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Light-Emitting Diodes (LEDs) in Dermatology

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Light-emitting diode photobiomodulation is the newest category of nonthermal light therapies to find its way to the dermatologic armamentarium. In this article, we briefly review the literature on the development of this technology, its evolution within esthetic and medical dermatology, and provide practical and technical considerations for use in various conditions. This article also focuses on the specific cell-signaling pathways involved and how the mechanisms at play can be put to use to treat a variety of cutaneous problems as a stand-alone application and/or complementary treatment modality or as one of the best photodynamic therapy light source.

Semin Cutan Med Surg 27:227-238 © 2008 Elsevier Inc. All rights reserved.

Light therapy is one of the oldest therapeutic modalities used to treat various health conditions. Sunlight benefits in treating skin diseases have been exploited for more than thousands of years in ancient Egypt, India, and China. Solar therapy was later rediscovered by Niels Ryberg Finsen (Fig. 1, Fig. 2), a Danish physician and scientist who won in 1903 the Nobel Prize in Physiology or Medicine in recognition of his contribution to the treatment of diseases, notably lupus vulgaris. Phototherapy involving the use of an artificial irradiation source was born.[1]

It was only many years later that light therapeutic benefits were uncovered again using other segments of the electromagnetic spectrum (EMS) with visible and near-infrared wavelengths. In the late 1960s, Endre Mester, a Hungarian physician, began a series of experiments on the carcinogenic potential of lasers by using a low-powered ruby laser (694 nm) on mice. To his surprise, the laser did not cause cancer but improved hair growth that was shaved off the animal's back for the purpose of the experiment. This was the first demonstration of "photobiostimulation" with low-level laser therapy (LLLT), thereby opening a new avenue for medical science. This casual observation prompted him to conduct other studies provided support for the efficacy of red light on wound healing. Since then, medical treatment with coherent-light sources (lasers) and noncoherent light (light-emitting diodes, LEDs) has expanded. The use of LLLT and LEDs is now applied to many thousands of people worldwide each day for various medical conditions.

LED photobiomodulation is the newest category of nonthermal light therapies to find its way to the dermatologic armamentarium and will be the focus of this review. Initial work in this area was mainly developed by National Aeronautics and Space Administration (NASA). NASA research came about as a result of the effects noted when light of a specific wavelength was shown to accelerate plant growth. Because of the deficient level of wound healing experienced by astronauts in zero-gravity space conditions and Navy Seals in submarines under high atmospheric pressure, NASA investigated the use of LED therapy in wound healing and obtained positive results. This research has continued and innovative and powerful LEDs are now used for a variety of conditions ranging from cosmetic indications to skin cancer treatment (as a photodynamic therapy light source).

LED Technology

LEDs are complex semiconductors that convert electrical current into incoherent narrow spectrum light. LEDs have been around since the 1960s but have mostly been relegated to showing the time on an alarm clock or the battery level of a video camera. They have not until recently been used as sources of illumination because, for a long time, they could not produce white light—only red, green, and yellow. Nichia Chemical of Japan changed that in 1993 when it started producing blue LEDs which, combined with red and green, produce white light, opening up a whole new field for the technology. The industry has been quick to exploit it. LEDs are based on semiconductor technology, just like computer processors, and are increasing in brightness, energy efficiency, and longevity at a pace reminiscent of the evolution of computer processors. Emitted light are now available at wavelengths ranging from ultraviolet (UV) to visible to near infrared (NIR) bandwidth (247 to 1300 nm).

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Figure 1 Niels Ryberg Finsen (1860-1904). Courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center.

LED arrays are built using diverse methods each hinging on the manner in which the chips themselves are packaged by the LED semiconductor manufacturer. Examples of packaged, lensed LEDs are t-pack LED and surface mount LEDs (Figs 3-5). These packages can be affixed to a heat-sinking substrate by using either a "through hole" mounting or surface mounting. Through hole mounted devices are often referred to as t-pack LEDs. Importantly, it is also possible to procure wafers of bare, unpackaged chips, also called "dice." By using automated pick-and-place equipment, some manufacturers take such individual chips and affix them to printed circuit boards, creating so-called "chip-on-board" LED arrays. LED array is thus assembled on a printed circuit board. The pins or pads or actual surfaces of the LED chips are attached to conductive tracks on the PCB (printed circuit board). Assemblies built from t-pack LEDs are often unsatisfactory in that they do not always provide sufficiently uniform lighting, are not well heat-sinked, and they are bulky due to the size (several millimeters) of each t-pack device. Nonetheless, for certain applications, t-packs prove to be the most appropriate, cost-effective solution. However, when t-packs cannot provide the required performance, however, chip-on-board emerges as the answer.

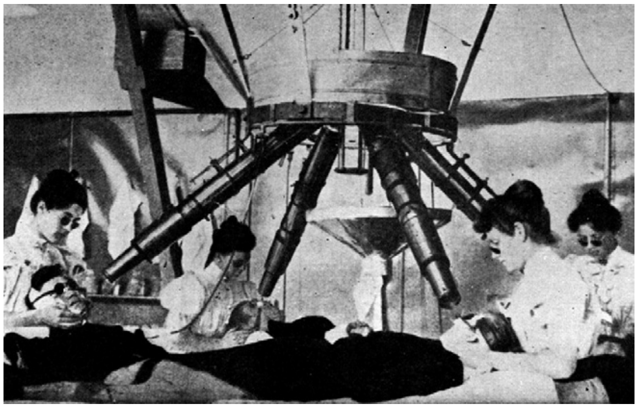


Figure 2 Finsen's phototherapy. Due to expense of carbon arc lighting, single lamp directed light through four water-cooled focusing lenses, allowing several patients to be treated simultaneously. Each patient had nurse attendant to focus light to single small region for

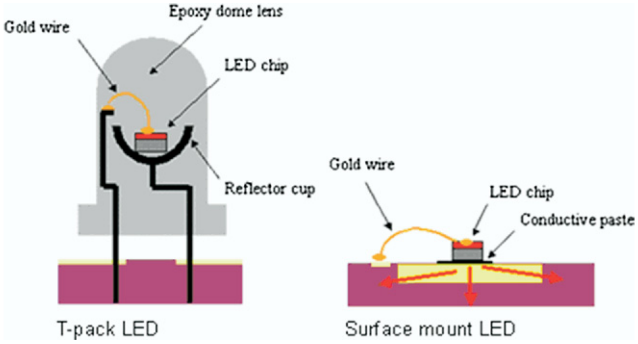


Figure 3 LED technology. The red arrows indicate the flow of heat. Courtesy of Stocker Yale, Inc.

A significant difference between lasers and LEDs is the way the light energy is delivered [optical power output (OPD)]. The peak power output of LEDs is measured in milliwatts, whereas that of lasers is measured in watts. LEDs provide a much gentler delivery of the same wavelengths of light compared to lasers and at a substantially lower energy output. LEDs do not deliver enough power to damage tissues and do not have the same risk of accidental eye damage that lasers do. Visible/NIR-LED light therapy has been deemed a nonsignificant risk by the Food and Drug Administration and has been approved for use in humans. Other advantages over lasers include the possibility to combine wavelengths with an array of various sizes. LED disperses over a greater surface area than lasers and can be used where large areas are targeted, resulting in a faster treatment time.

Mechanism of Action

In the same way that plants use chlorophyll to convert sunlight into plant tissue, LEDs can trigger natural intracellular photobiochemical reactions. To have any effect on a living biological system, LED-emitted photons must be absorbed by a molecular

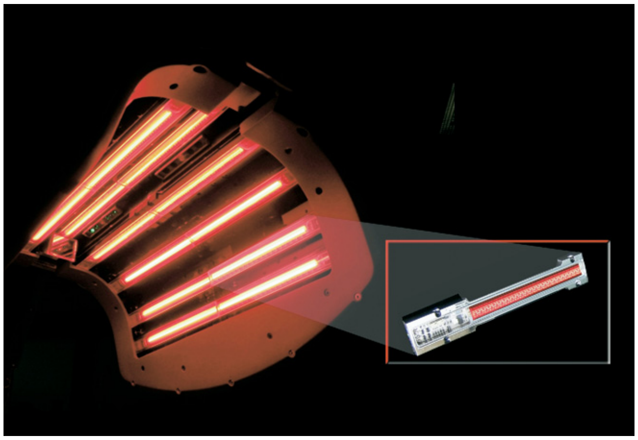


Figure 5 Linear chip-on-board LEDs.

chromophore or photoacceptor. Light, at appropriate doses and wavelengths, is absorbed by chromophores such as porphyrins, flavins, and other light-absorbing entities within the mitochondria and cell membranes of cells.

A growing body of evidence suggests that photobiomodulation mechanism is ascribed to the activation of mitochondrial respiratory chain components resulting in the initiation of a cascade of cellular reactions. It has been postulated that photoacceptors in the red to NIR region are the terminal enzyme of the respiratory chain cytochrome *c* oxidase with 2 copper elements. The first absorption peak is in the red spectrum and the second peak in the NIR range. Seventy-five years ago, Otto Warburg, a German biochemist, was given a Nobel prize for his ingenious work unmasking the enzyme responsible for the critical steps of cell respiration, especially cytochrome oxidase governing the last reaction in this process. Two chemical quirks are exploited: carbon monoxide (CO) that can block respiration by binding to cytochrome oxidase in place of oxygen, and a flash of light that can displace it, allowing oxygen to bind again.

Nowadays, it has been reported that cells often use CO and, to an even greater extent, nitric oxide (NO) binding to cytochrome oxidase to hinder cell respiration.[2] Mitochondria harbor an enzyme that synthesizes NO. So why would cells go out of their way to produce NO right next to the respiratory enzymes? Evolution crafted cytochrome oxidase to bind not only to oxygen but also to NO. One effect of slowing respiration in some locations is to divert oxygen elsewhere in cells and tissues, preventing oxygen sinking to dangerously low levels. Fireflies use a similar strategy to flash light (see section “Pulsing and Continuous Modes”). Respiration is about generating energy but also about generating feedback that allows a cell to monitor and respond to its environment. When respiration is blocked, chemical signals in the form of free radicals or reactive oxygen species are generated. Free radicals had a bad reputation, but now they can be considered signals. The activity of many proteins, or transcription factors, depends, at least in part, on free radicals.[3] These include many proteins such as those involved in the p53 response, between the mitochondria and genes in the nucleus for which we are just beginning to explore the mechanism at play.[4,5] If we can better modulate this signaling, we might be able to influence the life or death of cells in many pathologies as it is more and more demonstrated in its antiaging effects on collagen metabolism.

A recent discovery has revealed that NO eliminates the LLLT-induced increase in the number of cells attached to the glass matrix, supposedly by way of binding NO to cytochrome c oxidase.[6] Cells use NO to regulate respiratory chain processes, resulting in a change in cell metabolism. In turn, in LED-exposed cells like fibroblasts increased ATP production, modulation of reactive oxygen species (such as singlet oxygen species), reduction and prevention of apoptosis, stimulation of angiogenesis, increase of blood flow, and induction of transcription factors are observed. These signal transduction pathways lead to increased cell proliferation and migration (particularly by fibroblasts), modulation in levels of cytokines (eg, interleukins, tumor necrosis factor-α), growth factors and inflammatory mediators, and increases in antiapoptotic proteins.[7]

The photodissociation theory incriminating NO as one of the main players suggests that during an inflammatory process, for example, cytochrome *c* oxidase is clogged up by NO. LED therapy would photodissociate NO or bump it to the extracellular matrix for oxygen to bind back again to cytochrome c oxidase and resume respiratory chain activity. Understanding the mechanisms of cutaneous LED-induced specific cell-signaling pathway modulation will assist in the future design of novel devices with tailored parameters even for the treatment of degenerative pathologies of the skin.

Optimal LED Parameters

In LED, the question is no longer whether it has biological effects but rather what the optimal light parameters are for different uses. Biological effects depend on the parameters of the irradiation such as wavelength, dose (fluence), intensity (power density or irradiance), irradiation time (treatment time), continuous wave or pulsed mode, and for the latter, pulsing patterns. In addition, clinically, such factors as the frequency, intervals between treatments and total number of treatments are to be considered. The prerequisites for effective LED clinical response are discussed hereafter.

Well-Absorbed Deeply Penetrating Wavelength

Light is measured in wavelengths and is expressed in units of nanometers (nm). Different wavelengths have different chromophores and can have various effects on tissue (Fig. 6). Wavelengths are often referred to using their associated color and include blue (400-470 nm), green (470-550 nm), red (630-700 nm) and NIR (700-1200) lights. In general, the longer the wavelength, the deeper the penetration into tissues.[8-10] Depending on the type of tissue, the penetration

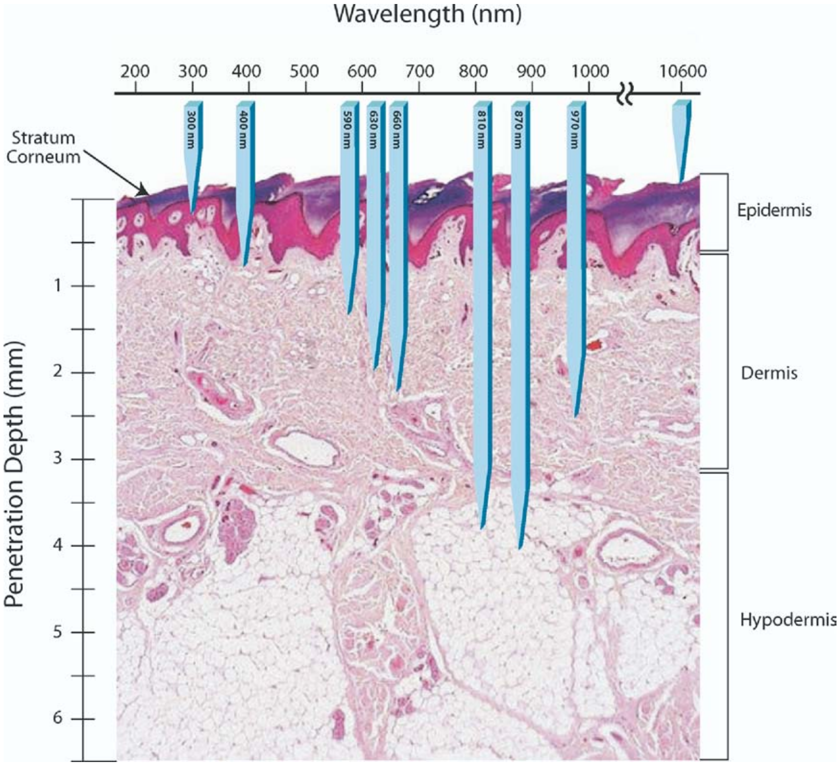


Figure 6 Optical penetration depth.

The various cell and tissue types in the body have their own unique light absorption characteristics, each absorbing light at specific wavelengths. For best effects, the wavelength used should allow for optimal penetration of light in the targeted cells or tissue. Red light can be used successfully for deeper localized target (eg, sebaceous glands), and blue light may be useful for the treatment of skin conditions located within the epidermis in photodynamic therapy (PDT) (eg, actinic keratoses). To reach as many fibroblasts as possible, which is often the aim of LED therapy, a deeply penetrating wavelength is desirable. At 660 nm, for instance, light can achieve such a goal reaching a depth of 2.3 mm in the dermis, therefore covering fibroblasts up to the reticular dermis. The wavelength used should also be within the absorption spectrum of the chromophore or photoacceptor molecule and will often determine for which applications LEDs will be used. Because cytochrome *c* oxidase is the most likely chromophore in LLLT, 2 absorption peaks are considered in the red (~660 nm) and NIR (~850 nm) spectra.[6]

Two major wavelength boundaries exist for LED applications: at wavelengths <600 nm, blood hemoglobin (Hb)

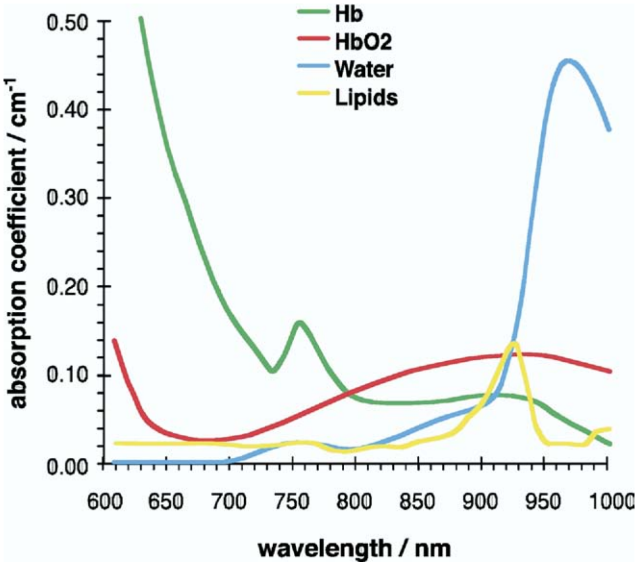
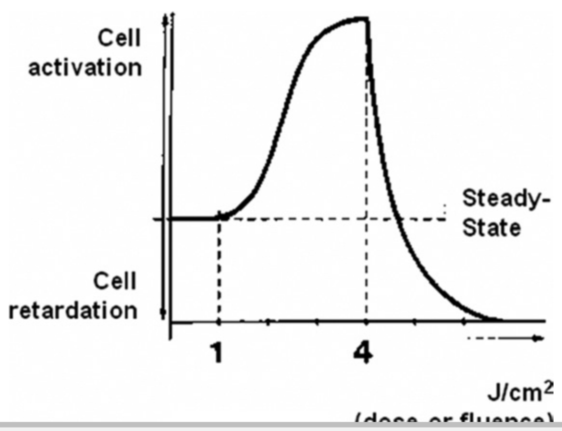


Figure 7 Main tissue constituents absorbing in the 600–1000 nm spectral range. Adapted with permission from Taroni P, Pifferi A, Torricelli



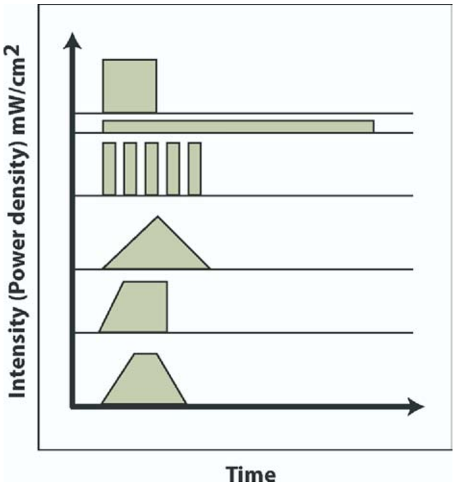


Figure 9 Different light delivery patterns with similar fluence.

is a major obstacle to photon absorption because blood vessels are not compressed during treatment. Futhermore, at wavelengths >1000 nm, water is also absorbing many photons, reducing their availability for specific chromophores located, for instance, in dermal fibroblasts. Between these 2 boundaries, there is a valley of LED possible applications (see Fig. 7).

Fluence and Irradiance

The Arndt-Schulz law states that there is only a narrow window of opportunity where you can actually activate a cellular response using precise sets of parameters, i.e. the fluence or dose (see Fig. 8). The challenge remains to find the appropriate combinations of LED treatment time and irradiance to achieve optimal target tissue effects. Fluence or dose is, indicated in joules per cm^2 (J/cm^2). The law of reciprocity states that the dose is equal to the intensity × time. Therefore, the same exposure should result from reducing duration and increasing light intensity, and vice versa. Reciprocity is assumed and routinely used in LED and LLLT experiments. However, the scientific evidence supporting reciprocity in LED therapy is unclear.[11]

Dose reciprocity effects were examined in a wound healing model and showed that varying irradiance and exposure time to achieve a constant specified energy density affects LED therapy outcomes.[12] In practice, if light intensity (irradiance) is lower than the physiological threshold value for a given target, it does not produce photostimulatory effects even when irradiation time is extended. Moreover, photoinhibitory effects may occur at higher fluences.

In Fig. 9, different light delivery patterns are shown. Interestingly, they are all of the same fluence but over time, the energy of photons does not reach the biological targets in the same way. This may alter the LED biological response significantly. The importance of pulsing will be discussed in the next section.

Certainly a minimal exposure time per treatment is necessary, otherwise, tissue response is evanescent and no clinical outcome is expected. The ideal treatment time has to be tailored according to the skin condition or degree of inflammation present at the time of treatment.

Pulsing and Continuous Modes

Both pulsed wave and continuous wave (CW) modes are available in LED devices, which add to the medical applicability. The influence of CW versus pulsing mode, as well as precise pulsing parameters (eg, duration, interval, pulse per train, pulse train interval), on cellular response has not been fully studied. To date, comparative studies have shown conflicting results.[13] In our own experience, sequentially pulsed optical energy (proprietary pulsing mode with repeated sequences of short pulse trains followed by longer intervals) has been shown to stimulate more collagen production than CW mode.[14]

Under certain conditions, ultra-short pulses can travel deeper into tissues than CW radiation.[15,16] This is because the first part of a powerful pulse may contain enough photons to take all chromophore molecules in the upper tissue layer to excited states, thus literally opening a road for itself into tissue. Moreover, too long a pulse may produce cellular exhaustion whereas too short a pulse may deliver insufficient energy for a biologic effect to occur. Targeted molecules and cells may-on a smaller scale than selective photothermolysis-have their own thermal relaxation times.[14]

The NO photodissociation theory could also be part of the answer, especially the need for pulsing characteristics during LED therapy. Interestingly, fireflies use such pulsing phenomenon. There, oxygen reacts with the luciferyl intermediate to produce a flash of light. The glory is that the flash switches itself off. Light dissociates NO from cytochrome oxidase, allowing oxygen to bind again. Then, the mitochondria consume oxygen once more, allowing the luciferyl intermediate to build up until another wave of NO arrives.[17]

Precise Positioning of Treatment Head

Very precise positioning or working distance is mandatory to ensure optimal beam delivery intensity covering the treatment area so as to achieve maximum physiological effects. Accurate positioning ensures that the proper amount of photons is delivered to the treated skin to avoid hot or cold spots in the treatment field. This is especially important in photobiology as a required amount of energy must be delivered to the target to trigger the expected cell response. If insufficient photons reach the target, no cell response will result. Some LED devices even provide optical positioning systems to allow reproducible treatment distance within precise limits (±3 mm).

Timing of Treatments Outcomes

There are some indications that cellular responses after light irradiation are time dependent. A recent study suggests that responses such as ATP viability can be observed directly (1

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