Phototherapy: From Ancient Egypt to the New Millennium

Antony F. McDonagh, PhD

Phototherapy with ultraviolet light was widely and successfully used in the past for treatment of a variety of diseases. Phototherapy with visible light alone has no benefit except in the therapy and prophylaxis of unconjugated hyperbilirubinemia. For this purpose, radiation in the region of ~480 to 500 nm is most effective and radiation above ~550 nm is useless. The principle effect of the treatment is not photodegradation of bilirubin, but conversion of the pigment to structural isomers that are more polar and more readily excreted than the normal, more toxic "dark" form of the pigment. This, coupled with some photooxidation of bilirubin, diminishes the overall pool of bilirubin in the body and lowers plasma levels. In the future, phototherapy may be supplanted by pharmacologic treatment, but in the near future, the most likely advance will be the introduction of novel forms of light production and delivery.

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INTRODUCTION

Phototherapy is the use of light for the treatment and prevention of disease. The term is not usually considered to include treatments in which intense light, such as laser light, is used solely to ablate, anneal, or cauterize tissues, and it should be distinguished from photochemotherapy or photodynamic therapy, in which light is used in conjunction with some photosensitizing agent. Strictly speaking, phototherapy refers to the use of visible radiation (from ~400 to 760 nm), but the word is also used to include treatments that use infrared or ultraviolet radiation lying outside the visible region of the spectrum.

HISTORY

Until very recent times, the only sources of light were fire, luminescent organisms, and the sun. As the first two are too weak to

induce significant phototherapeutic responses, heliotherapy was the only possible form of phototherapy up until the end of the 19th century. From the time of the Pharaohs, most ancient civilizations and cultures have worshipped the sun or sun gods and appear to have made some connection between sunlight and health.^{1,2} The use of sunbaths by the ancient Romans and Greeks for maintaining general health and for therapeutic purposes is particularly well documented. Whether connections between specific disorders and sunlight exposure were ever made by these ancient cultures is difficult to know, but certainly sunlight can be used successfully to treat many skin disorders.³ If nothing else, heliotherapy would have had an antirachitic and bactericidal action.

In ancient China, what has been termed heliotherapy was one of the immortalizing techniques of early Daoism, introduced by Lingyan Tzu-Ming in the first century AD during the Han dynasty.⁴ One technique, described about four centuries later during the Tang dynasty, was to stand in early morning sunshine holding in the right hand a piece of green paper on which 日, the character for the sun, was written in red circumscribed by a red rectangle. At the end of the ritual, the insolated paper was shredded in water and consumed in an attempt to trap some of the essence of the sun in the body. Curiously, this technique was used only by men; women were instructed to follow a somewhat similar procedure, but in moonlight!

Despite these early practices of sunbathing and heliotherapy, the scientific foundations for modern phototherapy were not laid until the end of the Ming and beginning of the Qing dynasties in the 17th and 18th centuries. Seminal were the observations by Sir Isaac Newton in England of the refraction of sunlight into its component colors by a prism (1666), the recognition of the wave nature of light by Christian Huygens in Holland (1678), and the discoveries by Sir Frederick Herschel (1800) in England and Johann Ritter (1801) in Germany of the infrared and ultraviolet components of sunlight that are invisible to the eye. Then, near the end of the 19th century, Arthur Downes and Thomas Blunt (1877) in England showed that the ultraviolet (actinic) component of sunlight is lethal to bacteria and other microorganisms,⁵ thus providing the first link between sunlight and human disease and the basis for the extensive clinical use of phototherapy for the following 60 to 70 years.

The pioneer of modern clinical phototherapy was Nobel Laureate Niels Finsen. His early publications dealt with the use of red light to prevent suppuration and scarring in patients with smallpox.⁶ Probably unknown to Finsen, this method had appeared much earlier in the *Rosa Medicinæ*, the first printed medical pharmacopoeia in the English language written by John of

Division of Gastroenterology and the Liver Center, University of California — San Francisco, San Francisco, CA.

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Address correspondence to Antony F. McDonagh, PhD, Division of Gastroenterology and the Liver Center, Room S-357, Box 0538, University of California — San Francisco, San Francisco, CA 94143-0538.

Gaddesden in England in the 14th century. It was not really phototherapy, as it depended for its questionable success only on the exclusion of all ultraviolet and visible radiation except for red light or candlelight. Soon, however, Finsen turned to real phototherapy, in particular for treatment of tubercular infections of the skin (*lupus vulgaris*). As a light source, he first used the sun and designed devices containing quartz lenses and filters that removed infrared and visible radiation and focused the bactericidal ultraviolet component on the lesion being treated. Sunlight was soon replaced by carbon arc lamps, an inefficient source of ultraviolet radiation. Eventually these were replaced by much more convenient sealed quartz mercury-vapor lamps cooled by water or air. From *lupus vulgaris*, the use of phototherapy then spread to the treatment of two other scourges of the Northern European industrial revolution: pulmonary tuberculosis and rickets. Again, heliotherapy, preferably at high altitudes, was used at first and then supplanted by artificial ultraviolet light sources. By the end of the first quarter of the 20th century, the clinical use of phototherapy in northern Europe and northern cities of North America was extensive.

The gradual introduction of antibacterial agents eventually made phototherapy for tubercular diseases redundant, but it did not diminish the medical use of phototherapy because the emphasis shifted from therapeutic use to prophylactic use for prevention of rickets or just to maintain general health. In some places phototherapy was used on an industrial scale. For example, The Spalding School for Crippled Children in Chicago had a device that could treat some 250 children per hour,¹ and in 1953 in the heavily polluted densely populated cities of Manchester and Glasgow in the United Kingdom over 34,000 light treatments were given to children.⁷ (In the 1930s, ultraviolet light was advocated, and even actually used, as a method for branding newborn babies and their mothers in hospital for identification purposes!*) Gradually, however, with improvements in social conditions, air quality, and diet; the introduction of drug therapy; and the increasing recognition that ultraviolet radiation might cause skin cancers, this type of phototherapy disappeared from general clinical use. Today ultraviolet phototherapy is still used in dermatology, often in combination with a sensitizing agent (photochemotherapy).

The increasing use of ultraviolet phototherapy from the Finsen era to the 1950s was paralleled by claims for the therapeutic benefits of various types of visible light phototherapy. However, proponents of this type of phototherapy were predominantly cranks and charlatans. One of the earliest was a retired American Civil War general, Augustus J. Pleasonton, who, in 1876, published a blue book with blue print and a very long title that advocated the use of blue light for treatment of disease, relief of pain, and improving the growth of crops and cattle.⁹ Another was the physician John Harvey Kellogg of Battle Creek, Michigan, inventor of the word granola, developer of cornflakes, and cofounder, with his brother, of the now multinational Kellogg Company. He devised various types of apparatus for local or

whole-body exposure of patients to visible light.¹⁰ These contained only incandescent tungsten filament lights, and any perceived benefit was undoubtedly caused by infrared thermal effects rather than by the visible component of the light. Perhaps the most colorful of these chromopaths was Dinshah Ghadiali who founded the Spectrochrome Institute of Malaga, New Jersey, and drew the wrath of the American medical establishment and the newly founded Food and Drug Administration with his claims to have cured a variety of diseases with his Spectro-Chrome instrument.^{11,12} This instrument was simply a box containing a tungsten light bulb and fitted with colored filters. He was reported to have sold more than 9000 of these instruments along with various ancillary equipment and training courses. Although Dinshah Ghadiali was eventually put out of business, at least temporarily, one of his sons continued his mission and the Dinshah Health Society is still proselytizing, particularly through the World Wide Web.

The recent fashion for "alternative" and "holistic" medicine has been accompanied by a revived interest in various forms of color therapy and the publication and reprinting of many scientifically nonsensical books on these treatments. The limited acceptance of acupuncture by the occidental medical establishment together with the increased Western public interest in oriental medicine has also led to a new hybrid of acupuncture and color therapy, sometimes referred to as "colorpuncture." In colorpuncture, light of specific colors is aimed at specific acupuncture points or meridians for general "healing" or to treat specific diseases. Various expensive types of devices for doing this are now marketed, some simply containing inexpensive red light-emitting diodes (LEDs) or diode lasers of the sort used in laser pointers, others being ordinary flashlights with colored tips.

Despite what may be claimed, these types of phototherapy or color therapy are invariably worthless and not based on firm scientific data. Any beneficial effects can be ascribed to placebo effects or local thermal stimulation of the circulation. Although not harmful, they cannot be considered harmless because they may persuade patients with serious illnesses to abandon conventional treatment in favor of some ineffective color therapy, just as Ghadiali advised diabetics to abandon insulin in favor of phototherapy.¹¹

In their zeal for "alternative medicine," the many proponents of quack color treatments invariably overlook fundamental laws of photobiology and photochemistry. There are simple scientific reasons why these treatments rarely have any beneficial therapeutic effect, and those same reasons account for the success, safety, and uniqueness of phototherapy for neonatal jaundice. For light to have a therapeutic effect, it must first be absorbed by a chromophore molecule in the body. Absorption leads to transient excitation of the chromophore to a higher energy level. Second, excitation must lead to a therapeutically useful photochemical reaction. However, most molecules in the body are colorless, do not absorb light in the visible region of the spectrum, and do not

undergo photoexcitation. Therefore, they are totally unaffected by phototherapy with visible light. Apart from the photoreceptor pigments in the eye, the principal compounds that do absorb visible light are melanin- and heme-containing proteins; however, these do not undergo photochemical reactions *in vivo* on excitation with visible light and are photobiologically inert. In addition, the longer lower-energy wavelengths of visible light can cause only vibrational excitation of chemical bonds and do not generally lead to photochemical reactions. Therefore, it is not surprising that color therapy with visible light — whether red, orange, yellow, green, blue, indigo, violet, or white — rarely has any beneficial physiologic effect. The unique exception is phototherapy of neonatal jaundice.

PHOTOTHERAPY FOR UNCONJUGATED HYPERBILIRUBINEMIA

This form of phototherapy was introduced by Cremer et al.¹³ in 1958, but it was not widely adopted until further studies by Lucey et al.¹⁴ nearly a decade later proved its safety and efficacy. Originally introduced to reduce the need for exchange transfusions, it is now used both therapeutically and prophylactically in neonates and has been a lifesaver for people with severe forms of Crigler–Najjar syndrome, a rare metabolic disease. Its discovery was not based on sound scientific principles, but was largely serendipitous. It stemmed from the careless accidental exposure of some blood to sunlight, an astute incidental observation by a nurse, and an unwarranted extrapolation from *in vitro* to *in vivo* data.^{13,15} The accidental exposure of the blood sample led to the finding that bilirubin in serum undergoes oxidation to biliverdin and degradation to colorless compounds when exposed to light *in vitro*. The observation by the nurse, Sister J. Ward, was that the skin of jaundiced infants becomes bleached on exposure to sunlight, whereas unexposed skin does not.

Putting these two observations together and oblivious of the danger in extrapolating from *in vitro* to *in vivo* photochemistry, the investigators then tested whether exposure to sunlight would oxidize or degrade bilirubin *in vivo* in a jaundiced infant. They found that sunlight exposure did indeed lower the serum bilirubin concentration of icteric newborns and, further, that the same effect could be achieved using blue fluorescent light in lieu of sunlight. They assumed, reasonably enough, that the processes leading to bilirubin disappearance in the *in vitro* and *in vivo* experiments were the same. However, consistency between experimental data and a mechanistic hypothesis is never adequate proof of the latter. Nonetheless, for years thereafter (and even today) it was generally accepted that photodegradation of bilirubin (and/or photooxidation to biliverdin) is responsible for the effectiveness of phototherapy. There is, however, now much evidence that photodegradation of bilirubin plays a relatively minor role in the treatment and that by concentrating on photooxidation and overirradiating solutions in their *in vitro*

studies, early investigators missed the most interesting and magical aspect of phototherapy.

We now know that phototherapy causes photochemical reactions that change the shape, but not the constitution, of bilirubin and that are not degradative or oxidative in nature. In contrast to photo-oxidation, which is a slow process, these reactions are relatively much faster and more efficient. They produce two families of mutant bilirubin isomers (Figure 1) and are somewhat similar to the photochemical reactions undergone by rhodopsin in the retina of the eye, provitamin D₃ in skin, and phytochrome in plants. The photochemically produced isomers differ from the parent isomer of bilirubin in two important respects: They are more polar, and they can be excreted from the liver into bile with undergoing conjugation. Furthermore, unlike bilirubin glucuronides, they do not require the presence of the canalicular multispecific organic anion transporter cMOAT (alias MRP2) for their efficient excretion from the liver into bile.

Production and excretion of bilirubin isomers *in vivo* can be strikingly demonstrated with the Gunn rat model. Gunn rats have a genetic defect in bilirubin metabolism. Homozygous animals lack the glucuronosyl transferase enzyme that is required for conjugation of bilirubin and facilitation of its canalicular secretion into bile. Consequently, bilirubin glucuronides are absent from Gunn rat bile and the animals exhibit lifelong unconjugated hyperbilirubinemia. Figure 2 shows the analysis by high-pressure liquid chromatography (HPLC) of bile samples taken from a jaundiced adult Gunn rat before and after exposure to blue fluorescent phototherapy lights. The bile samples were collected from an implanted bile duct catheter, the back of the animal was shaved and depilated to expose the skin to the light, and the HPLC detector was set at ~450 nm to visualize yellow pigments. Because of the instability of bile pigments, special precautions

Figure 1. Chemical structures of bilirubin (**6**) and its five photoisomers. The structures are numbered in order of increasing lipophilicity.

Figure 2. HPLC chromatograms of bile from a homozygous Gunn rat before (lower) and after (upper) 60-minute exposure of the animal to blue light. Numbers above the upper chromatogram refer to the chemical structures in Fig. 1. Because isomers of bilirubin do not have identical extinction coefficients at 450 nm the relative heights or areas of the peaks in the upper chromatogram do not reflect accurately the relative amounts of the individual photoisomers present. The two minor peaks near 9 minutes in the lower chromatogram are not photoisomers of bilirubin, though they have similar retention times. The apparent increase in the biliary concentration of the normal isomer of bilirubin (**6**) during phototherapy (upper chromatogram) is an artefact caused by thermal reversion of photoisomers **4** and **5** back to **6** during their passage down the short biliary cannula.

were taken in the collection and manipulation of samples. As shown in Figure 2, bile collected before the light was switched on showed only weak peaks in the HPLC chromatogram. But, within minutes of switching on the light new peaks were detectable in chromatograms of bile. These peaks increased in intensity with time, eventually reaching a constant photostationary state after about 1.5 hours. All of the emergent peaks have been identified as isomers of bilirubin and their identities are indicated in the figure.

Experiments such as that shown in Figure 2 prove that the response to phototherapy is immediate, even though the attendant decrease in circulating bilirubin levels might not be immediately detectable, and that there is no lower light threshold for phototherapy. Because of the optics of the skin and the absorbance and photochemical properties of bilirubin, the best wavelengths to use for phototherapy seem to be in the blue-green region near ~480 to 500 nm, as used in some of the earliest studies.¹⁶ Although the relative amounts of individual bilirubin photoisomers produced in humans during phototherapy are different from those produced in the rat, the basic mechanisms in the two species seem to be the same.

Thus, most evidence suggests that phototherapy works principally by converting bilirubin to less lipophilic isomers that are excreted more readily in urine and bile and to a lesser extent by degrading bilirubin to colorless water soluble degradation products that are excreted in urine. If the phototherapy is intense enough, this rapid light-stimulated excretion of isomers and degradation products of bilirubin leads to a significant decrease in the total amount of bilirubin present in the body and eventually to a decrease in plasma levels. Photoisomerization of bilirubin is not restricted to patients with hyperbilirubinemia undergoing phototherapy, but occurs in anyone exposed to sunlight or to artificial light with emission in the blue region of the spectrum. This phenomenon can be seen in patients with Gilbert's syndrome. Their blood (at least, in California) invariably contains bilirubin photoisomers in addition to the parent form of the unconjugated pigment. Thus, phototherapy can be considered to be an extension of a natural process that has always taken place in humans. And, if blue or blue green light is used, phototherapy is completely specific. Unfortunately, it is cumbersome and often does not lower plasma bilirubin concentrations as rapidly as desired.

When Daoists practiced heliotherapy during the Han and Tang dynasties they were attempting to immortalize themselves by capturing the Qi (气) of the sun.⁴ In phototherapy, it is bilirubin that captures a specific component of the Qi, the energy, of light, thereby undergoing a therapeutically useful change in structure and metabolism. Although phototherapy does not immortalize patients, it has saved many from shedding their mortal coil prematurely.

FUTURE PROSPECTS

For the immediate future, the therapeutic and diagnostic applications of light in medicine will likely continue to grow, particularly in the areas of imaging and photochemotherapy. Phototherapy of neonatal jaundice is now so well entrenched in pediatric care, so easy to use, and so safe that its demise in the near future is unlikely. Its main challenge is likely to come from nonphotochemical methods for preventing accumulation of unconjugated bilirubin. Four approaches to doing this can be envisaged, based on the metabolic pathway by which bilirubin is synthesized and excreted (Figure 3).

Figure 3. Overall pathway of heme and bilirubin metabolism.

Heme Oxygenase Inhibitors

Heme oxygenase is the enzyme that cleaves heme to give biliverdin, the immediate precursor of bilirubin. Heme oxygenase inhibitors would block heme catabolism and prevent bilirubin formation. Such inhibitors have already been developed and tested clinically, but have yet to find favor with most neonatologists. The most effective one to date is the heme analog, tin-mesoporphyrin.¹⁷ Although effective at low doses and rapidly cleared from plasma, it has a prolonged half-life in the body and can cause photosensitivity. A particular concern about heme oxygenase inhibitors is that they might upset the homeostasis of heme, which is a vital component of a multitude of essential heme proteins.

Biliverdin Reductase Inhibitors

The abundant cytoplasmic enzyme biliverdin reductase catalyzes the conversion of biliverdin to bilirubin. Preventing bilirubin formation by inhibiting biliverdin reduction is a therapeutically more appealing strategy than inhibiting heme oxygenase because it would not interfere with heme catabolism and homeostasis of heme, but would still prevent bilirubin formation. In addition, unreduced biliverdin would not accumulate because it is readily excreted in bile and urine without the need for conjugation. Unfortunately, no suitable biliverdin reductase inhibitor has yet been developed. Hopefully, the recent elucidation of the crystal structures of two biliverdin reductase enzymes will encourage research in this area.^{18,19}

“Photon Analogs”

Research on phototherapy and on the metabolism of bilirubin and bilirubin model compounds has shown that rather small changes in the three-dimensional structure of the bilirubin molecule make it easily excretable in bile. Studies have also shown that the NH and lactam C=O groups in the two component halves of bilirubin are well disposed for hydrogen bonding. Therefore, it is not preposterous to suggest that it might be possible to design a compound that would bind specifically to bilirubin in vivo and change the structure of the pigment in such a way as to make the hydrogen-bonded complex a substrate for the MRP2 canalicular transporter or polar enough to be excreted into bile or urine without the need for a transporter. Such a compound would achieve in the dark what photons of blue light do during phototherapy.

Implantable Reactors

Neonates develop jaundice because they have a transient deficiency of UGT1.1, the enzyme that glucuronidates bilirubin and its monoglucuronides. Although the technology is not yet available, it is possible to envisage the development of a miniature implantable removable bioreactor containing immobilized UGT1.1 that would serve to conjugate enough bilirubin to reduce its blood level to a safe range.

Although these future developments are highly speculative, it is more certain that the design and technology of phototherapy

equipment will change. The basic technology of phototherapy lights has not changed since the treatment began. This is largely because the basic technology of interior lighting has not changed much during the same period. Fluorescent mercury-vapor discharge tubes were used for the first phototherapy studies and they continue to be used today. Incandescent filament light sources are also used, with the light being delivered through filters and fiber optic devices, but the efficiency of such sources is notoriously low. They generate large amounts of heat, and their spectral output is not rich in the wavelengths that are most effective for phototherapy. However, in the last few years there has been a significant advance in lighting technology with the development of bright light-emitting diodes (LEDs). LEDs convert electrical energy to light energy much more efficiently than fluorescent tubes or incandescent filament devices. They have a long lifetime, emit little heat, and inexpensive LEDs are now available that emit in the wavelength region that is best for phototherapy. Of course, the power output from a single LED is low. But groups of them can be wired together to give arrays that vie with fluorescent tubes in light intensity. Because they do not emit infrared or ultraviolet radiation, these arrays could be placed very close to the infant. Further, it may be possible to shape such lights to the patient's body, leading to more efficient and convenient phototherapy and abrogating the need for eye protection. Prototype LED units have already been introduced and tested²⁰ and it is likely that most phototherapy units of the future will use lights based on semiconductor or other emergent luminescent technologies.

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