This issue features Photobiomodulation (PBM)

- Dr. Gerald Ross and Ms. Alana Ross explain how PBM is utilized in many dental procedures
- Dr. Lawrence Kotlow demonstrates how PBM is used in his pediatric dental practice
- Dr. Steven Parker demonstrates the use of a PBM laser for photodynamic antimicrobial chemotherapy
- Dr. Nelson Marquina and Dr. Fred Stalley provide a clinical study about the effects of PBM in orthodontic treatment

- A Tribute to Professor Endre Mester, the Father of Photobiomodulation
- Research Abstracts: The Effect of Low-Level Laser Therapy on Growth Factors Involved in Wound Healing
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**TABLE OF CONTENTS**

**EDITOR’S VIEW**  
More Adventures with Lasers in Dentistry ................................................. 115  
Donald J. Coluzzi, DDS

**COVER FEATURE**  
**CLINICAL REVIEW AND CASE REPORTS**  
Photobiomodulation: An Invaluable Tool for All Dental Specialties .................. 117  
Gerald Ross, DDS and Alana Ross, BScH, Tottenham, Ontario, Canada

**COVER FEATURE**  
**CLINICAL REVIEW AND CASE REPORTS**  
Photobiomodulating Lasers and Children’s Dental Care ................................. 125  
Lawrence Kotlow, DDS, Albany, New York

**COVER FEATURE**  
**CLINICAL REVIEW AND CASE REPORTS**  
Photodynamic Antimicrobial Chemotherapy in the General Dental Practice ........ 131  
Steven Parker, BDS, LDS RCS, MFGDP, MALD, Harrogate, United Kingdom

**COVER FEATURE**  
**CLINICAL RESEARCH**  
Biostimulation Effects of Superpulsed, High-Intensity, Low-Average Power Laser Application on the Timing of Orthodontic Aligner Sequencing of the Invisalign® System ..................................................... 139  
Nelson Marquina, MSc, PhD, DC, Richmond, Virginia; Fred Stalley, DDS, Redondo Beach, California

**TRIBUTE**  
Professor Endre Mester, the Father of Photobiomodulation ............................ 146  
Professor Lajos Gdspar, DDS, PhD, Budapest, Hungary

**RESEARCH ABSTRACTS**  
The Effect of Low-Level Laser Therapy on Growth Factors Involved in Wound Healing .................................................. 149
The *Journal of Laser Dentistry* publishes articles pertaining to the art, science, and practice of laser dentistry. Articles may be scientific and clinical in nature discussing new techniques, research, and programs, or may be applications-oriented describing specific problems and solutions. While lasers are our preferred orientation, other high-technology articles, as well as insights into marketing, practice management, regulation, and other aspects of dentistry may be of interest to the dental profession, may be appropriate. All articles are peer-reviewed prior to acceptance, modification, or rejection.

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<th>Preferred Format</th>
<th>Required Resolution</th>
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<tbody>
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More Adventures with Lasers in Dentistry

Donald J. Coluzzi, DDS, Portola Valley, California

J Laser Dent 2009;17(3):115-116

This issue of the Journal will continue to present articles from some of the presenters at the Academy's April 2009 16th Annual Conference in Las Vegas. As mentioned previously, their manuscripts give those of us who were in attendance a chance to remember their discussions, and enable all of our members to read their topics. These articles offer us extensive details about using low-level lasers. To be clear, the term ‘low-level laser’ refers to a device whose emission power is substantially below ‘surgical’ lasers – in other words, a low-level laser cannot produce coagulation, protein denaturation, vaporization, and/or ablation of dental tissue. Low-level lasers have been used in some branches of medical and veterinary offices for some time; in addition, some dental practitioners have employed a laser-based carious lesion detector, or a laser to cure composite resin. The term ‘photobiomodulation’ (PBM) is generally substituted for low-level laser therapy. It more accurately describes the reported biologic effects of the coherent energy that is absorbed by cellular elements, resulting in stimulation of tissue-healing mechanisms. Another application of the use of low-level laser output is called ‘photodynamic therapy’ (PDT), where a photosensitizing chemical is applied to tissue and is activated by laser energy, producing a singlet oxygen radical which can destroy adjacent cells. Certain tumors can be treated with this method. A dental development of this technique, termed ‘photo-activated disinfection’ (PAD) or ‘photodynamic antimicrobial chemotherapy’ (PACT), can be used to treat infections. Curiously, and perhaps expect-edly, the availability of these devices varies according to geographic region. The U.S. Food and Drug Administration (FDA) has granted marketing clearances to a number of devices, although none of those clearances are specifically for dentistry, which should be considered off-label uses. The manufacturers and distributors generally sell to licensed practitioners of all the health sciences. A typical clearance might read: “The device is used when heat is indicated for temporary increase in local blood circulation, temporary relief of minor muscle and joint aches, pains and stiffness and relaxation of muscles; for muscle spasms, minor pain and stiffness associated with arthritis” (FDA 510(k) clearance K082727, October 1, 2008, MedX LPT 200 and MedX LPS 200 (OraLase) portable laser, MedX Health Corp., Mississauga, Ontario, Canada). There are seven authors in this section:

- Dr. Gerald Ross offers an overview of PBM for dental applications. Dr. Ross and his co-author, Alana Ross, have extensive experience providing education about this technology.
- Dr. Lawrence Kotlow writes about how PBM lasers are used in his pediatric dental practice, from the reduction of pain to the elimination of the gag reflex.
- Dr. Steven Parker’s manuscript describes the use of PACT in his general dental practice to reduce bacteria with clinical case examples showing treatment of periodontal and peri-implant inflammation.
- Dr. Nelson Marquina and Dr. Fred Stailey illustrate the use of PBM in a study of patients undergoing a specific orthodontic treatment plan. These two authors are colleagues of Dr. Robert Gougaloff, one of the speakers in the PBM section of ALD’s 2009 Las Vegas conference.
- As an added highlight, Professor Lajos Gáspár, an Academy member in Hungary, offers a short biographical sketch of Endre Mester, MD, DSc, who is internationally recognized as the father of PBM. Despite the possible confusion with the ‘alphabet soup’ of the above acronyms, I hope that you, the reader, will have a good understanding of this use of laser energy.

In addition, the Research Abstracts section offers several current summaries using PBM for wound healing and tissue repair. You will note the titles use various phrases, like low-level, low-power, and low-intensity to describe laser irradiation parameters.

As usual, I hope you enjoy this issue. Please don’t hesitate to contact me with your comments, or, better yet, your articles.

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Disclosure: Dr. Coluzzi is a past and present presenter at various local, state, and national dental meetings. He has no financial interest in any company.
Photobiomodulation: An Invaluable Tool for All Dental Specialties

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*J Laser Dent* 2009;17(3):117-124

**INTRODUCTION**

Although low-level lasers are being used successfully in many dental clinics, the wide range of applications is still largely unknown to many practitioners, especially dental specialists. In these fields, there is the potential to see the most definitive results of what laser therapy can do to improve clinical outcomes and patient satisfaction.

Photobiomodulation (PBM), also commonly referred to as low-level laser therapy (LLLT) or cold laser therapy, uses light energy to elicit biological responses from the cell and normalize cell function. Numerous studies have shown that PBM affects the mitochondria of the cell, primarily cytochrome-c oxidase in the electron transfer chain and porphyrins on the cell membrane. It has been proposed that when light photons are absorbed by these receptors, three events occur: stimulation of adenosine triphosphate (ATP) synthesis by activation of the electron transport chain; transient stimulation of reactive oxygen species, which increases the conversion of adenosine diphosphate (ADP) to ATP; and a temporary release of nitric oxide from its binding site on cytochrome-c oxidase. These factors contribute to the clinical effects seen with PBM, including tissue repair, relief of inflammation and pain, and repair of nerve damage.

Figure 1 depicts a flowchart showing these interactions. Studies have documented beneficial effects of PBM, such as stimulation of fibroblasts and osteoblasts, as well as a reduction of the depolarization of nerve fibers.

From a clinical perspective, PBM offers dental practitioners a noninvasive and nonthermal treatment modality that can be used as an adjunct to traditional therapies or as a therapeutic tool on its own.

Examples of these clinical applications, which will be discussed below, include dental analgesia, treatment of dentin hypersensitivity, healing of soft tissue lesions, reduction of pain and swelling after surgical procedures, better integration of implants into bone, and faster movement of teeth during orthodontic procedures.

**Determining the Appropriate Dose**

Treatment dose is probably the most important variable in laser treatment. Dose is measured in joules per square centimeter (J/cm²) and is a measure of the amount of energy that is conducted into the tissue. Clinical effects of the laser, such as wound healing, pain relief, or muscle relaxation, are all sensitive to different irradiances or doses. An example of this is the stimulation of fibroblasts; a dose of 5 J/cm² will stimulate the cellular activity of fibroblasts, whereas higher doses inhibit cell viability and proliferation. Thus, for wound healing, the clinician should ideally use a dose lower than 5 J/cm².

The biostimulatory and inhibitory effects of lasers are governed by the Arndt-Schultz Law, which indicates that weak stimuli will increase physiological processes and strong stimuli will inhibit physiological activity. A therapeutic window, which includes both biostimulatory and bioinhibitory effects, is evident and is the intended target for PBM treatments. A depiction of the law, based on Baxter, is shown in Figure 2.
The importance of dose should always be kept in mind when using PBM; if the clinician is not achieving the anticipated response to laser treatment, the dose should be re-evaluated to ensure it is within the optimal range. Additionally, treatments may need to be modified over time to ensure the practitioner is achieving the ideal effect from the laser dose (pain relief vs. wound healing).

**Acute vs. Chronic Pain**

Treatment dose and duration will largely be governed by the status of the injury. PBM can effectively speed the resolution of acute inflammation and pain, conditions that should be treated frequently (daily). The reverse applies to chronic pain; treatments should be done using lower doses over a longer period of time (e.g., treat 2 to 3 times per week for 3 to 4 weeks).

**Clinical Applications of Photobiomodulation in Dental Specialties**

**Oral Surgery**

Dental surgeons can utilize PBM in almost every facet of their practice. Many procedures a dental surgeon performs, especially extraction of molars, create an acute inflammatory response that can result in edema, bruising, and pain. Currently, the primary method of dealing with the pain and discomfort of the surgical procedures is prescription of pain analgesics, many of which carry side effects or decreased mental alertness. Studies have demonstrated that PBM in acute pain reduction compares well to standard nonsteroidal anti-inflammatory drug (NSAID) treatment, with a better risk-benefit profile. Healing is also accelerated by stimulation of fibroblasts and osteoblasts, which produce soft tissue and bone, respectively, as noted in an animal study conducted by Gerbi et al.

**Dry Socket**

Tunér and Hode describe the benefits of PBM in helping to prevent alveolitis after a tooth extraction. The following case study illustrates PBM treatment for a painful ‘dry socket.’

**Oral Mucositis**

Oral mucositis, presenting as an open sore over the oral soft tissue, is a life-altering condition that is a side effect of chemotherapy and radiation therapy. Laser therapy has been investigated as a preventative application to mucositis and as a treatment modality for healing erupted sores, with positive results. A 2006 study by Corti et al., using a light-emitting diode device with an emission of 645 ± 15 nm, demonstrated that PBM accelerated the healing rate of oral mucositis by 117% to 164%. Often, oral mucositis can be so debilitating for patients that they cannot continue their cancer treatments, so a tool that can treat or
prevent the sores will have considerable clinical importance. Consultation with the oncologist should always be done prior to commencing laser treatments.

Fractures and Orthognathic Surgery
PBM accelerates healing of bone after fractures or orthognathic surgery through the stimulation of osteoblasts. A 2005 study in rats demonstrated that laser irradiation resulted in an increase in bone neoformation, with better quality bone on the irradiated groups when compared to the control group, who received no radiation. 11

Soft Tissue Lesions
Soft tissue lesions, such as herpes simplex, denture sores, and angular cheilitis respond positively to low-level laser irradiation. Schindl and Neumann investigated the effect of LLLT on recurrent herpes simplex and demonstrated that 10 daily irradiations significantly lowered the incidence of local recurrence and is a beneficial treatment alternative to commonly used drugs such as acyclovir and famciclovir. 17 Further, the author has clinically observed that laser irradiation of herpes simplex decreases the incidence of lesion recurrence. Marei et al. examined the effect of laser irradiation on denture sores and noted that LLLT eased the pain caused by denture lesions, while at 4 weeks post-treatment the laser-irradiated areas showed clinically superior healing, and histological epithelialization and vascularization of the lesion. 18 Tunér and Hode report successful treatment of angular cheilitis with PBM, but warn of its recurrence if the fundamental cause is not dealt with. 19 It is advantageous to treat any soft tissue lesion in its most acute stage. For example, herpetic lesions are most susceptible to LLLT during their prodromal stage. Figure 4 demonstrates the treatment of a lesion on the lip using an 830-nm PBM device.

Dental Infections
For infections and edema, PBM has been reported to dilate lymphatic vessels and reduce the permeability of blood vessels. 20 Figure 5 demonstrates the application to the lymph nodes using a PBM device.

Primary Tooth Restorations
A variety of factors contribute to the analgesic effect produced by PBM which allows dental practitioners to perform many primary tooth restorations without anesthesia. Small animal studies show that laser irradiation promotes a release of endorphins and serotonin; inhibits the conduction of C fibers, the fibers that carry pulpal pain; and increases oxygenation and lymphatic drainage, which are responsible for pain relief after the first minutes of tissue irradiation. 6, 21-22

CASE STUDY: DRY SOCKET
Treating Dentist: Dr. Gerald Ross
A 45-year-old male patient had a lower first molar extracted. During the postoperative instructions, the patient (a smoker) was advised to avoid smoking cigarettes for a minimum of 2 days. The patient presented the following day with dry socket and admitted to smoking the previous evening.

An 830-nm PBM device was used. The intraoral light guide was placed in the socket and the socket was irradiated until pain relief was felt by patient (in this case 48 J/cm² of energy was applied before the patient started to experience a reduction in discomfort). A dressing was placed into the socket and the patient was sent home without any pain medications. The patient returned the next day for a dressing change and the laser was applied into the socket using 4 J/cm² before application of the new dressing for stimulation of the epithelium in the socket. The patient did not require any additional treatments and the area healed in 7 days.

CASE STUDY: ORAL MUCOSITIS
Treating Dentist: Dr. Gerald Ross
A 61-year-old female patient undergoing chemotherapy for terminal cancer presented with numerous sores over the inside of her mouth. The patient could not eat, drink, or swallow without extreme pain. Treatments (mouth rinses) assigned by the oncologist had no effect on healing of the sores. A visible red laser (660 nm) was applied intraorally overlapping throughout the mouth for 2 days in a row. When the patient came in on the second day, the pain was markedly decreased and she was able to eat soup. By the fourth day, she was able to eat normally. The patient passed away in the following month but no sores returned during that time.

NOTE: Prior to laser treatment, the dentist contacted the oncologist who was willing to try any treatment that could work on the mucositis.
Laser irradiation is applied to the apex of each root for analgesia and again after the tooth has been prepared for reduction of pain and inflammation, as shown in Figure 6. Distraction techniques are recommended to help the patient deal with the mental fears or anxiety surrounding the dental appointment. Dental analgesia does not seem to be as effective in permanent teeth because of the increased size and sensitivity of the dental pulp; however, it has been shown clinically to be effective for pain relief during crown cementations and decreased sensitivity during scaling appointments.

**Nausea and Gagging**

Application of the laser to the P6 (Pericard 6) acupuncture point on the wrist can decrease or eliminate the nausea and gagging some patients feel during impression-taking or X-ray procedures. As shown in Figure 7, the P6 is located on the underside of the wrist, approximately 1 inch from the distal palmar crease (approximately the width of the distal thumb phalanx). For patients who are extremely nauseous or anxious, application to three acupuncture points in the wrist can be effective; H7, LU9, and P6 are the parasympathetic calming points and stimulation of these points can be very effective in reducing anxiety.

A 1998 report in the *British Journal of Anaesthesia* investigated the effectiveness of laser irradiation to the P6 acupuncture point on postoperative vomiting. In the laser stimulation group, the incidence of vomiting was significantly lower (25%) than in the placebo group (85%), and the patients were quite receptive to the painless procedure.

**Uptake and Elimination of Anesthesia**

Based on the mechanisms of PBM therapy’s ability to increase blood circulation, the author has found that there is an increase in uptake and elimination of anesthesia. PBM is applied to the submandibular lymph nodes and the site of injection after the injection and upon completion of the dental appointment, for uptake and elimination, respectively.

**Implant Placement**

Three papers indicate that PBM can reduce inflammation following implant placement, help speed the integration of the implant into the bone, and improve the quality of the bone around the implant. A study using rabbits utilized Raman spectroscopy and electronic microscopy to investigate the effect of infrared light on the loading time of dental implants, and found a significantly greater amount of mature bone, a better distribution of bone, and more organization of bone after laser irradiation, when compared to the control group that received no laser irradiation.

Another study used rats to examine the effect of laser therapy on bone and demonstrated that the laser group had an abbreviated initial inflammatory response and a rapid stimulation of bone matrix formation at 15 and 45 days. An earlier rabbit study showed that bone healing is improved and those authors concluded that it is possible to reduce the loading time of implants in the mandible of humans from 4 months to approximately 2 months and 24 days, and in the maxilla, from 6 months to 4 months and 6 days.

**Orthodontics**

Orthodontic treatments are lengthy and often painful for many patients. As mentioned previously, Gerbi et al. have shown that PBM irradiation on bone increases osteoblastic proliferation, collagen deposition.
and bone neoformation when compared to non-irradiated bone.\textsuperscript{11}

A 2008 study investigating the effect of laser therapy on orthodontic movement showed that the velocity of canine movement was significantly higher in the laser-irradiated teeth compared to teeth that received no irradiation. In addition, the pain intensity was also at a lower level in the lased group throughout the entire retraction period.\textsuperscript{28} Histological observations made during another study on rabbits showed that both osteoblasts and osteoclasts remained more active on the lased side which could account for the accelerated movement.\textsuperscript{29} Finally, Turnhani \emph{et al.} showed that a single application of LLLT reduced the pain at 6 and 30 hours after banding treatment.\textsuperscript{30}

**Periodontics**

The use of PBM as a treatment modality in periodontics is effective, either as a treatment method on its own or as an adjunct to the increasingly popular surgical lasers. A recent study investigated the gingival inflammatory response and dental plaque reduction following scaling and root planing combined with PBM in 60 patients. The authors found a significant decrease in the clinical indices (plaque, gingival, and sulcular bleeding), which they thought could be beneficial in the treatment of chronic advanced periodontitis.\textsuperscript{31}

**Periodontal Surgery**

Healing after periodontal surgery is often a lengthy and painful process. PBM has been shown to stimulate fibroblasts for faster regeneration of soft tissue, while providing analgesia and a modulation of the inflammatory chemicals that cause pain and discomfort. A 2006 study showed a statistically significant decrease in pocket depth at 21 and 28 days post-surgery. Moreover, the laser-treated wounds presented with factors suggestive of better healing, including color, contour, and mucosa healing when compared with non-laser treated area, which served as a control.\textsuperscript{32} To further exemplify these positive responses, a study by Ozcelik \emph{et al.} demonstrated that LLLT enhanced epithelialization and improved wound healing after gingivectomy and gingivoplasty operations.\textsuperscript{33} Figure 8 shows an 830-nm PBM device being used to irradiate a closed incision.

**Endodontics**

PBM is effective for reducing pain and inflammation after endodontic treatments, for dentin hypersensitivity, and as a diagnostic tool for pulp hyperemia.\textsuperscript{34}

**Figure 8:** LLLT irradiation after flap surgery

**Laser Therapy as a Diagnostic Tool**

Occasionally, a patient will present to a dental practitioner with excessive tooth pain, the source of which cannot be accurately identified. Traditional diagnostic methods such as thermal or electrical stimuli often do not show any indication of the problem, making the diagnosis and treatment stressful for both the patient and the doctor. As stated previously, PBM irradiation increases circulation, thus a patient with a hyperemic pulp will feel a sharp pain when the laser is applied to a tooth.\textsuperscript{35} Figure 9 shows a diagnostic outline that could be used in endodontics.

**Dentin Hypersensitivity**

A study by Marsilio \emph{et al.} demonstrated that LLLT treatment of dentin hypersensitivity in two different groups of patients was effective for 86\% to 88\% of all the participants.\textsuperscript{36} Another study compared LLLT to topical fluoride varnish application for treatment of dentinal hypersensitivity and found that 86\% of the laser irradiation group achieved absence of pain compared to 27\% of the fluoride group.\textsuperscript{37}

**Figure 9:** Flowchart for endodontic diagnosis

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\textsuperscript{11} A 2008 study investigating the effect of laser therapy on orthodontic movement showed that the velocity of canine movement was significantly higher in the laser-irradiated teeth compared to teeth that received no irradiation. In addition, the pain intensity was also at a lower level in the lased group throughout the entire retraction period.\textsuperscript{28} Histological observations made during another study on rabbits showed that both osteoblasts and osteoclasts remained more active on the lased side which could account for the accelerated movement.\textsuperscript{29} Finally, Turnhani \emph{et al.} showed that a single application of LLLT reduced the pain at 6 and 30 hours after banding treatment.\textsuperscript{30}

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**Figure 9:** Flowchart for endodontic diagnosis
TMJ and Facial Pain
When treating temporomandibular joint (TMJ) or facial pain, PBM is a useful tool to add to the therapeutic arsenal. From simple acute cases like facial pain after long appointments to chronic TMJ cases, laser therapy will help reduce pain and inflammation, and significantly resolve muscle trismus. In a systematic review of postoperative pain relief in patients after undergoing third molar extraction, a PBM irradiation was shown to be beneficial in reducing acute inflammatory pain. In a clinical study of 74 patients complaining of TMJ pain, 64% were pain-free or had improvement in comfort after 12 PBM sessions over a six-week period. Pinheiro and colleagues analyzed the effect of PBM on maxillofacial disorders by irradiating 141 female and 24 male patients twice a week for 6 weeks. At the end of the treatment 72% of patients were asymptomatic and 15% had improved considerably.

Neuropathic Pain
Neuropathic facial pain is a debilitating condition for a patient that results in their living with excruciating pain or with a continuous dose of prescription analgesics. As stated above in the study by Bjordal et al., PBM permits many patients to live a life free from discomfort or with less pain.

CONCLUSION
Although PBM has been available to health care professionals since the 1960s, low-level laser therapy did not really begin to gain popularity until the 1980s when controlled and randomized studies began to be published.

In 2007, Karu reported that the effects of PBM are dependent on the initial redox status of a cell. If a cell is damaged, or in a reduced redox state, the cellular response to PBM will be stronger. Conversely, a cell which is at an optimal redox potential will have a weak or absent cellular response to PBM. Thus, cells that are damaged will respond to PBM better than cells that are healthy and functioning normally.

However, there are precautions all laser users should take and areas to avoid treating when using PBM. Specifically, those include avoiding exposure to the thyroid gland, to pregnant women, and to radiation therapy patients. Also important to note is that the laser will be ineffective if the patient has had a steroid injection in the last six months. All laser users should consult their laser manufacturer for any questions regarding contraindications and appropriate treatment doses, as well as for instructions about safety eyewear for everyone within the nominal hazard zone of the beam.

Photobiomodulation is an evolving technology. With every passing day, more is being discovered about the mechanisms of laser therapy, doses, treatment locations, and diseases in which a laser will have an effect. At our hands is a tool that can reduce pain, stimulate wound healing, and modulate the inflammatory response.

Photobiomodulation can be used effectively in dental specialties to better manage treatments that are often deemed painful by patients, without prescribing pharmaceuticals that often have a number of side effects. All healthcare professionals, including dentists and dental specialists, should further investigate photobiomodulation to enhance their clinical treatments and outcomes.

CASE STUDY: TMJ PAIN
Treating Dentist: Dr. Gerald Ross
A 55-year-old patient presented with pain in the left temporomandibular joint and a limited ability to open the mouth. The computed tomography (CT) tomogram (R = right, SMV = submental vertex, L = left) showed degenerative joint disease (osteoarthritis) of the left TMJ with no disc present.

Six applications of the laser were performed over a three-week period, with treatment applications to the joint, joint capsule, and the lateral pterygoid muscle. This treatment resulted in the patient being pain-free for the last two years and with the ability to open the mouth wider.
CASE STUDY: NEUROPATHIC PAIN

Treating Dentist: Dr. Gerald Ross

A 61-year-old male patient presented with pain and felt it was coming from the lower left molar. The tooth was extracted and the socket healed uneventfully but the pain got worse. At that point, there were no other problems with teeth in that quadrant, however the pain was worsening and the patient was taking Tylenol® No. 3 (30 mg) approximately 4 times per day, every day. Laser irradiation was applied to the trigeminal nerve, the molar site, and the trigeminal ganglion. After 1 application, the patient said he was no longer taking Tylenol No. 3 and took only 2 Advil® at bedtime. Three days later a second application was done to the same site, and the patient reported as pain-free and no longer needing medication. The pain-free status has lasted for three months.

REFERENCES


Clinical Review and Case Reports


INTRODUCTION

Peer-reviewed, evidenced-based studies describing the benefits of using hard and soft tissue lasers are well documented in the dental literature. The use of the erbium family of lasers, Nd:YAG lasers, diode lasers, carbon dioxide lasers, and argon lasers and are well understood and used around the world.

Photobiomodulating (PBM) lasers are devices that produce energy levels below 0.5 Watt and are not used for invasive surgical procedures. PBM lasers do not produce or require temperature elevation in a target tissue (i.e., photothermal effects), but rather create a photobiomodulation effect within the target tissue. The benefits and usage of these lasers are gaining acceptance within the dental community and are often identified by different names. The most common descriptions are cold lasers, healing lasers, and low-level laser therapy (LLLT). The beneficial effects are described as a photobiological or photochemical effect on the target tissue. Low-level lasers produce energy in a range of 50-500 milliwatts (mW). PBM lasers produce a stimulation and/or suppression of biological processes and allow the tissue to generate an intracellular or biological response. The present body of knowledge of PBM suggests that one of the major effects is created within the cell mitochondria and results in an increase of the cell’s fuel for energy and repair, or adenosine triphosphate (ATP).

PBM lasers are often semiconductor diode lasers. The author is familiar with two general types: one, consisting of InGaAIP (Indium-Gallium-Aluminum-Phosphide) in the visible light range of 630 to 680 nm; and two, GaAlAs (Gallium-Aluminum-Arsenide) in the invisible range of 750 to 910 nm. Other wavelengths can also be used. PBM lasers affect damaged cells and do not produce harmful or negative effects on healthy cells.

The U.S. Food and Drug Administration (FDA) categorizes photobiomodulating lasers as posing no significant risk (NSR) and therefore these devices are considered safe. In the medical community, the FDA has given marketing clearance for such procedures as pain control and carpal tunnel syndrome treatment. At this time, all dental applications should be considered off-label usage in the United States. Essentially, this means that there is no ‘indication for use’ statement in the operating manual. (For more information on regulatory approval, please refer to Sulewski JG.)

Clearing the FDA hurdle, from initial device application through regulatory approval to the clinical operator: An update on dental laser marketing clearances, J Laser Dent 17(2):81-86.) In spite of the NSR designation, the author avoids using PBM lasers on patients who are pregnant or who have malignancies.

There are three types of effects of photobiomodulating laser therapy: a primary local event which is simply absorption of the light directly by the cellular chromophores or cytochromes; and secondary changes induced by cells that have absorbed photons which initiate cell-specific responses such as increased cell metabolism and blood circulation. These beneficial effects can occur in areas of the body not being directly irradiated. It should be mentioned that there is some controversy in the scientific community about PBM effects; however, more than 2500 articles have been written and accepted.

The effects produced by nonsurgical lasers are not limited to low-level lasers. Hard and soft tissue lasers, which are used for surgical procedures, also are capable of producing beneficial PBM effects when used in noncontact, defocused modes. Thus at low energy output levels (less than 500 mW) they do not appear to produce heat build-up within the irradiated tissue. Examples of PBM effects that may be attributed to the nonthermal effect of hard and soft tissue lasers are treatment of postsurgical discomfort; treatment of postsurgical or acute infection, pain, and swelling due to trauma; and maintaining vitality of injured teeth.

ABSTRACT

Many laser instruments are available for treating oral disease. Some treatments involve removal of hard and/or soft dental tissue. However, other beneficial therapeutic results can occur without a photothermal event, and these effects are known as photobiomodulating or low-level laser effects. They can be produced by all lasers; however, specific photobiomodulating laser instruments are available that operate at levels below 500 mW and can be used to provide a wide range of benefits. This article will describe the many uses for these devices used in the author’s pediatric dental practice.
PBM devices may consist of a nonlaser cluster of light-emitting diodes (LEDs) of various wavelengths or may be a single wavelength laser probe emitting at 660, 808, or 830 nm. Examples of both such devices as used by the author are shown in the accompanying table. Typically the cluster type used for treatment provides between 4 to 12 Joules (J) per minute externally, and intraoral probes provide between 2 to 8 J per minute.

**PBM USES IN TREATMENT OF PEDIATRIC PATIENTS**

1. **Reduction of pain and creation of an analgesic effect during restorative dental procedures**

   The capability to produce an analgesic effect allows PBM devices to reduce and often eliminate the need for a local anesthetic during restorative dental procedures. A tooth being treated is not numb, however the ability of the body to recognize or feel pain appears to be significantly reduced. Teeth exposed to laser therapy have lower levels of pain as compared to those with the placebo treatment. A photobiomodulating effect can be accomplished by using PBM lasers that are limited to low-level energy (a 660-nm probe on either the Q1000 or the AcuLASER in a contact mode) or by using an erbium family laser (2940-nm Er:YAG or 2780-nm Er,Cr:YSGG) in a defocused mode. To achieve an analgesic effect, the author places the tip of the laser in a defocused mode (noncontact, 1 to 3 mm from the tooth surface) when using a 660-nm probe over the crown of the tooth for 1 to 2 minutes, as shown in Figure 1. When an erbium family laser is used, as depicted in Figure 2, the laser’s tip is maintained in a defocused mode in continuous motion. This will prevent production of thermal effects within the tooth. Using this technique, the author has found that it is often possible to complete a cavity preparation with the erbium laser without a need for anesthesia. In most instances, while preparing primary teeth and many permanent teeth, it is possible to also use a high-speed dental handpiece to complete the cavity preparation without causing the patient discomfort. (If the patient has not previously experienced the vibrations of the high-speed or low-speed handpiece, there is no preconceived fear factor.) Regardless of the final restoration, the patient is able to leave the dental office without a numb lip, tongue, or cheek. This is especially important in young children, where the potential for developing a lip or tongue injury due to the child’s biting is often a concern.

**PHOTOTOBIOMODULATING DEVICES**

<table>
<thead>
<tr>
<th>Model</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Wavelength(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcuLASER</td>
<td>Laserex Technologies, Unley, Australia</td>
<td>LED Cluster</td>
<td>660 nm</td>
</tr>
<tr>
<td>Q1000</td>
<td>2035, Inc., Rapid City, S.D., USA</td>
<td>LED Cluster: 8 LEDs/12 diodes</td>
<td>470-940 nm, 660-nm probe, 808-nm probe</td>
</tr>
<tr>
<td>MedX Home Unit</td>
<td>MedX Health Corp., Mississauga, Ontario, Canada</td>
<td>Diode cluster: 9 red diodes and 40 infrared diodes</td>
<td>633 and 880 nm</td>
</tr>
<tr>
<td>DioBeam 830</td>
<td>Laser Light Canada, Tottenham, Ontario, Canada</td>
<td>Single Probe</td>
<td>830 nm</td>
</tr>
</tbody>
</table>

16 Teeth exposed to laser therapy have lower levels of pain as compared to those with the placebo treatment. PBM has been shown to be beneficial, and the author has treated infants and toddlers, ranging from 7 months to 5 years of age, with a 660-nm laser probe. After receiving injuries to this area, those patients have had the involved tooth or teeth remain vital. In instances where these teeth were slightly mobile, partially avulsed, or displaced and were treated within 24 to 48 hours after an injury, the teeth demonstrated both clinically and radiographically the ability to remain normal in color, maintain vitality, and remain asymptomatic over three or four years.

Successful treatment consists of...
placing a PBM laser probe on the facial and palatal area of the traumatized tooth for 1 minute. It may be advantageous, in some instances, to re-treat the affected tooth or teeth similarly at 3- and 5-day intervals after the accident.

Case 1: A child presented who had fallen and partially extruded the maxillary central incisors. The initial radiograph in Figure 3 shows the initial injury. Treatment consisted of repositioning the teeth with manual pressure and then placing the 660-nm laser probe over the labial surface of the crowns and roots for 1 minute each on the facial and lingual aspects for a dosage of approximately 4 J/min. Figure 4 depicts the successful maintenance of the teeth 1 year later.

3. Treatment of permanent tooth trauma

Case 2: A 10-year-old female child was seen due to tooth #9 being partially avulsed. A clinical and radiographic examination revealed the tooth was extruded from the tooth socket approximately 5 mm (Figure 5). The tooth was gently repositioned into the correct position by having the patient slowly bite on a crown seater. Once the tooth appeared to be in correct alignment, it was splinted into place with a band of composite (Figure 6). The tooth was then exposed to the 660-nm probe for 1 minute facially and 1 minute palatally. This procedure was repeated in three days and again at 7 days post-trauma. At the end of 23 months (Figure 7) the tooth remained vital and asymptomatic, both clinically and radiographically.

4. Treatment of inability to open the oral cavity due to cellulitis and muscle trismus

Patients seen for emergency visits due to oral infections may have difficulty opening their mouth adequately to allow an accurate examination of the oral cavity, as shown in Figure 8. PBM therapy could provide some relief. This condition may be due to trauma or infection of an abscessed tooth. This lack of access may prevent drainage and relief of pain of an infected tooth. Placing the Q1000 instrument over the affected area in a contact position for three minutes gave the patient enough relief to allow for adequate opening and drainage of the infected tooth area.

5. Treatment of temporomandibular joint (TMJ) and postorthodontic adjustment discomfort

PBM therapy has been shown to be effective in treatment of TMJ pain as well as for alleviation of discomfort during orthodontic procedures.

Case 3: A 13-year-old female patient presented with a history of morning pain in the areas of both left and right ears. An oral examination revealed many TMJ discomfort signs: ringing in the ears, jaw pain upon chewing and opening her mouth fully. The patient was treated for three visits (using the Q1000 for a 3-minute cycle on the left side and the MedX cluster on the right side), externally over the TMJ areas on alternate days (Figure 9). In addition, the 660-nm laser (2.2 Joules)
was applied intraorally for 1 minute on each trigger point (Figure 10). The patient indicated she felt relief immediately and after 3 days was essentially pain-free.

Figure 11 shows the Q1000 device being used for treatment of post-orthodontic adjustment discomfort.

6. Elimination the gag reflex

A simple solution for many gaggers is to place a small dab of salt on the tip of the tongue. Unfortunately, this method does not work on all patients. Stimulation of the acupuncture point on the inside area of the wrists, known as the P6 meridian, can reduce the nausea and gagging sensations. The P6 point is positioned on the undersurface of the wrist approximately 1 inch from the wrist crease; this is approximately the width of the distal thumb phalanx. Applying laser energy using 4 Joules of the MedX (either the 633- or 880-nm wavelengths) held in contact, perpendicular to the tissue on the P6 point can often provide sufficient relief to eliminate a gag reflex. Strong gag reflexes prevent the taking of intraoral radiographs, placement of rubber dam, or visualization and treatment of dental caries, especially in the most distal point of upper molars. Such areas may be successfully treated when the PBM laser is placed on the P6 acupuncture point for 1 minute, as shown in Figure 12.

7. Treatment of soft tissue injuries

Benefits of pretreatment of surgical sites or post-traumatic soft tissue injuries with the PBM laser include reducing postsurgical pain and allowing the inflammatory response to start earlier. These effects are thought to be the result of laser light affecting both the cell membrane and components within the nucleus of the cell. This results in stimulating and accelerating the rate of healing; reducing and resolving tissue inflammation; providing significant pain relief; improving tensile strength of the wound; and stimulating the immune system to resolve infection. The tertiary effect of irradiating one area of the body and having similar effects manifest elsewhere on other wounds of the body suggests a systemic effect of PBM laser energy. This appears to be a significant reason why it is difficult to create a study using the left and right side of the same patient. The systemic effects prevent the examiner from determining whether there is a difference between a placebo effect and the laser’s effect.

Case 4: A 4-year-old boy received an injury to his upper teeth and soft tissue when playing “roller coaster” at home on furniture. The anterior teeth were treated with the DioBeam 830 intraorally at 4 J/min and the MedX cluster laser extraorally at a setting of 3 J/min. This treatment was performed on the initial appointment and again on the following day (Figures 13-16). The patient has been seen for two years following the incident, and the teeth have remained stable without infection.

8. Treatment of intraoral lesions

Children presenting with viral stomatitis or herpetic-like lesions can benefit from PBM treatment using a variety of devices, especially if the treatment can begin near the first appearance of the problem.

Case 5: A 10-year-old patient presented with multiple lesions intraorally and significant discomfort. The Q1000 was placed extraorally for 3 minutes (Figure 17). The patient returned 4 days later with reports of no discomfort and with most of the lesions healed. In the author’s experience, since the laser energy scatters through the tissue, some areas may absorb different amounts of that energy and not fully resolve. Those lesions would require additional treatment on a subsequent appointment.

Case 6: As a final example, a surgical laser (DioDent Micro 980®, HOYA ConBio, Fremont, Calif.) was used to treat a child who presented with herpes labialis. For further information, see Kotlow L. Treatment of aphthous ulcers and herpes labialis. J Laser Dent
Treatment consisted of lasing the entire upper left quadrant for 2 minutes using a defocused tip according to the manufacturer’s instruction for this indication for use. The power density is within the parameters of PBM. Figures 18-19 show the perioperative and two-day postoperative views.

CONCLUSION
Photobiomodulating lasers provide pediatric dental patients many benefits including reducing the discomfort and pain from surgical sites and injuries; reducing the duration of healing from trauma and soft tissue surgery traumatic injuries; eliminating or reducing the gag reflex and nausea; and relieving muscle discomfort from postorthodontic adjustments. The mechanisms of these benefits are still undergoing investigation and need more scientific studies to allow for proper understanding.

AUTHOR BIOGRAPHY
Dr. Lawrence Kotlow has had a private dental practice located in Albany, New York since 1974, specializing in Pediatric Dentistry. He is a graduate of the University at Buffalo The State University of New York (SUNY), New York University College School of Dentistry, and the Cincinnati Children’s Hospital pediatric dental postgraduate program. He is Board-certified in Pediatric Dentistry. Dr. Kotlow has Advanced Proficiency certification from the Academy of Laser Dentistry in the erbium laser and has Standard Proficiency in the Nd:YAG and diode lasers. He is a Recognized Course Provider for the Academy of Laser Dentistry and has achieved Mastership in the Academy of Laser Dentistry. Dr. Kotlow has published many articles on using the erbium laser in pediatric dentistry and contributed a chapter to the October 2004 edition of Dental Clinics of North America: Lasers in Clinical Dentistry entitled “Lasers in Pediatric Dentistry.” He has lectured throughout the United States, Canada, Australia, and Taiwan about pediatric dentistry and lasers. Dr. Kotlow may be contacted by e-mail at lkotlow@aol.com.

Disclosure: Dr. Kotlow has evaluated and beta-tested new equipment for various dental and laser companies such as Lares, Schick, HOYA ConBio, and Innovative Optics.

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Photodynamic Antimicrobial Chemotherapy in the General Dental Practice

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J Laser Dent 2009;17(3):131-138

INTRODUCTION

Laser photonic energy can be absorbed by target tissue and molecular elements. In the surgical excision of tissue, such energy is rapidly converted into thermal energy that causes physical disruption and possible vaporization. Relative to each target tissue and corresponding incident laser wavelength exists a thermal threshold, below which the incident photonic energy values are insufficient to initiate disruption, resulting in reversible warming.1

At much lower incident energy levels, intracellular structures such as cell mitochondria can absorb incident photonic energy, resulting in stimulation of adenosine triphosphate and ultimately in an increase in cell respiration.2 Such “low-level laser” action has been well documented,2 reflecting a general process of energy transfer within such structures. A procedure used in cancer treatment called photodynamic therapy (PDT) utilizes this energy transfer.3

Allied to investigations into low-level laser effects, it has been shown that certain chemotherapeutic agents possess similar capacity for electron transfer in the presence of photonic energy.2 Where this occurs in close proximity to absorb tissue and in particular tissue oxygen, reactive oxygen species can be formed simultaneously with singlet oxygen. Ultimately, these reactions will kill cells through apoptosis or necrosis.4,5,6

The major outcome of such knowledge has been seen in the general principles of photodynamic therapy in the treatment of neoplastic tumors.7,8 However, similar effects have been demonstrated in vitro, using low-level photonic energy on selected bacterial species with some success. This has led to the emergence of photodynamic antimicrobial chemotherapy (PACT) in treating a broad range of bacterial infections in the mouth.

This paper reviews the process of energy transfer in PACT, the development of clinical protocols, and the applications of PACT in clinical dentistry.

COMPONENTS AND MECHANISMS

Light has been used for therapeutic purposes for several centuries. Initially, ultraviolet radiation was applied in the treatment of acne vulgaris, skin tuberculosis, and rickets.9,10 With the development of light-absorbing properties and fluorescence of various dyes, it was realized that these chemicals, when photoexcited, were capable of exerting destructive effects on target cells. This process was termed photodynamic action and further research11,12 into the mechanisms involved gave rise to an understanding of “dye-sensitized photo-oxidation of molecular oxygen.”

A photosensitizer is a chemical compound that readily undergoes photoexcitation and then transfers its energy to other molecules.1 Usually the photosensitizer is excited from a ground singlet state (quantum state with zero spin angular momentum) to an excited singlet state. It then undergoes intersystem crossing to a longer-lived excited triplet state. In this state, two reactions are possible as mentioned above. When the photosensitizer and an oxygen molecule are in proximity, an energy transfer can take place that allows the photosensitizer to relax to its ground singlet state and create an excited singlet-state oxygen molecule. Singlet oxygen is a very aggressive chemical species and will very rapidly react with any nearby biomolecules.7

There are more than 400 compounds that have been shown to exhibit photosensitizing properties, either in vitro or in vivo.14 Some of the more significant may be summarized as follows:

- phenothiazine dyes – e.g., methylene blue (MB) and toluidine blue O (TBO; toluidine chloride)15,16
- phthalocyanines17,18
- chlorines19
- porphyrins – e.g., hematoporphyrin HCl, Photofrin®, 5-ALA (aminolevulinic acid)20,21
- xanthenes – e.g., erythrosine.22

The basic principle of PACT is to utilize a photosensitizer in combination with a light source to activate it.23 Wilson and Pratten reported that neither the light source alone in the absence of the photosensitizer nor the photosensitizer alone in the absence of the light source had any significant effect on the simulated
antibacterial therapy.\textsuperscript{18} In contrast, Dörtbudak \textit{et al.} demonstrated that application of toluidine blue O alone resulted in significant reduction of some, but not all, bacterial species tested.\textsuperscript{24} In the above studies,\textsuperscript{15-22} all of the compounds except erythrosine were activated by visible red light in the wavelength range of 630 to 662 nm produced by a laser; an ordinary tungsten lamp was used in a study of erythrosine’s effectiveness,\textsuperscript{27} but that compound has a maximum absorption in the 500 to 550-nm range, which is blue and green light. Wilson and Patterson have suggested a 700 to 850-nm range of energy for an ‘ideal’ photosensitizer. Nonetheless, a diode laser is usually used for photodynamic procedures.\textsuperscript{25}

As outlined above, the photosensitizer compound in its ground state is activated by light and transformed into a high energized triplet state. Two mechanisms of action explain the effectiveness of PACT:\textsuperscript{26}

- The triplet compound interacts with the cell’s organic substrate molecule, producing free radicals and radical ions. These in turn react with endogenous oxygen and reactive oxygen species (ROS) such as hydrogen peroxide and hydroxyl radicals which irreversibly damage the cell’s membrane. ROS compounds can also damage subcellular organelles and enzymes as well as DNA.\textsuperscript{26}

- The triplet compound interacts directly with the molecular oxygen to produce a singlet oxygen, which is highly reactive. It also causes irreparable cellular damage, including the cell wall.

Although both mechanisms exist in relation to each other, singlet oxygen generally produces the lethal bacterial effects of PACT. The interaction is extremely rapid, since the radius of action of singlet oxygen is estimated to be on the order of 0.01 to 0.02 μm, corresponding to a lifetime of 0.01 to 0.04 μs in cells.\textsuperscript{27} There is limited migration of the molecule from its formative site, thus its effect is very localized. The advantage is that surrounding structures can be preserved;\textsuperscript{26} however, the placement of the photosensitizer should be as close to the infection as possible.

**CLINICAL APPLICATIONS**

The majority of the common disorders within the oral cavity are due either to bacterial causes or are exacerbated by secondary bacterial contamination. Notwithstanding the need for the clinician to correctly diagnose the condition and address all local and systemic contributory factors, the elimination of pathogenic bacteria has represented a core objective. In addition to the presence of bacterial colonies, the existence of a biofilm can constitute a formidable barrier to many local applied therapies\textsuperscript{15-22} and systemic antibiotic use has led to inconsistent results. Of significance to the latter, antibiotic resistance and systemic side effects may present a challenge and deter the casual use of such therapies.\textsuperscript{20-33}

The consequence of risk associated with concomitant bacteremia during periodontal and restorative treatment has been the subject of a recent review.\textsuperscript{24} Over more than 40 years, prophylactic administration of systemic antibiotics has been considered best practice in those patients at risk of bacterial endocarditis and, despite recommendations to the contrary, the controversy remains.\textsuperscript{35}

Mechanical instrumentation, including scaling and root planing and the use of ultrasonics, has been advocated to provide adjunctive debridement in periodontal and peri-implantitis treatment. The efficacy of such treatment may be compromised by lack of direct access to the treatment site and the possible risk to underlying healthy tissue.

The photothermal interaction of lasers, using supra-ablation threshold values, can produce tissue temperatures to aid in bacterial reduction.\textsuperscript{26}

With regard to the sole use of ablative laser energy in bactericidal effects, the following phenomena may be considered as limiting factors:

- Primary bactericidal action linked to absorption characteristics
- Primary interaction coaxial with laser beam
- Risk of collateral damage associated with nontarget absorption and thermal rise
- Other difficulties – access, limitations of delivery tip design, etc.

Conversely, the use of a nonablative, low-level laser wavelengths to initiate photodynamic antimicrobial chemotherapy in a suitably administered photosensitizer may be seen to have the following advantages over “conventional” laser use:

- Nonsurgical (subablative) photonic energy values employed
- Primary (indirect) interaction through chemical mediator (photosensitizer)
- Little risk of collateral damage within confined target sites.

Methylene blue as a photosensitizer should be used with caution and in dilute doses, to avoid possible toxicity.\textsuperscript{27}

- The use of noncollimated light through a diffuser tip can overcome limited access and be further compensated by scatter through the body of the liquid sensitizer.

Local infections such as those that occur within the oral cavity may be potential targets for antibacterial photodynamic therapy, in addition to other mechanical debridement techniques. The supra- and subgingival plaque biofilm on tooth surfaces is often easily accessible for flushing with the dye and activation with the low-level laser light.

During the last decade, an increasing number of studies have been published that describe the effect on periodontal pathogenic bacteria by photodynamic methods. These investigations have underlined the introduction of PACT into the practice of periodontology.\textsuperscript{36-42}

Other investigations have shown the use of PACT in the treatment of a number of pathogenic bacterial and fungal infections, summarized as follows:

- Tooth surface disinfection prior to dental treatment.\textsuperscript{41}
Current developments in commercial low-level laser emission have given rise to several devices which emit light in the visible red region of the electromagnetic spectrum. One such instrument (PAD™ Plus, Denfotex Light Systems Ltd., Inverkeithing, Fife, UK) uses toluene chloride solution as the supplied photosensitizer and is designed primarily for antibacterial action within the tooth (cavity preparation and endodontics). Another device (Periowave™, Ondine Bio-pharma Corp., Vancouver, British Columbia, Canada, shown in Figure 1) supplies a methylene blue solution for use in periodontology, peri-implantology, and oral mucosal infection sites. The author’s experience has been with the latter instrument. Figure 2 shows the device’s fiber-optic delivery system, and Figure 3 shows the laser activated with emission through the diffuser tip.

Use of PACT is seen as adjunctive to the reduction of bacterial pathogens and is part of the overall treatment necessary to address causative factors and repair, remodel, or restore the tissue site as required. Safety regulations must be applied as per National statutes and guidance and the Class III classification of the laser defines the use of wavelength-specific protective eyewear for patient and operator. The photosensitizer solution is supplied in single-use disposable vials, onto which a blunt, side-release cannula is fitted; the cannula is applied to the tissue site and a small amount of photosensitizer expelled. The laser unit is configured by the manufacturer to deliver a fixed cycle of continuous-wave light emission, enabled through a foot switch, with the following power parameters: 220 mW / 60 seconds / 13 joules. The nature of the diffuser delivery tip helps ensure that laser photonic energy is applied evenly throughout a volumetric zone of photosensitizer and is considered effective within a 1 to 2-mm distance from the diffuser tip. Therefore, in the periodontal pocket disinfection of a single root tooth site, the tip is applied at four sites (mesial, distal, facial, palatal), with additional application at bifurcation sites for molar teeth; each site is exposed to the fixed cycle of light emission.

**CLINICAL CASES**

The following clinical cases present examples of PACT. Figures 4 to 7 show adjunctive treatment of a periodontal pocket during the placement of a new crown.

Figures 8 to 11 also present the use of PACT for adjunctive treatment of periodontitis.

Figures 12 to 16 illustrate a case of peri-implantitis adjunctively treated with PACT.

Figures 17 to 20 portray treatment of candidal cheilitis of the lip using methylene blue photosensitizer.

Figures 21 to 23 depict a similar candidiasis-type lesion on the palate, treated with PACT.

Figures 24 to 31 show the adjunctive use of PACT during osseous surgery as part of the treatment to resolve periodontal breakdown associated with failed fixed bridgework.
Figure 6: Single-use photosensitizer syringe, blunt needle cannula, and diffuser tip

Figure 7: Completed new PFM crown with healthy tissue (right) at three weeks post-treatment

Figure 8: Preoperative probing demonstrating presence of periodontal disease

Figure 9: After methylene blue solution had been applied to post-scaling treatment sites, the pockets are exposed to laser photonic energy

Figure 10: Immediate postoperative view

Figure 11: One-month postoperative view. Clinical appearance shows lack of inflammation and bleeding

Figure 12: Probing of a diseased area of peri-implantitis. PACT will be used adjunctively with an open flap procedure that will also employ an Er:YAG laser for debridement

Figure 13: Debridement of implant fixtures using an Er:YAG laser

Figure 14: Treatment site immediately prior to application of the photosensitizer

Figure 15: Photosensitizer exposed to laser photonic energy, delivered through diffuser tip. After PACT is completed, guided bone regeneration (GBR) is employed in the defect

Figure 16: Postoperative clinical appearance at three months

Figure 17: Close-up view of a persistent candidal cheilitis lesion of the lower lip
Figure 18: Application of methylene blue solution to the lesion

Figure 19: Exposure of treatment site to activated diffuser tip. The tip is placed alongside the lesion to allow intimate exposure

Figure 20: Healing of lesion at two weeks, showing appearance of resolution of the fungal infection

Figure 21: Pretreatment view of candidal denture stomatitis, showing characteristic epithelial hyperplasia and inflammation

Figure 22: Application of laser photonic light diffuser tip

Figure 23: Follow-up view at two weeks post-treatment, showing appearance of resolution of inflammatory changes in epithelium

Figure 24: View of probing of the periodontal defect, which is an infrabony defect associated with teeth #11 and 12 (upper left canine, first premolar). Tooth #11 is a distal abutment for a failing fixed bridge and the defect is considered secondary to an open tooth contact. PACT will be used adjunctively to an open flap procedure, in which an Er:YAG laser will also be employed

Figure 25: Pretreatment radiograph showing bone loss

Figure 26: The bridge has been removed and the periodontal defect is debrided using a surgical Er:YAG laser application

Figure 27: Additional use of an Er:YAG laser allows selective removal of subgingival calculus from root surfaces
In the author’s clinical experience, the benefits to be derived from the adjunctive use of PACT in providing treatment of conditions of a bacterial origin may be summarized as follows:

- Straightforward clinical technique
- Nonsurgical protocol required for application of photosensitizer
- Topical / systemic antibiotics not required
- Useful as an adjunct to restorative / endodontic / surgery site pathogen reduction
- PACT can disrupt plaque biofilm, thus making it an adjunctive for use with ultrasonics, surfactant

Facilitates access into deep / limited-access sites (furcations, invaginations)
- Reduced need for surgery / direct flap approach. Patient comfort enhanced
- Reduced risk of bacteremia
- Useful in treatment of mucosal pathologies – candida, herpes, cheilitis
- GBR success enhanced following PACT

Potential drawbacks to PACT include:

- Possible impairment of benign oral flora which may lead to an overgrowth of a single resistant species. Staining the target selectively is seen as a way to help avoid this unwanted, potentially phototoxic reaction.
- Photosensitizers can adhere strongly to the soft tissue of the periodontal pocket and may affect periodontal attachment during wound healing. Routine removal of the dye solution after photosensitization procedures will mitigate this concern.
- Photosensitizers can compromise patient esthetics by producing temporary pigmentation of the periodontal tissues. Excess dye should be removed with water spray. The use of photosensitizers in a paste base rather than liquid may facilitate removal through irrigation with a saline solution.
- Should higher-powered diode lasers be used to irradiate the photosensitizer, extended duration of exposure at the same spot should be avoided to prevent thermal accumulation or injury to deeper tissues, such as bone or dental pulp.

**CONCLUSION**

The majority of pathologies treated in everyday general dental practice can be considered to be primary bacterial infections or are complicated by secondary bacterial contamination. Many techniques have been advocated to address the need for elimination of bacterial pathogens as part of treatment and one of the claimed advantages of surgical laser use is a bacterial reduction of target sites in both hard and soft tissue management. However, the limitations of the coaxial emission of the laser beam and difficulty in accessing all sites may compromise the desired outcome.

The use of laser photonic energy to activate an intermediate chemical and achieve bacterial destruction through secondary effect has been shown to offer advantages over surgical laser use.

This paper has presented the underlying principles of PACT action and considered some of the areas of clinical treatment where PACT has been shown to be of benefit. Potential drawbacks are described, along with suggested measures to mitigate concerns.

Differing regulatory policies have restricted a more widespread uptake of this treatment modality.
in dental practice. However, the general principles and instrumentation of photodynamic therapy in general medicine have been long-accepted globally and it is hoped that the opportunity to integrate PACT into general dental practice will allow this modality to gain in popularity.

AUTHOR BIOGRAPHY
Dr. Steven Parker is in private practice in Harrogate, United Kingdom, and a visiting professor in laser dentistry at the University of Genoa, Italy. He has been active in the use and teaching of laser applications in dentistry since 1990 and has lectured extensively on all aspects of laser use. He is a past president of the Academy of Laser Dentistry and currently is chair of the Academy’s Education Committee.

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Disclosure: Dr. Parker has no commercial affiliations or conflicts of interest.

REFERENCES
CLINICAL REVIEW AND CASE REPORTS


Biostimulation Effects of Superpulsed, High-Intensity, Low-Average Power Laser Application on the Timing of Orthodontic Aligner Sequencing of the Invisalign® System

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INTRODUCTION

The scientific rationale behind orthodontic movement of teeth began more than 100 years ago with a book by Sandstedt that was subsequently published as a three-part article in 1904 and 1905. Sandstedt constructed a unique experimental model in which the six maxillary incisors of a dog were attached to an appliance and moved 3 mm into the lingual direction within a three-week period. His histological analysis revealed that bone had formed on the alveolar wall of the tension side of the tooth, where the newly formed bone spicules were in the same alignment as the periodontal ligament fibers. These findings were consistent with the application of both light and heavy orthodontic forces. On the pressure side, however, he found that bone was resorbed by osteoclastic activity (as evidenced by the presence of Howship lacunae) with light orthodontic forces, and found certain cell-free areas (as a result of capillary thrombosis and cell death) which he referred to as hyalinization zones under heavy orthodontic forces (Figures 1-2). It was hypothesized that some form of molecular signaling mechanism was responsible for the mechanotransduction which stimulates osteoblasts to generate newly formed bone and osteoclasts to resorb bone. The necessity of mechanical stimuli for the proper maintenance of bone in

ABSTRACT

Purpose: The aim of this study was to ascertain the biostimulatory effects of a superpulsed, high-intensity laser on the bone remodeling cycle under load of orthodontic forces. Furthermore, this study tested whether the bone remodeling process can be accelerated enough in order to show a clinically significant reduction of the timing between aligner changes of the Invisalign® system (Align Technology, Inc., Santa Clara, Calif.), referred to below as the ‘orthodontic system.’

Background: It is common knowledge that bone, as an organ, will respond to pressure above a certain threshold with remodeling. In orthodontic applications, the type of remodeling response will depend on whether bone is under compression (direction of tooth movement) or under tension (the side opposite the direction of movement). On the compression side, the periodontal ligament (PDL) fibers are compressed, which initiates a signaling cascade leading to osteoclastic resorption of bone. On the tension side, the stretching of the periodontal ligament fibers appears to promote osteoblast-mediated bone proliferation. Research has also shown that biostimulation light energy from a low-average power laser can have a stimulating and acceleratory effect on tissue regeneration by promoting an increase in cell populations and signaling molecules responsible for the tissue regeneration and repair cycle. With this information, it stands to reason that laser-induced accelerated bone remodeling will also effectively accelerate the orthodontic movement of teeth without an increase of the orthodontic force applied.

Methods: Forty patients undergoing orthodontic system treatment were selected for this study. These patients were randomly divided into two groups of 20 patients: GL, which received laser treatment, and GC, which served as a control. Each patient was instructed to wear the aligners for a minimum of 20 hours per day. Each patient in GL presented for phototherapy twice a week with at least two days between each of the phototherapy sessions. GC presented for progress checks once a week. Phototherapy was conducted with a superpulsed, high pulse power, and low-average power 910-nm GaAs laser. Tracking progress of all moving teeth for both groups was evaluated at every appointment, during which the computerized progression model was compared to the actual in vivo alignment. Once the in vivo alignments of the teeth matched the computer model for a particular aligner, the aligner was switched to the next in sequence.

Results: At the termination of the study GL had statistically significant fewer days between aligner exchanges (mean = 9.6 days) than GC (mean = 14.6 days).
Moreover, Frost and Peverali reported that the bone tissue within the periodontium to either osteogenesis or bone resorption. An examination of the basic molecular architecture of cell attachments will help illuminate this pathway. Cells such as osteoblasts or fibroblasts have integral membrane proteins which interact with the extracellular matrix (ECM) and mediate a variety of intracellular signals or attach to other cells. These integral membrane proteins are thus classified as cell surface receptors and collectively referred to as integrins.

It has been shown that numerous signaling pathways can be activated by integrins, which “sense” a mechanical distortion between the cytoskeletal elements they are attached to the inside of a cell and the ECM attachment outside the cell. Basdra et al. showed that concentration levels of integrin-mediated signaling proteins (rab and rho guanosine triphosphatases) were altered in mechanically stretched PDL fibroblasts, and Peverali et al. have shown similar results for the mitogen-activated protein kinase family in osteoblasts. Harell et al. suggested in 1977 that a specific sequence of molecular events is initiated in osteoblast-like cells undergoing mechanical deformation in an in vitro environment. During this sequence of events adenylate cyclase is activated, leading to a transient increase of cyclic adenosine monophosphate (cAMP), an increase intracellular [Ca++], and the initiation of DNA synthesis and mitosis, thereby initiating a repair process, as Ngan et al. reported in their in vitro study involving human gingival fibroblasts.

In summary, DNA synthesis, mitosis, and cell differentiation of fibroblasts and osteoblasts are a direct result of a shift in mechanical pressures within the PDL space.

Furthermore, recent in vitro studies have shown that low-average power laser light can stimulate and enhance the proliferation and differentiation of bone marrow stem cells (BMSCs) as well as increase the secretion of growth factors. The biostimulatory effects of certain nonablative lasers have been reported in the literature of the late 1960s and early 1970s. Since then, numerous publications have elevated phototherapeutic laser applications into mainstream medicine and dentistry. Laser energy interacts with tissues through chromophores. Chromophores are parts of the molecule responsible for its color. In biological molecules that serve to absorb or detect light energy, the chromophore is the moiety that causes a conformational change of the molecule when hit by light. Water is one of the most predominant chromophores in human tissue, capable of absorbing light in various amounts throughout the infrared spectrum where dental lasers operate. However, between approximately 600 and 1000 nm, there is a narrow bandwidth in which the absorptive power of water is greatly reduced, and infrared light can penetrate deeply into tissues.

Virtually all phototherapeutic lasers today have emissions within the 600-to-1000 nm spectral range. The basis of the biostimulatory effects of phototherapeutic lasers is actually a synergistic amalgamation of two separate effects:

- The photochemical effect, in which the photon energy of the laser is absorbed by cytochrome-c oxidase, a large transmembrane protein found in the mitochondrial cell
wall. This will cause a short-term activation of the respiratory chain in which the resulting changes of redox states of the mitochondrial plasma and membrane help establish a chemiosmotic potential that the adenosine triphosphate (ATP)-synthase enzyme then uses to synthesize ATP.20 This sudden increase in ATP within cells will lead to the ability to not only initiate but also accelerate the physiology of irradiated tissues.

- The photomechanical effect, in which the photons from a high-intensity, low-average power, pulsed laser interact with the target tissues to promote gene expression.16,19 Gene expression is an important step during the transformatory phase of mesenchymal stem cells into osteoprogenitor cells such as osteoblasts.

When these biochemical effects of laser therapy are considered, it stands to reason that, with the correct laser dosage and wavelength, bone remodeling is one of the cellular processes that can be accelerated in an in vivo environment. Bone remodeling is the cornerstone of the translation of teeth in the orthodontic process. Consequently, our hypothesis was that properly dosed laser therapy can accelerate the bone remodeling, initiated through mechanical force changes around teeth, and thus accelerate the orthodontic movement of teeth, given a constantly applied pressure.

**SELECTION CRITERIA**

This investigation was characterized as a Phase I study with less than 50 subjects. Selection criteria included men and women between the ages of 20 and 40 who were candidates for the orthodontic movement of teeth utilizing the specific orthodontic system identified above. Participation was strictly voluntary. The Institutional Review Board from Texas Applied Biomedical Services (Houston, Texas) approved the study protocol.

Patients who qualified for this research project were properly informed of the system’s procedure, biostimulatory laser therapy, as well as the associated risks and benefits. In addition, alternative treatment modalities and their associated risks and benefits were discussed. A brief synopsis of the research project – its goals, expectations, and possible benefits – was also given to each patient.

Exclusion criteria were as follows:

- Patients under the age of 20 and over the age of 40 were not considered in order to obtain a more homogeneous population sample.
- Patients with potential neoplasms in the head-and-neck region were excluded, since a possibility exists that laser application might accelerate carcinogenesis in patients suffering from such pathologies, although there is currently no research demonstrating such clinical effects.
- Patients who were smokers were excluded because nicotine has a very strong vasoconstricting effect on microvasculature and may interfere with the normal regeneration process of bone.
- Patients who were undergoing bisphosphonate therapy were excluded since studies are emerging that indicate cancer patients being treated with bisphosphonates may be at risk for osteonecrosis of the jaw.21

**MATERIALS AND METHODS**

Each potential research subject was screened and categorized as “eligible” or “not eligible” based on the inclusion and exclusion criteria identified above.

The orthodontic system takes advantage of the dramatic developments in CAD/CAM technology in recent years.22,23 A patient’s impression is scanned to produce a computerized three-dimensional image of the initial alignment of teeth. The desired final alignment is done virtually with computer software and then translated into a sequence of aligner trays which are necessary to achieve that goal. The number of aligners necessary for a case will vary from patient to patient and can be as few as 10 and as many as 40. The Invisalign protocol calls for aligner change every 14 days, if the alignment of the teeth in vivo matches the alignment of the teeth on the computer model (ClinCheck® 2.6 software, Align Technology, Inc., Santa Clara, Calif.).

Those subjects who were selected were randomly assigned to one of two groups of 20 individuals each:

- **Group L (GL):** Patients received the orthodontic system and also presented twice a week for laser treatments and progress checks, with at least two days between laser treatments.
- **Group C (GC):** Patients received the orthodontic system only, and presented weekly for progress checks only.

Each patient was instructed to wear the aligners for a minimum of 20 hours per day.

Progress checks were performed with ClinCheck, which displays a three-dimensional image of the dentition within each aligner sequence. Individual tooth positions were measured in relation to adjacent teeth with the help of a millimeter grid overlay in the software (Figure 3).

![Invisalign case analysis. The overlay grid is used to measure distances and angulations of individual teeth to each other, which is then compared to the intraoral environment](image-url)
These measurements were synchronized in vivo with a periodontal probe (Hu-Friedy, Chicago, Ill.) for each tooth that was being moved orthodontically. The computer model measurements were then compared to the intraoral measurements. If the intraoral alignments of the teeth matched the computer model, the patient was given the next aligner in the sequence. These progress checks were conducted for both groups.

Laser treatments were performed with a free-running, pulsed 910-nm GaAs laser (Lumix 2, USA Laser Biotech Inc., Richmond, Va.). The laser was used at 45 Watts peak power at 30 KHz for this study. The diameter of the emitter tip is 8 mm and has a divergence angle of 12 degrees. Each arch was divided into six “illumination spots,” three on each side of the arch, so that there was slight overlap between the illuminated areas to cover the whole arch (Figure 4). Each of the six spots was illuminated for 90 seconds, for a total duration of 9 minutes per arch. This translates into 27 joules of energy per spot and 162 joules per arch. The emitter tip was held at approximately 5 mm from the buccal surfaces, just apical to the cementoenamel junction (CEJ) (Figure 5). Once the patients completed their aligner sequence, the following data were collected:

- Total number of aligners used
- Average number of days between aligner switches
- Number of midcourse corrections (additional trays used to correct abnormal tracking of teeth in midcourse).

Statistical analysis was done with the SPSS statistical software (PASW Statistics 18.0, SPSS Inc., Chicago, Ill.).

RESULTS

Both, the laser group (GL) and the control group (GC) samples consisted of 20 patients each. The longest and shortest treatment course for GL was 240 days and 99 days, respectively. The longest and shortest treatment course for GS was 425 days and 143 days, respectively. The average number of aligners needed to complete the case was 18.1 for GL and 19.85 for GC, which was not statistically different at a significance level alpha of 0.05. The average number of days between aligner exchanges was 9.57 for GL and 14.63 for GC, which produced statistically highly significant results using a one-tailed t-test P value of 0.000 at an alpha level of 0.01. Therefore, the laser group had a 34.6% faster aligner sequencing. Furthermore, of the 20 subjects in the control group, 5 needed midcourse corrections, whereas only 3 subjects needed midcourse corrections in the laser group (Table 1). On a subjective side note, patients in the laser treatment group reported fewer complaints of moderate-to-severe soreness the first two days after a new aligner had been fitted than the patients in the no laser treatment (control) group.

DISCUSSION

Teeth move in a certain direction by applying pressure on the teeth in the direction of translation. This will cause a deformity of the PDL on the pressure side as well as the tension side of the individual teeth. The deformation of certain cells in the PDL environment (fibroblasts and osteoblasts) is “sensed” by the integrins in their cell wall, which then release specific signaling molecules to activate the remodeling process. This process is called “mechanotransduction.” Some of these integrin-mediated signaling proteins (rab and rho guanosine triphosphatases, and mitogen-activated protein kinase) cause the proliferation of osteoclasts on the pressure side of the teeth and proliferation of osteoblasts on the tension side of the teeth. Furthermore, other signaling molecules will initiate an inflammatory reaction and mesenchymal stem cell division and transformation as part of the healing response.

All of these cellular processes are energy-intensive activities for cells, especially DNA synthesis, mitosis, and transformation of stem cells into new fibroblasts or osteoblasts. The basic energy molecule for all cells is adenosine triphosphate (ATP). Cells use this molecule to power their various activities. If a particular cell lacks sufficient quantities of ATP, certain cellular activities cannot take place. A sufficient quantity of ATP is therefore the prerogative for various cellular activities, especially in the repair and remodeling process of bone.

Phototherapy laser energy has been shown to increase the rate of cell division, cell transformation (mesenchymal stem cells), production of signaling molecules, and development of osteoblasts, fibroblasts, and osteoclasts. All of these cellular...
events are involved in the bone remodeling processes of orthodontic movement of teeth. It is therefore a reasonable assumption that a low-average power laser can also accelerate the rate of tooth movement in the orthodontic process.

As previously mentioned, of the two groups that were studied, the laser group showed a faster aligner sequencing. One can speculate, based on the information given above, that the chromophores of the cells in question were able to absorb the photon energy of the laser and convert this energy into their own usable energy in the form of ATP. This process is governed by very specific pathways; in particular, the main chromophore in the mitochondria is the protein molecule cytochrome-c oxidase, which is a component of the respiratory chain. It is the terminal enzyme that mediates the transfer of electrons from cytochrome-c to molecular oxygen. Additionally, ferrocytochrome-c is oxidized, dioxygen is reduced, and protons are pumped from the mitochondria to the cytosol. The electrochemical potential generated across the inner membrane of the mitochondrion by this redox drives the oxidative photophosphorylation of ADP into ATP. Once the concentration of ATP had increased inside the cells, they were able to initiate and execute the remodeling cascade with more efficiency and speed. It is our hypothesis that these were the most predominant precipitating factors in the accelerated tray sequencing we observed in the laser group. Indeed, there are studies using rats as well as one using a group of 15 patients that demonstrate how a low average power laser can contribute to a more rapid movement of teeth.

**CONCLUSION**

Within the confines of this study we have shown that low-average power, high-pulse intensity laser phototherapy can potentially accelerate orthodontic movements of teeth for the Invisalign platform. Future studies should compare these results with variations in wavelength, energy deliverance, and exposure durations. The limitation of this study was the small sample size. Larger-scale studies need to be done, perhaps on a multicenter level, in order to confirm and expand these results. It is our opinion that...

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Table 1: This table shows the data distribution of all 40 subjects in both groups. Group GL is the table on the left side and group GC is on the right side. The results show a statistically significant difference between GL and GC with respect to the actual days between aligner exchanges and the recommended 14 days.
this study is synergistic to the ever-growing body of evidence showing that low-power laser phototherapy may have a positive effect on overall healing, since the molecular healing cascade is similar for various tissue types in the human body.

AUTHOR BIOGRAPHIES
Dr. Nelson Marquina is the president of USA Laser Biotech Inc., a medical device developer focused on lasers and bioelectromagnetic devices for USA and Canadian markets. He has earned a Master of Science degree in statistics from Worcester Polytechnic Institute and doctoral degrees in systems engineering from the University of Houston and in chiropractic medicine from Logan University. He is an adjunct associate professor of biophysics at Virginia State University and a consultant to the National Foundation for Alternative Medicine (Washington, D.C.). Dr. Marquina is a former senior scientist at NASA/Johnson Space Center (Texas) and Director of Research at Logan University (Chesterfield, Mo.). He was Director of Information Systems in Mars, Inc. (New Jersey) and former partner in Coopers & Lybrand’s Information Technology Consulting Services (New York, N.Y.). He is an executive, consultant, and educator with more than 25 years of combined management, teaching, and technical experience in information systems, statistical analysis, and bioelectrical and bioelectromagnetic systems. Dr. Marquina is also a developer of bioelectrical, biophotonics, and bioelectromagnetic systems and their treatment protocols. He has chaired national conferences in computer expert systems, high technology in alternative medicine, and computer vision. He can be reached at Marquina@comcast.net.

Disclosure: Dr. Marquina is a paid consultant to Harris Medical Resources and BEMER USA. He is a stockholder in USA Laser Biotech Inc.

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Disclosure: Dr. Stalley has nothing to disclose relative to this manuscript.

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Professor Endre Mester, MD, DSc, was born in Budapest, Hungary, in 1903. As a schoolboy, he excelled as a violin player and developed an interest in medicine. With such diverse interests, he decided to sit university entrance examinations in both medicine and music. He succeeded in gaining a place to read medicine at the University of Budapest. His continued interest in music was relegated to social enjoyment with friends on weekends.

Having successfully completed his undergraduate medical study and graduation, he was invited to receive training in surgery as a resident staff member of the 3rd Department of Surgery at the University of Budapest. He subsequently obtained his first position outside the university as head of children’s surgery in St. Steven’s Hospital in Budapest. His continued interest in music was relegated to social enjoyment with friends on weekends.

Having successfully completed his undergraduate medical study and graduation, he was invited to receive training in surgery as a resident staff member of the 3rd Department of Surgery at the University of Budapest. He subsequently obtained his first position outside the university as head of children’s surgery in St. Steven’s Hospital in Budapest. From there, greater recognition beckoned and his next position was head of a major hospital in Budapest, the Bajcsy Zsilinszky. There he combined clinical work with administration, being appointed director of the hospital.

During this period, Mester undertook research and scientific work in the field of abdominal surgery, with a special focus on bile duct surgery. His interest in the skin of laboratory rats and exposed them to a customized ruby laser, based on Maiman’s earlier model. To his surprise, the tumor cells were not destroyed by doses of what was presumed to be high-power laser energy. Instead, it was observed that in many cases the skin incisions made to implant the abnormal cells appeared to heal faster in treated animals, compared to incisions of control animals that were not treated with light. Mester was baffled as to how a device that was intended to destroy tumor cells had instead promoted tissue repair. His custom-designed ruby laser was weak and certainly not as powerful as he thought it to be. Instead of being photo-ablative, the low-power light had no effect on the tumor. Indeed, it stimulated the skin to heal faster. This fortuitous encounter opened the field of monochromatic light treatment.

Like others of his era, Mester attempted to use a “high-power” laser to destroy malignant tumors. Early in his experiments, he implanted tumor cells beneath the skin of laboratory rats and exposed them to a customized ruby laser, based on Maiman’s earlier model. To his surprise, the tumor cells were not destroyed by doses of what was presumed to be high-power laser energy. Instead, it was observed that in many cases the skin incisions made to implant the abnormal cells appeared to heal faster in treated animals, compared to incisions of control animals that were not treated with light. Mester was baffled as to how a device that was intended to destroy tumor cells had instead promoted tissue repair. His custom-designed ruby laser was weak and certainly not as powerful as he thought it to be. Instead of being photo-ablative, the low-power light had no effect on the tumor. Indeed, it stimulated the skin to heal faster. This fortuitous encounter opened the field of monochromatic light treatment.

This casual observation led him to design an experiment to ascertain his suspicion that treatment with red light accelerated healing of the surgical skin incisions he made to implant the cells. The experiment was successful as it showed that treatment with red light indeed produced faster healing of the skin wounds. Baffled but fascinated by this development, he carried out

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Professor Endre Mester, MD, DSc (1903-1984)
other experiments in which he showed that experimental skin defects, burns, and human cases of ulcers arising from diabetes, venous insufficiency, and infected wounds also healed faster in response to his laser treatment.\(^5\)^\(^7\)

In direct opposition of contemporary theory that the future of lasers lay solely in the domain of reductive surgery, Mester had discovered a new application of laser energy – repeated low-intensity laser irradiation to determine radio-biological effects. He was the first to describe the “biostimulation” effect of lasers. Following his earlier observations on skin, he developed studies into accelerated healing: hair growth in mice, where depilated skin was prepared for such irradiation studies, appeared to be faster after exposure to laser energies as low as 1 Joule/cm\(^2\) per day.\(^9\)

Experimental research into laser biostimulation continued most actively during a period of 6 years and Mester was awarded a Scientific Doctorate by the Hungarian Academy of Sciences in recognition of his work. His experimental studies showed that many different beneficial effects associated with healing might be due to photobiostimulation.

Mester measured effects of different laser doses on the mucosal surface of dog’s intestinal mucosa. He proved fibroblast activation led to increased collagen production. During healing of vasculitis ulcers in rheumatoid arthritis patients, he observed anti-inflammatory and pain-decreasing effects as well. Measurement of increased phagocytosis in granulocytes was shown to be directly due to the effects of his low-level ruby laser. These observations promoted \textit{in vitro} studies of lymphocytes, where systemic immunological effects were proved. He organized large numbers of collaborator researchers to undertake widespread studies. Results showed different laser effects on anti-inflammatory versus pro-inflammatory prostaglandins, resulting in decreased inflammation.

Since Mester first uncovered the therapeutic value of red light, different wavelengths of light have been shown to promote healing of skin, muscle, nerve, tendon, cartilage, bone, and dental and periodontal tissues.\(^6\)^\(^9\) In studies, when healing appears to be impaired, such tissues respond positively to the appropriate doses of light, especially light that is within 600 to 1,000 nm wavelengths. The evidence suggests that low-energy light speeds many stages of healing as it accelerates inflammation, promotes fibroblast proliferation, enhances the synthesis of type I and type III procollagen mRNA, quickens bone repair and remodeling, promotes re-vascularization of wounds, and accelerates tissue repair in experimental and clinical models.

The inspiration showed by Mester led to many Hungarian workers achieving eminence in the field of low-level laser therapy. His sons Andrew and Adam were co-workers, and Andrew, living in California, published studies about neuro-olfactory biostimulation. Lajos Hazay irradiated urinary bladder ulcers using a low-level laser and a fiber-optic delivery system. Attila Torok began work into duodenal ulcers and treated ulcerative colitis with a similar laser system. Judit Ortuaty published rheumatologic studies. Eniko Korchma published results in oral and dental photobiomodulation. Judit Horvath wrote a book about experiences of a general practitioner using low-level lasers.

Other notable Hungarian workers have achieved success through Endre Mester:
- Lajos Kovacs was awarded a Scientific Doctor title with experimental and clinical studies in gynecology
- Gyorgy Szabo successfully submitted a PhD thesis in ear-nose-throat biostimulation
- Klara Barabas achieved a PhD in experimental and clinical double-blind evaluation of laser treatment of rheumatoid arthritis
- Timea Berki wrote a PhD thesis about immunological effects of laser irradiation on B-lymphocytes
- His elder son Adam Mester completed a PhD thesis about laser irradiation of T-lymphocytes. He is currently head of the National Laser Centre for biostimulation-based wound and arthritis healing in Budapest, Hungary.

It is inappropriate to consider the development of low-level laser therapy without the acknowledgement of many other international researchers and clinicians. Equally, it is pertinent to record that the basic investigations of Mester into a phenomenon known as “biostimulation” have shown that, far from active stimulation, many of the processes observed, such as pain suppression, are in fact inhibition. Therefore, it is now customary to look at the area of low-level laser therapy as “photobiomodulation” (PBM). The Academy of Laser Dentistry is proud of its association with current leaders in the field, such as Jan Tunér and Mary Dyson. The growing interest in PBM in clinical dentistry may lag that shown in other medical disciplines, but opinions are gradually changing in areas outside Eastern Europe and investigations continue to drive the understanding of nonablative, coherent photonic energy as an adjunct to tissue healing.

Professor Endre Mester passed away in 1984. His legacy is that his unforeseen results obtained using a rudimentary laser device has led to a far-reaching and routine treatment modality that is used in all branches of medicine and dentistry on a daily basis.

**AUTHOR BIOGRAPHY**

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Disclosure: Professor Gáspár has no commercial relationships relative to this manuscript.

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Many of the articles in this issue of the Journal discuss wound healing to varying degrees. One generally accepted definition of wound healing identified by Gottrup is “a reaction of any multicellular organism to tissue damage in order to restore the continuity and function of the tissue or organ.” To be sure, wound healing is a dynamic, continuous, interactive process involving cells and extracellular matrix (material produced by cells and excreted to the extracellular space within tissues), and is dependent on numerous internal as well as external processes.

Wound healing may be divided into three phases: inflammation, proliferation or regeneration, and remodeling. Numerous factors affect the entire wound healing process, including individual tissue cells (such as platelets, polymorphonuclear leukocytes, macrophages, fibroblasts, endothelial cells, pericytes or undifferentiated mesenchymal cells, and epithelial cells); blood circulation and oxygenation; infection; presence of foreign bodies; patient characteristics such as age, and indulgences such as smoking and alcohol.

An in-depth discussion of wound healing is beyond the scope of this article. One area of laser-related study has been commanding increasing attention in the literature in recent years: the effect of low-level laser irradiation on growth factors involved in wound healing. As described by Storgård Jenson, growth factors are a group of polypeptides involved in cellular chemotaxis (directional movement of a cell in response to a chemical concentration gradient), differentiation, proliferation, and synthesis of extracellular matrix. Further, all wound healing events in soft and hard tissues are affected by growth factors, which can be released from the traumatized tissue, brought to the area by macrophages or neutrophils, or harbored in the blood clot.

Growth factors may improve wound healing in numerous ways:

- Induce differentiation of mesenchymal precursor cells to mature secreting cells
- Stimulate mitosis of relevant cells, thus increasing proliferation
- Increase angiogenesis (the formation of new blood vessels)
- Affect secretion and breakdown of extracellular matrix components.

The most significant growth factors involved in the wound healing process, along with some of their primary effects and tissue responses, are summarized below:

- **Platelet Derived Growth Factor (PDGF)** stimulates cells proliferation and extracellular matrix production of fibroblasts, contributes to the repair of damaged vascular walls, and activates macrophages to debride the wounded area.
- **Transforming Growth Factors (TGFs)**, most notably the TGF-β subtype, strongly promote extracellular production of many cell types including periodontal ligament fibroblasts, and also help regulate the immune and inflammatory processes.
- **Epidermal Growth Factor (EGF)** encourages cells to continue through the cell cycle, thereby promoting proliferation and wound healing.
- **Insulin-like Growth Factor (IGF)** combines with other growth factors to stimulate fibroblast proliferation, collagen synthesis, bone formation, and epithelialization.
- **Fibroblast Growth Factors (FGFs)** support cell survival under stress conditions and stimulate angiogenesis in the early formation of granulation tissue, and regulate tissue vascularization.
- **Vascular Endothelial Growth Factor (VEGF)** promotes tissue vascularization and angiogenesis in granulation tissue formation during development and repair.
- **Bone Morphogenetic Proteins (BMPs)** commit undifferentiated pluripotential cells to become bone- or cartilage-forming cells.
Shown below are examples of published *in vitro* and *in vivo* animal and human investigations examining the possible effects of low-level laser irradiation on various growth factors involved in wound healing. These and other researchers are building upon the foundation of understanding assembled by Endre Mester and other pioneers of photobiomodulation. As always, clinicians are advised to review the specific indications for use of their lasers and to review their operator manuals for guidance on operating parameters before attempting laser-assisted wound healing techniques on their patients.

**REFERENCE**

Biostimulatory effects of laser irradiation on cell proliferation and wound healing has been reported. However, little is known about the molecular basis of the mechanism. Interleukin 1β (IL-1β), tumor necrotic factor-alpha (TNF-α), and interferon-γ (IFN-γ) play an important role in inflammation, while platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and blood-derived fibroblast growth factor (bFGF) are the most important growth factors of periodontal tissues. The aim of this study was to investigate the effect of low-level He-Ne laser on the gene expression of these mediators in rats' gingiva and mucosal tissues. Twenty male Wistar rats were randomly assigned into four groups (A, A, B, B) in which A and A were cases and B and B were controls. An incision was made on gingiva and mucosa of the labial surface of the rats' mandibular incisors. Group A was irradiated twice with 24 hours interval, while the inflamed tissues of group A were irradiated three times with continuous He-Ne laser (632.8 nm) at a dose of 7.5 J/cm² for 300 s. An energy of 5.1 J was given to the 68 mm² irradiation zone. Rats were killed 30 min after the last irradiation of case and control groups, then excisional biopsy was performed. Gene expression of the cytokines was measured using reverse transcriptase-polymerase chain reaction (RT-PCR) technique. Results were analyzed with Kruskal-Wallis and Mann-Whitney U tests. The gene expression of IL-1β and IFN-γ was significantly inhibited in the test groups (P < 0.05), while the gene expression of PDGF and TGF-β were significantly increased (P < 0.05). The case and control groups did not have a significant difference in the gene expression of TNF-α and bFGF (P > 0.05). These findings suggest that low-level He-Ne laser irradiation decreases the amount of inflammation and accelerates the wound healing process by changing the expression of genes responsible for the production of inflammatory cytokines.

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LOW-INTENSITY LASER IRRADIATION STIMULATES BONE NODULE FORMATION VIA INSULIN-LIKE GROWTH FACTOR-I EXPRESSION IN RAT CALVARIAL CELLS

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Background and Objective: We previously reported that low-intensity laser irradiation stimulated bone nodule formation through enhanced cellular proliferation and differentiation. However, the mechanisms of irradiation are unclear. Thus, we attempted to determine the responsibility of insulin-like growth factor (IGF)-I for the action observed. Study Design/Materials and Methods: Osteoblast-like cells were isolated from fetal rat calvariae and cultured with rat recombinant (r) IGF-I, IGF-I-antibody (Ab), and/or the cells were irradiated once (3.75 J/cm²) with a low-intensity Ga-Al-As laser (830 nm). The number and area of bone nodules formed in the culture were analyzed, and IGF-I expression was also examined. Results: Treatment with rIGF-I significantly stimulated the number and area of bone nodules. This stimulatory effect was quite similar to those by laser irradiation, and this stimulation was abrogated dose-dependently by treatment with IGF-I-Ab. Moreover, laser irradiation significantly increased IGF-I protein and gene expression. Conclusion: The stimulatory effect of bone nodule formation by low-intensity laser irradiation will be at least partly mediated by IGF-I expression.

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Background Data: Low-level laser therapy (LLLT) has been reported to modulate the healing of wounds by inducing an increase in mitotic activity, fibroblast number, synthesis of collagen, and neovascularization. Objective: In the present study we evaluated the effect of LLLT on expression of TGF-β2 and -β3, an immunosuppressive cytokine, at the site of tissue repair, using an experimental rat model to study cutaneous wound healing. In addition, we also investigated the presence of apoptotic cells in epithelial and connective tissue.

Materials and Methods: Thirty male Wistar rats were divided into two groups: group 1, which was subjected to surgical skin wounds only (n = 15), and group 2, which was subjected to surgical skin wounds followed by LLLT (n = 15). In group 2, the LLLT was given with these parameters: 15 mW of power, a dose of 3.8 J/cm², for 15 sec for three applications. At 10 d post-surgery and laser application the animals were sacrificed with an overdose of anesthetic and tissue samples from the wounds were submitted to immunohistochemistry and in-situ detection of apoptosis. Results: Most of the inflammatory cells and fibroblasts were TGF-β2-positive, and many apoptotic epithelial and fibroblasts were seen in the tissue samples from the LLLT-treated animals. However, a few apoptotic epithelial cells and fibroblasts were also seen in the samples obtained from control animals. Conclusion: Our results indicate that LLLT may be an important inducer of apoptosis during the process of tissue repair. In addition, we demonstrated that LLLT has an immunomodulatory effect on TGF-β2 expression at sites of wound healing.

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SUPERPULSED LASER IRRADIATION INCREASES OSTEOBLAST ACTIVITY VIA MODULATION OF BONE MORPHOGENETIC FACTORS

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Objective: To evaluate the efficacy of low-level laser therapy (LLLT) on collateral circulation and microcirculation if a blood vessel is occluded. Background Data: Investigators have attempted prostaglandin and ultrasound therapy to promote improvements in the vascular bed of deprived tissue after an injury, which may lead to occlusion of the blood vessels. Materials and Methods: Thirty-four adult rabbits were used in this study, two of them considered 0-h reading group, while the rest were divided into two equal groups, with 16 rabbits each: control and those treated with LLLT. Conclusions: The stimulatory effect is maximum on day 10, that is, 12-16 h; their levels declined gradually, reaching normal values 72 h after irradiation in the treated group. Numerous collateral blood vessels proliferated the area, with marked increases in the diameters of the original blood vessels. Copyright 2009 Mary Ann Liebert, Inc.

LOW-LEVEL LASER THERAPY ACCELERATES COLLATERAL CIRCULATION AND ENHANCES MICROCIRCULATION

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Background and Objective: Laser therapy is a new approach applicable in different medical fields when bone loss occurs, including orthopedics and dentistry. It has also been used to induce soft-tissue healing, for pain relief, bone, and nerve regeneration. With regard to bone synthesis, laser exposure has been shown to increase osteoblast activity and decrease osteoclast number, by inducing alkaline phosphatase (ALP), osteopontin, and bone sialoprotein expression. Studies have investigated the effects of continuous or pulsed laser irradiation, but no data are yet available on the properties of superpulsed laser irradiation. This study thus aimed to investigate the effect of superpulsed laser irradiation on osteogenic activity of human osteoblast-like cells, paying particular attention to investigating the molecular mechanisms underlying the effects of this type of laser radiation. Study Design/Materials and Methods: Human osteoblast-like MG-63 cells were exposed to 3, 7, or 10 exposures to superpulsed laser irradiation (pulse width 200 nanoseconds, minimum peak power 33 W, average out power 200 mW, frequency 30 kHz, total energy 60 J, exposure time 5 minutes), with an administered dose of 6.7 J/cm². The following parameters were evaluated: cell growth and viability (light microscopy, lactate dehydrogenase release), calcium deposits (Alizarin Red S staining), expression of bone morphogenetic factors (real-time PCR). Results: Superpulsed laser irradiation decreases cell growth, induces expression of TGF-β2, BMP-4, and BMP-7, type I collagen, ALP, and osteocalcin, and increases the size and the number of calcium deposits. The stimulatory effect is maximum on day 10, that is, after seven applications. Conclusions: Reported results show that superpulsed laser irradiation, like the continuous and pulsed counterparts, possesses osteogenic properties, inducing the expression of molecules known to be important mediators of bone formation and, as a consequence, increasing calcium deposits in human MG-63 cells. Moreover, the data suggest a new potential role for PPARγ as a regulator of osteoblast proliferation.
Objective: This study investigated and correlated the kinetic expression of vascular endothelial growth factor (VEGF)-A165 messenger ribonucleic acid (mRNA) with the associated use or not of an infrared laser and a visible red laser during the wound healing in rats.

Background Data: There is a lack of scientific evidence demonstrating the influence of low-level laser therapy (LLLT) on the expression of VEGF mRNA in vivo.

Materials and Methods: Forty-five Wistar rats were randomly allocated to one of three groups: I (n = 5, nonoperated animals), II (n = 25, operated animals), and III (n = 25, animals operated and subjected to laser irradiation). A surgical wound was performed using a scalpel in the right side of the tongue of operated animals. In group III, two sessions of laser irradiation were performed, one right after the surgical procedure (infrared laser, 780 nm, 70 mW, 35 J/cm²) and the other 48 h later (visible red laser, 660 nm, 40 mW, 5 J/cm²). Five animals each were sacrificed 1, 3, 5, and 7 days postoperatively in groups II and III, and samples of tongue tissue were obtained. The animals of group I were sacrificed on day 7. Total RNA was extracted using guanidine-isothiocyanate-phenol-chloroform method. The results of horizontal electrophoresis after reverse transcription polymerase chain reaction permitted the ratio of VEGF-A165 mRNA and glycer-aldehyde 3-phosphate dehydrogenase mRNA expression for groups I, II, and III to be assessed (two-way analysis of variance and Tukey test, p < 0.05).

Results: The expression of VEGF-A165 mRNA in group II (0.770 ± 0.098) was statistically greater than that observed in groups I (0.523 ± 0.164) and III (0.504 ± 0.069) in the first day after surgery (p < 0.05). Significant differences between the groups were not observed in other time periods. Conclusion: LLLT influenced the expression of VEGF-A165 mRNA during wound healing after a surgical procedure on the tongue of Wistar rats.

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