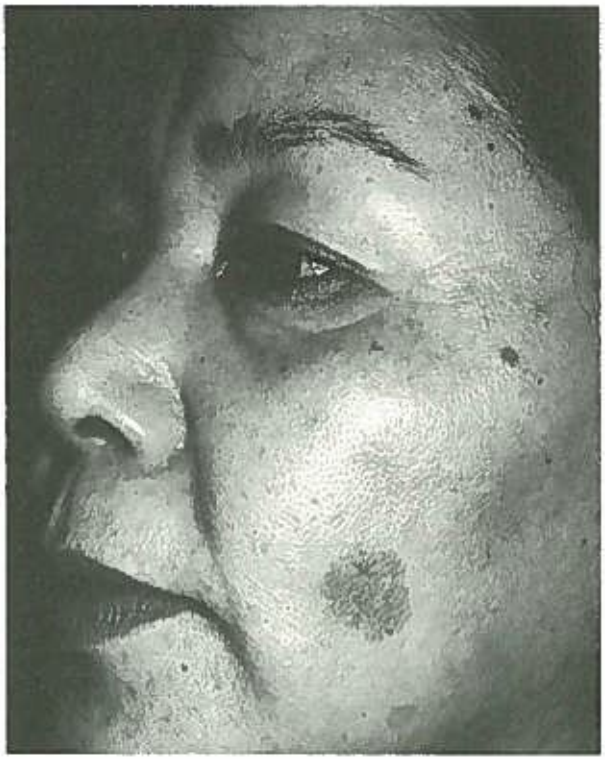


Figure 14. Senile fleck on left cheek of 41-year-old female

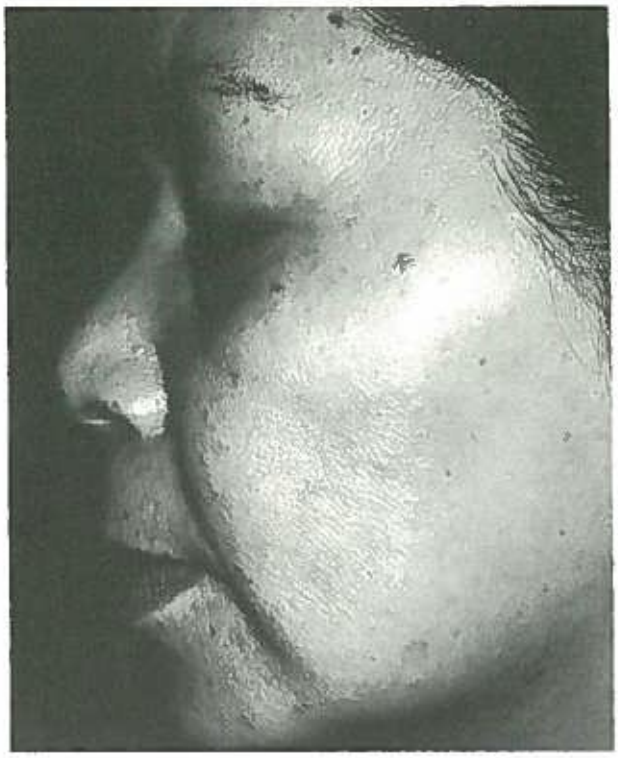


Figure 15. 1 year post-therapy with diode LLLT

case of restricted grip strength and low range of motion (ROM), a more objective record can be kept, both on film or video and in the records. Thermography is another possible assessment method. Thermograms typically show areas of elevated temperature indicative of acute inflammation. Chronic pain conditions are usually shown by areas of lowered temperature, although in some chronic disease entities, such as rheumatoid arthritis, the chronic pain condition is also accompanied by localized foci of acute inflammation: This can be seen very clearly in the thermography.

The following is a selection of some more visible cases where LLLT has proved effective in areas other than for pain attenuation, taken from my own clinic's records. In all of these, which are representative of a large number of similar cases, the balancing or normalizing effect of LLLT can be seen.

LLLT and the Blood Vessel Anomaly Group

Blood flows very close to the surface of the skin, through a vast network of interlinking vessels: It is therefore an excellent target for LLLT. LLLT has been shown successfully to increase blood flow, and therefore in cases of naevi of the blood vessel anomaly group involving sluggish, anoxic flow and pooling, LLLT can speed up the flow and restore oxygenation to the affected tissues, without surgical intervention.

The 3-month-old female infant in Figure 11 had

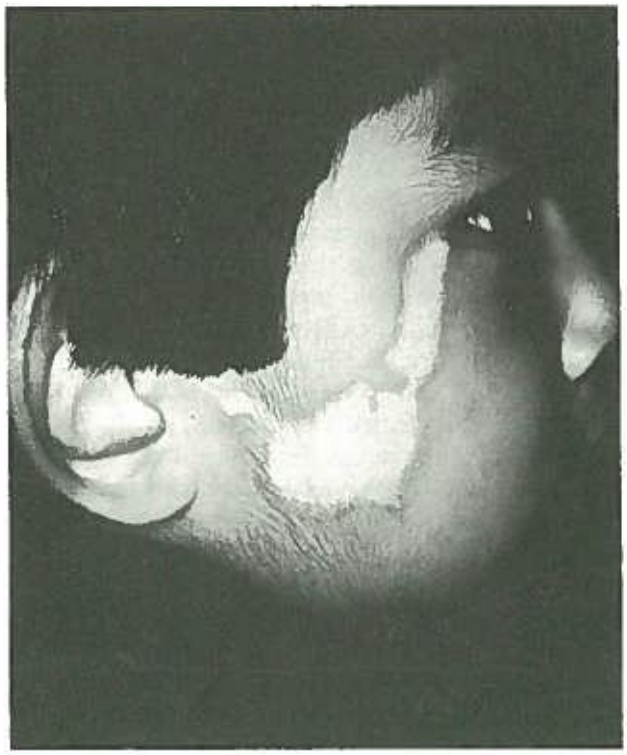


Figure 16. Systemic type of vitiligo on right face of 5-year-old boy

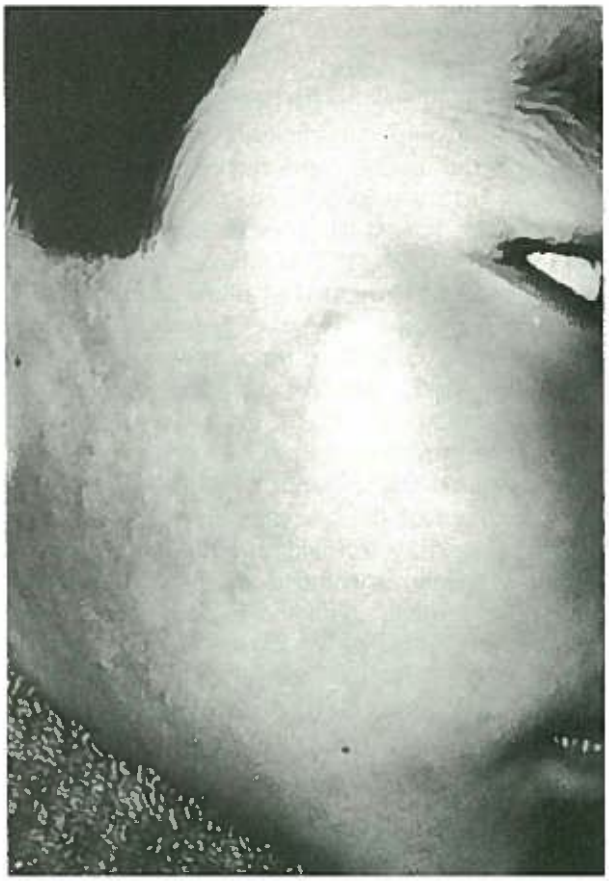


Figure 17. Hypopigmentation at first replaced by hyperpigmentation, following diode LLLT combined with steroid ointment

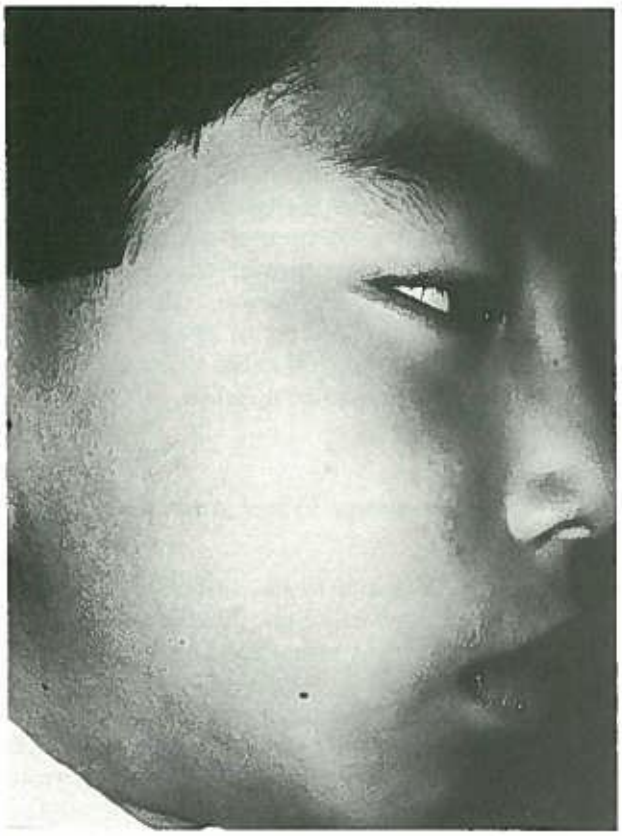


Figure 18. Two years after initial therapy session, normal colour and texture restored. No recurrence to date (2.5-year follow-up)

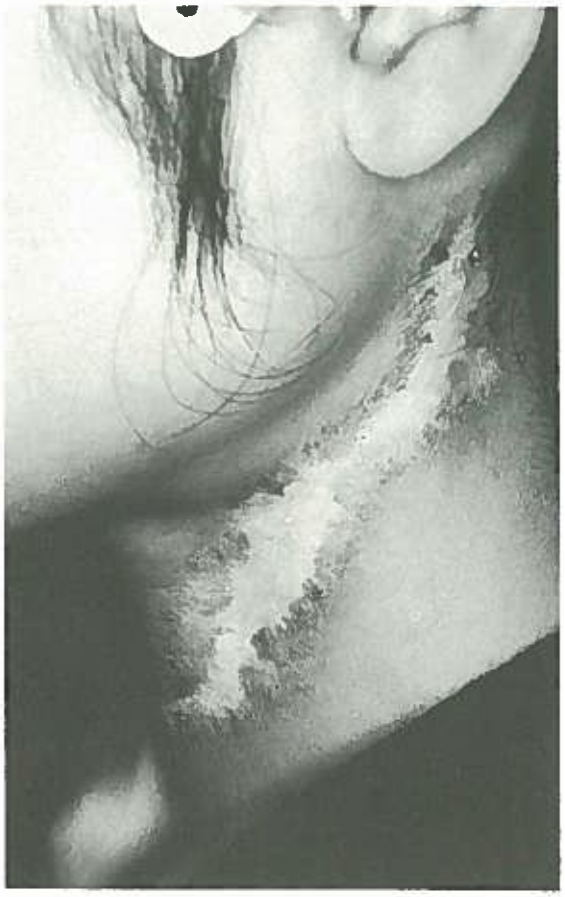


Figure 19. Iatrogenic cicatrical vitiligo on left neck of 28-year-old female, following extended PUVA treatment for systemic vitiligo elsewhere. Atrophy, a hyperpigmented border and thinning of the dermis can be seen

a large lobulated strawberry haemangioma of the left cheek involving the left eye to the extent that it was almost completely closed. Despite the extreme youth of the patient, intervention was deemed necessary in order to preserve the eyesight in the left eye. The haemangioma was increasing in size, and bled very easily. It also affected the interior of the left nostril. The GaAlAs diode laser was used in contact therapy over the lesion and around the periphery, 60 mW continuous wave, spot size 0.2 cm^2 (power density 3 W/cm^2) 1 min per irradiation (180 J/cm^2), 10 irradiated points per session, for two sessions per week for six weeks. The result after the six weeks can be seen in Figure 12. The colour of the haemangioma has lightened, the bleeding points were controlled, and the overall mass of the lesion was much less. The left eye was almost fully open. After a further three years' treatment, (average of twice per week for 4 weeks, once/week × 8 weeks, 2/month × 4 and 1/month × 30, each session 2 min), the lesion has continued its shrinkage and lightening, as can be seen in Figure 13.

LLLT and the Melanin Anomaly Group

The basal layer of the skin contains both normal skin mother cells (keratinocytes) and pigment manufacturing cells (melanocytes). The melanocytes deliver their black melanin granules to the ascending skin cells through a series of tentacle-like dendritic processes. If the melanin granules are for any reason overproduced, or do not fragment as usual, then an area of an abnormal brown to black colour is seen in the overlying skin. If the granules are not completely oxidized in their production process in the melanocyte, then the opposite phenomenon appears: an area partially or completely devoid of pigment. Hyperpigmentation, and hypopigmentation: LLLT can correct them both, restoring balance to the affected melanocytes.

The 41-year-old woman in Figure 14 has a senile fleck (member of the melanin anomaly group) on her left cheek. The GaAlAs diode laser was used on the lesion, at the same power parameters as in the previous case, 15 s per irradiation on four points, once per week for three weeks. Figure 15 shows the results one year post-therapy. The senile macula had resolved, with normal pigmentation and skin condition. There has been no recurrence in over 12 months' follow-up.

The 5-year-old boy in Figure 16 had a clearly circumscribed vitiligo lesion on the right cheek. His

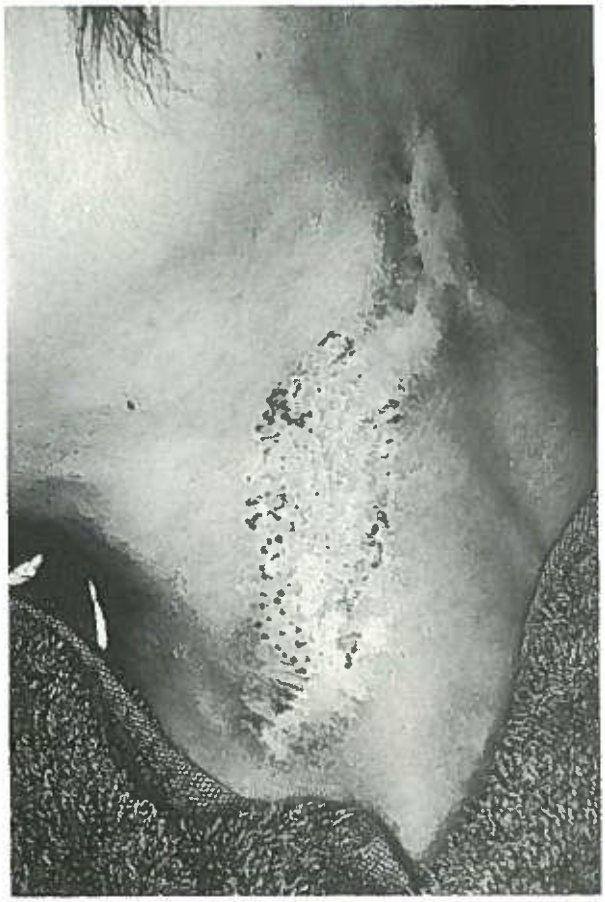


Figure 20. Immediately after contour treatment (HLLT) with argon laser on surrounding area of the lesion

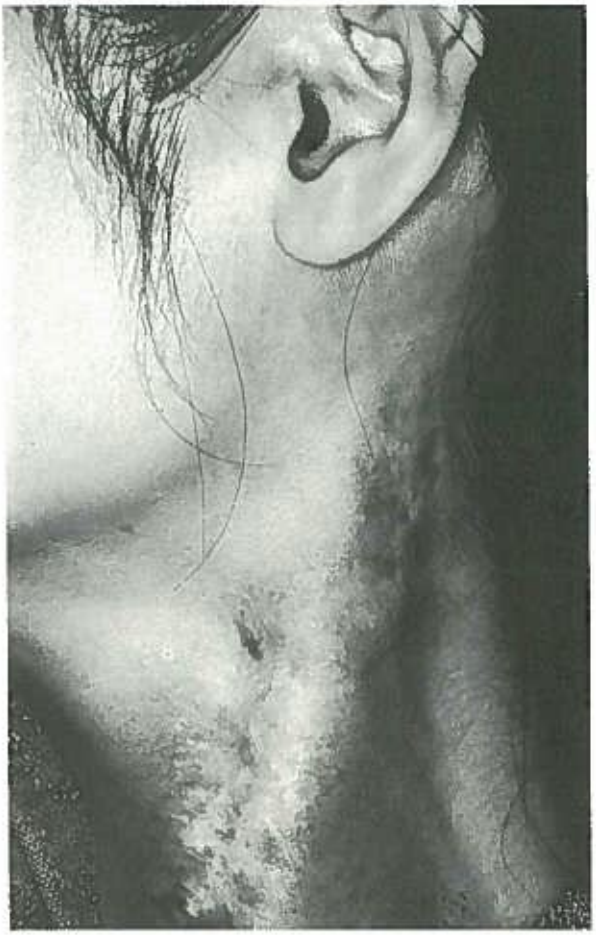


Figure 21. Thirty months after start of diode laser LLLT

school work was suffering, as he was constantly taunted by his schoolmates. The GaAlAs diode laser was used, once per two weeks, with seven exposures of 10 s each per session, and a further two treatments once per month. The LLLT sessions were alternated with steroid ointment treatment during the first part of the therapy. At first, the hypopigmented area was replaced by a *hyperpigmented* one (Figure 17), but this faded after 10 weeks to normal colour, as seen in Figure 18 (2 years after final therapy session). With 2 years' follow-up there has been no recurrence of the vitiligo. He has returned to a normal happy social and scholastic life.

In addition to systemic vitiligo, there is a style of vitiligo caused by scarring, which I refer to as cicatrical vitiligo. In this case, the melanocytes are almost nonexistent in the scar tissue, and have to be persuaded to migrate in from surrounding normal skin. The 28-year-old female in Figure 19 has this type. In fact, it started out as systemic vitiligo, but on presenting at my clinic she had received 25 years of PUVA therapy. This had resulted in a mixture of systemic vitiligo, iatrogenic cicatrical vitiligo, hypertrophic and depressed scarring, and thinned epidermis. LLLT alone cannot help completely remove this lesion, and so LLLT was combined in

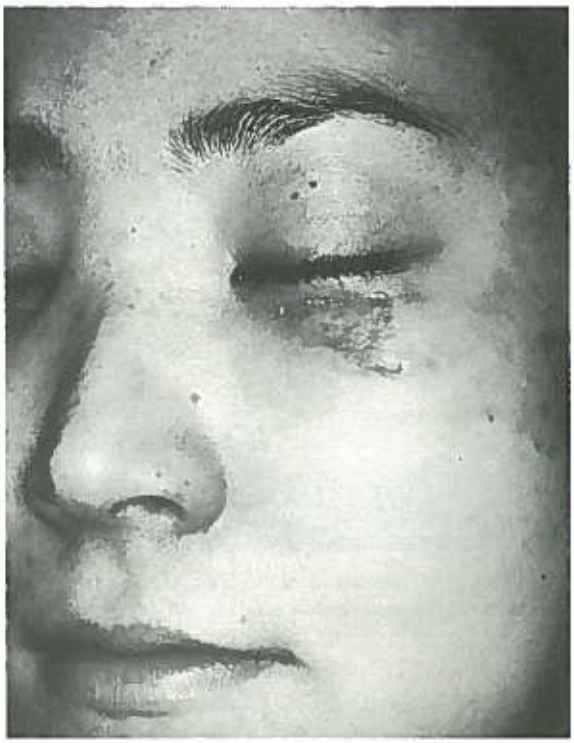


Figure 22. Infected ulceration of wound under left eye of 23-year-old female following dry ice treatment

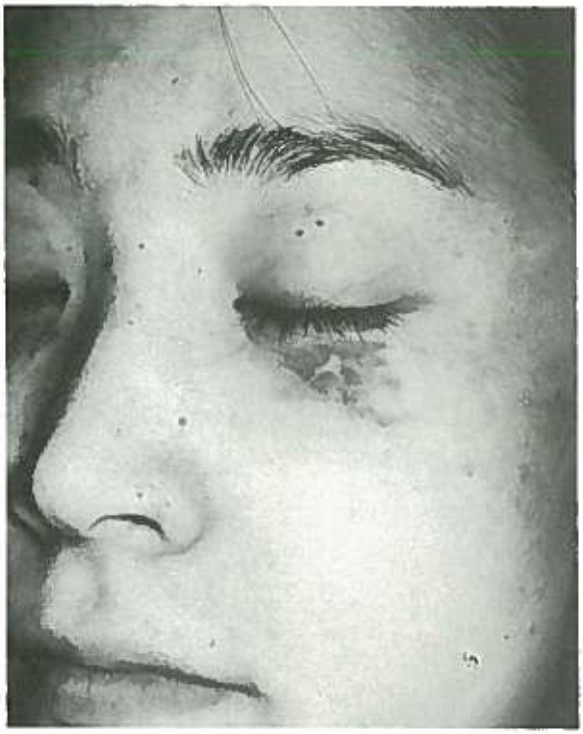


Figure 23. Result after 4 weeks of defocused Nd:YAG LLLT

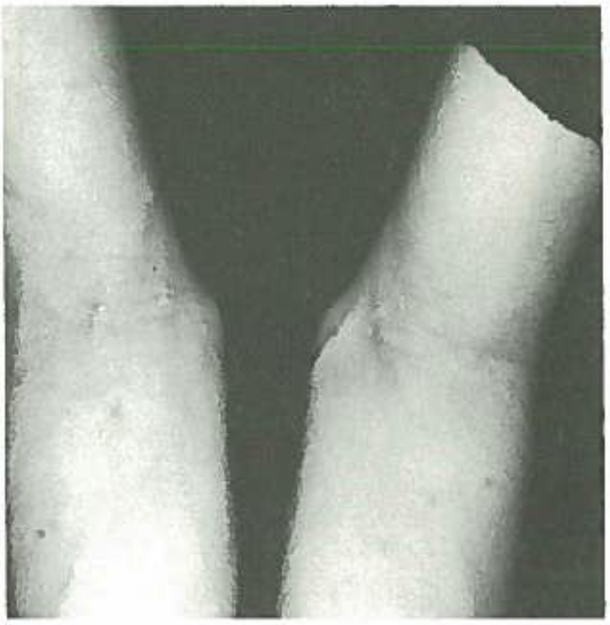


Figure 25. Severe bilateral atopic dermatitis on arms of 9-year-old girl

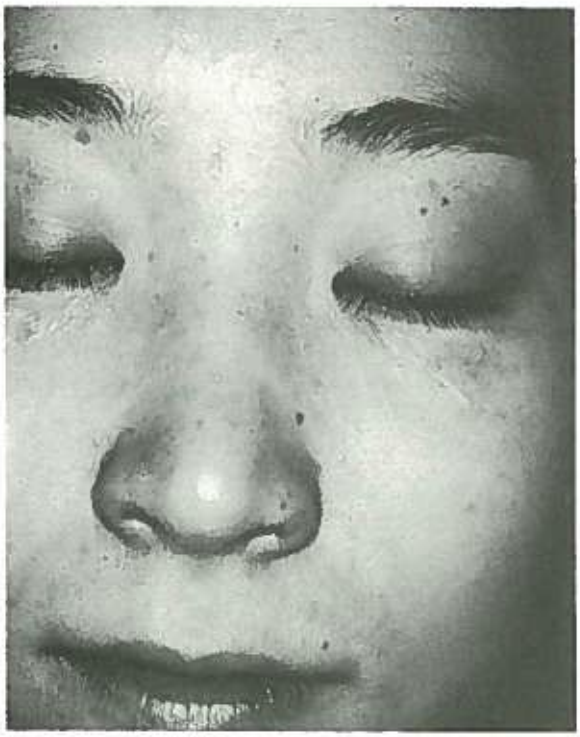


Figure 24. After 2 months of diode laser LLLT, good healing of the ulcer with minimal residual scarring and hyperpigmentation

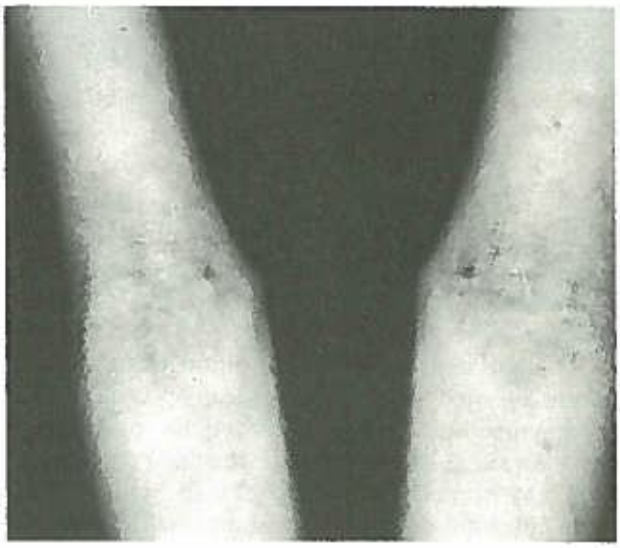


Figure 26. After 3 months' diode laser LLLT, only applied to the right arm, with marked improvement in lesions on both arms and return of normal skin texture

the early stages with HLLT using the argon laser, employing my 'contour technique' round the outer rim of the hypopigmented area.[29] This gave the result as in Figure 20. Thereafter, GaAlAs LLLT was used alone, a total of 32 sessions over a 30-month period, and gave the result as seen in Figure 21. The area is well-repigmented, and the unsightly depressive scarring has filled out with normal epidermis, concomitantly with the thinning of the hypertrophic areas. This is a good example of the important consideration of the need for flexibility in combining different treatment and therapeutic methodologies, and not sticking rigidly to a 'cook-book' approach.

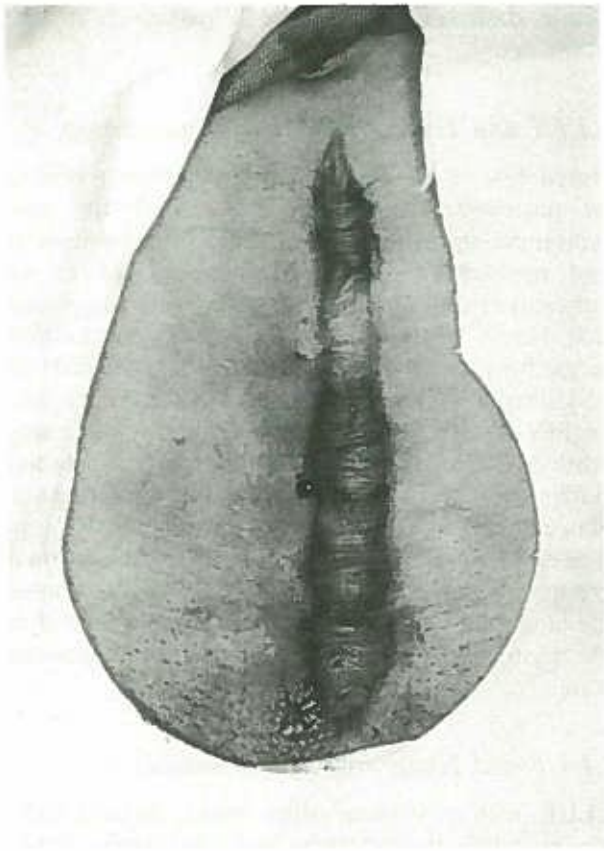


Figure 27. Hypertrophic scar, almost keloid in nature, on abdomen of 40-year-old female following Caesarean section

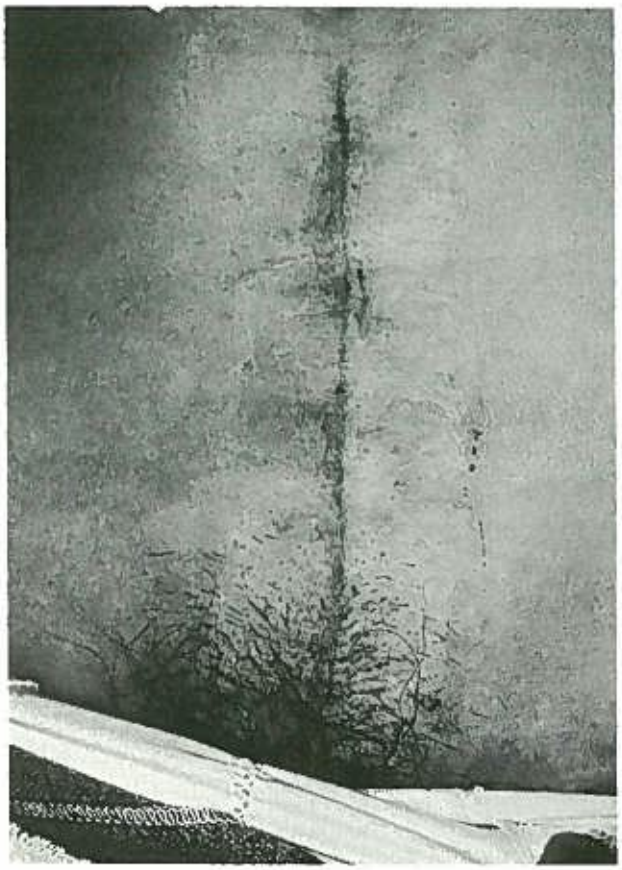


Figure 28. *Scar was excised with CO_2 laser and wound closed*

LLLT and Wound Healing

The aim of any surgeon is to get as perfectly healed a wound as possible after an operation. Very often, however, circumstances interfere in the healing process, and a wound which should heal in a perfectly straightforward manner develops infection, for example, and the potential result is not good.

Figure 22 shows a 23-year-old female who had received dry ice treatment for a lesion under her left eye. She was allergic to antibiotics, and anti-inflammatory drugs, and so did not take them although given them after the procedure. By the time she came for the third treatment session, the infection had developed into ulceration, and showed signs of spreading. At that time (13 years ago) I had not fully developed the GaAlAs laser for clinical applications, and I was using the Nd:YAG laser in LLLT dosage. Figure 23 shows the results after eight sessions with doses of 1 J/cm^2 (2 W c/w, exposure time 2 s, spot size 3.5 cm diameter), twice per week. Some improvement is seen. At that stage, I finally succeeded in developing a clinical version of the GaAlAs diode laser, (30 mW, c/w, 6 s, spot size 2 mm^2, 830 nm) and I used that instead of the YAG system twice per week, 1 min per side per session in contact mode around the periphery of the lesion (dose per session per side of 9 J/cm^2). After 2 months the ulcer had completely healed with good texture and colour (Figure 24).

LLLT and Allergy and the Autoimmune System

Figure 25 shows a 9-year-old girl with severe chronic atopic dermatitis in the inner aspect of both elbows. Her legs were also severely affected. Despite aggressive steroid therapy at another clinic, the lesions persisted, with pronounced thickening of the epidermis. Only the right arm was treated with the GaAlAs diode laser, 15 s per irradiation, on four points around each lesion in contact mode, and 30 s on the lesions in noncontact mode, once per week for two weeks. Figure 26 shows the result three months after the first session. The atopic dermatitis has almost completely resolved on both arms, and the thickened epithelium has returned to normal. The legs also healed well. This case illustrates the systemic whole-body effect, as the laser was only applied to the right arm, yet both arms and legs healed. These data are in accord with other reports in the literature on the whole-body systemic effect of LLLT.

As other examples of the effect of LLLT on the autoimmune system in immunoincompetent animal models, Skolbelkin and Dima have reported on the

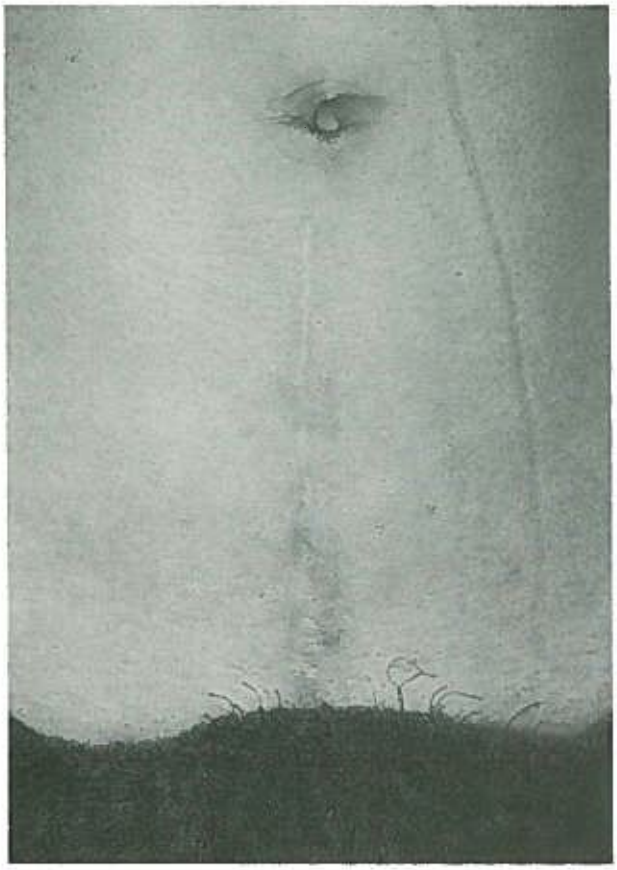


Figure 29. Result after 10 months of diode laser LLLT alternated with steroid injections. No recurrence to date (18 month follow-up)

effects of LLLT on implanted tumours in the mouse, both as controlled studies. Both authors reported extended survival periods in the treated animals, with a marked increase of the immunoglobulins concerned with the natural reaction to cancer virus cells.[30,31] Skobelkin carried on to report on the successful indication of doses LLLT following palliative tumourectomies in man. These findings go a long way to disproving or at least allaying the strong fear that LLLT would have a stimulatory effect on cancer cells as it does on fibroblasts, for example, thereby accelerating the growth of a tumour.

Circulatory Control

LLLT has been shown to boost poor circulation in Raynaud's disease, for example, and to restore failing microcirculation in patients with advanced Buerger's disease.[32] This is in addition to the earlier mentioned reports on the treatment of vascularly-compromised grafts and flaps. LLLT has also successfully accelerated the resorption of large haematoma, directly connected with the LLLT-mediated increase in prostacyclin (PGI_2) synthesis acceleration of the local microcirculature and lymphatic drainage, and quicker breakdown of the fibrin net.[33]

LLLT and Hypotension and Hypertension

Noted first as an unexpected side-effect reported by surprised patients following LLLT for pain symptoms, the use of LLLT to control hypertension and hypotension has now been applied as an indication in its own right.[34] It has been suggested that there is a blood pressure control centre located in the lower part brain stem, which is accessible to LLLT radiation from around the posterior C2 point, angling the laser probe up slightly under the lower border of the base of the skull. In the controlled study quoted, there was a significant difference between the treated hypertensive patients and the treated 'normal' patients. In some of the normal group, who were arguably hypotensive, a raising of the blood pressure was seen. This action is typical of the normalizing function of LLLT in an imbalanced state.

LLLT and Hypertrophy and Keloids

LLLT, with or without other lasers, surgical techniques, adjunctive ointment and conservative pressure therapy, has proved very successful in the revision and removal of hypertrophic scarring and keloids. Figure 27 shows a post-caesarian section large hypertrophic scar, almost keloid in nature, on the abdomen of a 40-year-old female. Following excision with the CO_2 laser (Figure 28), GaAlAs LLLT was applied in conjunction with steroid injections, applied alternately at two-weekly intervals. Figure 29 shows the results after 10 months. There has been no recurrence to date, in an 18-month follow-up. This is, in the author's opinion, one of the indications of the α-effect associated with the CO_2 laser discussed earlier in the article, and is in agreement with the work on large CO_2-excised keloids reported by Bailin and Wheeland,[35] although somewhat contrary to the opinions of Apfelberg. The combination of LLLT with conventional and conservative methodology is an important consideration in assuring consistent results in a wide variety of patients and conditions.

Conclusions

From these representative cases, taken from more than 12 000 over the past 13 years, it can be seen that the diode laser in pure LLLT works in both an accelerative and modulative way, thus making the term Low reactive-Level Laser Therapy the most appropriate one to describe this duality of action. It is also evident from clinical experimental studies that LLLT enhances weak or failing circu-

lation, and therefore is appearing as an ideal tool for the plastic and reconstructive surgeon, in addition to its more common role in pain attenuation. The application of LLLT in the successful resolution of atopic dermatitis also points to its possible applications in photoimmunological and photoallergic therapy. LLLT can consist of pure LLLT or simultaneous LLLT (secondary to a laser surgical procedure). Pure LLLT can be applied alone, in combination with HLLT (combined laser treatment), in combination with another LLLT system (combined laser therapy), or a combination of all of the above, plus conventional conservative therapy (total treatment concept).

Despite the fact that the actual mechanisms of LLLT are not entirely clear, enough work is appearing to substantiate the earlier anecdotal reports with scientific work. However, reporting of experimental and clinical procedures is all-too-often incomplete, so that any other researcher cannot repeat the experiments exactly. This may account for the apparent differences in conflicting results which have appeared in the literature.[36] One thing is very clear, however, LLLT is here, and here to stay.

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