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Photobiomodulation or low-level laser therapy

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It is not often that the globally accepted name of a scientific field has changed between the time at which a journal commissions a special issue and the time at which the actual issue goes to press. Such has been the case here. Low-level laser (light) therapy (formerly abbreviated as LLLT) is approaching its 50th anniversary. LLLT was discovered in 1967 by Endre Mester at the Semmelweis Medical University in Hungary. Mester was trying to repeat an experiment first conducted by Paul McGuff in Boston USA, who had successfully used the newly discovered ruby laser to cure malignant tumors in rats [1]. However, Mester's custom-made ruby laser possessed only a very small fraction of the power possessed by McGuff's laser. Despite not curing any tumors with his low-power laser beam, he did observe a heightened rate of hair growth and better wound healing in the rats in which he had surgically implanted tumors. This was the first indication that low-level laser light (rather than high power thermal lasers) could have its own beneficial applications in medicine [2, 3].

Since those early days, it has been consistently found that one did not, in fact, need to use a coherent monochromatic laser to obtain these beneficial biological effects, but rather non-coherent light-emitting diodes (LEDs) with comparable parameters to low power lasers performed equally well. Considering that lasers were shown not to be necessary, the fact that "low-level" was considered a subjective term and nobody knew exactly what the term "low" actually meant, the fact that both inhibition as well as stimulation of biological processes could be therapeutically useful, the decision was eventually made to change the name to "photobiomodulation (therapy)" abbreviated PBM(T) depending on whether the process or a treatment is being discussed [4].

Photobiomodulation has made, and is continuing to make, major progress in obtaining recognition from authorities in medical schools, scholarly journals, the popular press and media, medical practitioners, therapists and other bodies concerned with biomedical science. This progress was very necessary as only about ten years ago the general consensus was that LLLT was "snake oil" and only practised by charlatans. Several influential "systematic reviews" including the Cochrane Database Organization concluded that LLLT had found "no reliable evidence" for efficacy in diseases such as osteoarthritis, rheumatoid arthritis, etc. [5]. Another problem involved the prevailing use of a wide variety of different kinds of light sources (medical devices) and treatment protocols including, illumination parameters (such as: wavelength, fluence, power density, pulse structure, etc.) and the fact that there was no agreement on the treatment schedule. Unfortunately, these variations in study designs led to

an increase in the number of negative trials that were published and created some controversy, despite the overwhelming number of positive clinical results that were also obtained [6].

This change in perception that has occurred in recent years can be attributed to several factors, but perhaps the most important among these considerations is the progress that has been made in understanding the mechanisms of action at a molecular, cellular and tissue-based level [7]. The work of Tiina Karu in Russia was instrumental in putting the mechanism on a sound footing by identifying cytochrome c oxidase in the mitochondrial respiratory chain as a primary chromophore, and it introduced the concept of “retrograde mitochondrial signalling” to explain how a single relatively brief exposure to light could have effects on the organism that lasted for hours, days or even weeks [8].

Several professional and learned societies are now wholly devoted to photobiomodulation: World Association of Laser Therapy (WALT); North American Association for Photobiomodulation Therapy (NAALT); or partly devoted: SPIE Photonics West; American Society of Lasers in Medicine and Surgery (ASLMS); and (soon) Optical Society of America (OSA).

Many different diseases, conditions, and fields of medical treatment are now becoming amenable to the beneficial effects of PBM [9]. Several of these innovative applications are discussed in papers included in this special issue of Journal of Biophotonics. It is abundantly clear from surveying the countries of origin of many of the papers included in this issue, that Brazil (11 out of 15 contributions) has a remarkable number of productive laboratories investigating PBM-related topics.

Advances have been made in cell culture studies that have gone a great distance towards elucidating the mechanisms of action of PBM that previously was largely considered a “black box”. This lack of mechanism was often quoted by detractors as a reason why PBM should not be taken seriously. There are several studies related to *in vitro* studies in cell culture in the present special issue. A contribution from the Rogers laboratory at the Harvard School of Public Health looks at cochlear hair cells, which are of critical importance to loss of hearing, a disease increasingly being treated with PBM [p. 1125]. A study from the UNINOVE Biophotonics Program in Brazil shows that oral squamous carcinoma cells can be induced by light to become bone-destroying osteoclasts [p. 1136]. A paper from Praveen Arany at University of Buffalo Dental School investigates differences in the response of cells to light, looking at keratinocytes and fibroblasts subjected to PBM at different power densities which could possibly cause damage [p. 1148]. The study from Martha Ribeiro, also in Brazil, reports that PBM might be able to enhance radiotherapy treatment of cancer cells *in vitro* [p. 1157]. Another *in vitro* study from Jared Jagdeo at UC Davis showed that using PBM (especially at high fluences) on fibroblasts may be able to reduce skin fibrosis [p. 1167]. An interesting study from Felipe Sperandio showed that when human neutrophils were treated with PBM *in vitro* their ability to kill fungal cells by production of reactive oxygen species was increased [p. 1180]. PBM may therefore have a role to play in increasing the host resistance to fungal infections.

Another Brazilian contribution from Antonio Tedesco looks at the effects of photodynamic therapy with a nanoemulsion of chloroalumium phthalocyanine on explanted human skin biopsies (p. 1189). Since the effects found were broadly comparable to those found with PBM (light alone) this data reinforces the role of reactive oxygen species in the PBM mechanism.

A paper from Vivian Cury (also in Sao Paulo) shows that PBM can be effective in a mouse model of lung inflammation caused by intra-tracheal lipopolysaccharide [p. 1199]. Another report from Sao Paulo (Flavio Aimbire) studied the same problem of lung inflammation using a different mouse model, namely allergic sensitization with ovalbumin [p. 1208]. They found that PBM reduced leukocyte-attractant chemokines and boosted endogenous antioxidants. A second paper from the Ribeiro laboratory investigates the use of PBM relevant to the field of dentistry, looking at orthodontic tooth movement and bone metabolism in rats [p. 1222].

PBM is becoming a candidate platform approach that can be used to mitigate the side-effects of cancer therapy (radiotherapy and/or chemotherapy). One of the most debilitating of these side effects is oral mucositis that can not only be extremely painful but can also prevent patients from taking normal nourishment. A study from Alyne Simões demonstrated that PBM (using either high power laser or LEDs) could mitigate chemotherapy-induced oral mucositis in hamsters [p. 1236].

Two papers address one of the fastest growing medical problems in the modern world: the problem of diabetes which is rapidly assuming the proportions of an epidemic. A second study from Alyne Simoes used PBM on the salivary glands of diabetic rats and showed that blood glucose levels were reduced and insulin resistance was decreased [p. 1246]. A third paper from the Ribeiro laboratory used PBM directed to the abdominal area of obese hyperglycemic mice, and found reduced inflammatory infiltrate in the adipose tissue [p. 1255]. Chronic inflammation is one of the pathological abnormalities responsible for many of the adverse health effects of morbid obesity.

A report from my laboratory by Weijun Xuan continued a series of studies we have conducted on mouse models of traumatic brain injury [p. 1263]. A series of 14 daily PBM treatments initially appeared to be excessive, but the beneficial effects were not completely abrogated, but only delayed for several weeks. The reason for this delay in the response was found to be a temporary increase in neuroinflammation caused by too many PBM treatments.

Finally a review from Cleber Ferraresi (also in Brazil) reviews a large number of papers that have investigated PBM to increase muscle performance in humans [p. 1273]. Many of these studies have been conducted in athletes, where PBM can improve acute muscle performance and reduce muscle damage after exercise. PBM may also be used to advantage during a program of athletic training.

In conclusion it can justly be said that, after decades confined to the “scientific wasteland”, PBM may be finally emerging into the light of day (pun intended).

Biography

Michael R. Hamblin, Ph.D., is a principal investigator at the Wellman Center for Photomedicine at Massachusetts General Hospital, an associate professor of dermatology at Harvard Medical School, and a member of the affiliated faculty of the Harvard-MIT Division of Health Science and Technology. His research interests lie in the areas of photodynamic therapy (PDT) for infections, cancer, and stimulation of the immune system and in low-level light therapy or photobiomodulation for wound healing, traumatic brain injuries, neurodegenerative diseases, and psychiatric disorders. He directs a laboratory of around a dozen postdoctoral fellows, visiting scientists, and graduate students. His research program is supported by the NIH, CDMRP, USAFOSR, and CIMIT, among other funding agencies. He has published more than 340 peer-reviewed articles and more than 150 conference proceedings, book chapters, and international abstracts and holds 8 patents. He is an associate editor and editorial board member on numerous journals and serves on NIH study sections. For the past several years, Dr. Hamblin has chaired the annual conference at SPIE Photonics West entitled “Mechanisms for photobiomodulation therapy” and has edited proceedings, volumes, and major textbooks on PDT and photomedicine. In 2011 Dr. Hamblin was honored by election as a fellow of SPIE.

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