THE CURATIVE LIGHT

Whether from the sun or medical lamps, its healing properties are starting to shine.

by Michael Shodell

Babies, naked in their bassinets but for a narrow swath of bandages protecting their eyes, lie in pediatric wards bathed in the bright blue glow from encasing domes of fluorescent bulbs. In other hospital wards, patients enter tiny, windowless rooms with walls covered by banks of lamps for a treatment combining an ancient Egyptian remedy with the latest concepts in photobiology. And in the oncology wing optic fibers probe cancer patients, first to detect malignant growths and then to destroy them. In a variety of ways, scientists are turning the power of light, one of mankind's oldest symbols of beneficence and renewal, toward the cure of disease.

The blindfolded babies in the blue-illumed bassinets are receiving phototherapy for a common but potentially lethal condition known as neonatal jaundice, a form of hyperbilirubinemia. Hyperbilirubinemia denotes higher than usual levels of bilirubin in the blood. Bilirubin, a red pigment in bile, arises naturally as part of the process by which massive numbers of old, worn-out red blood cells are replaced by the fresh new ones continuously produced in the bone marrow. Adult livers usually have no problem disposing of bilirubin along with the used red blood cells, but the livers of newborns—premature babies in particular—are generally not yet fully functional. Just about every new baby has some degree of elevated bilirubin level, with its symptomatic jaundice. The real problem is that the buildup can easily reach dangerous levels. At very high levels, bilirubin can accumulate around the cells of the central nervous system, leading to extensive neural damage and possibly even death. But in most cases, basking in blue light is all they need.

The salubrious effect of light on this condition was discovered accidentally in a small premature baby unit in Rochford, England, during the mid-1950s. The nurse in charge of the Rochford unit, Sister Ward, was a firm believer in the benefits of fresh air and sunshine and took her tiny, yellowing charges out for nude basks in the sun whenever weather permitted. During an examination of one of these infants recently returned from an outing, the resident pediatrician, R.H. Dobbs, found a strange, triangular patch of yellow on the baby's abdomen. The significance was not that this part of the baby was yellow but that, relatively, the rest of the

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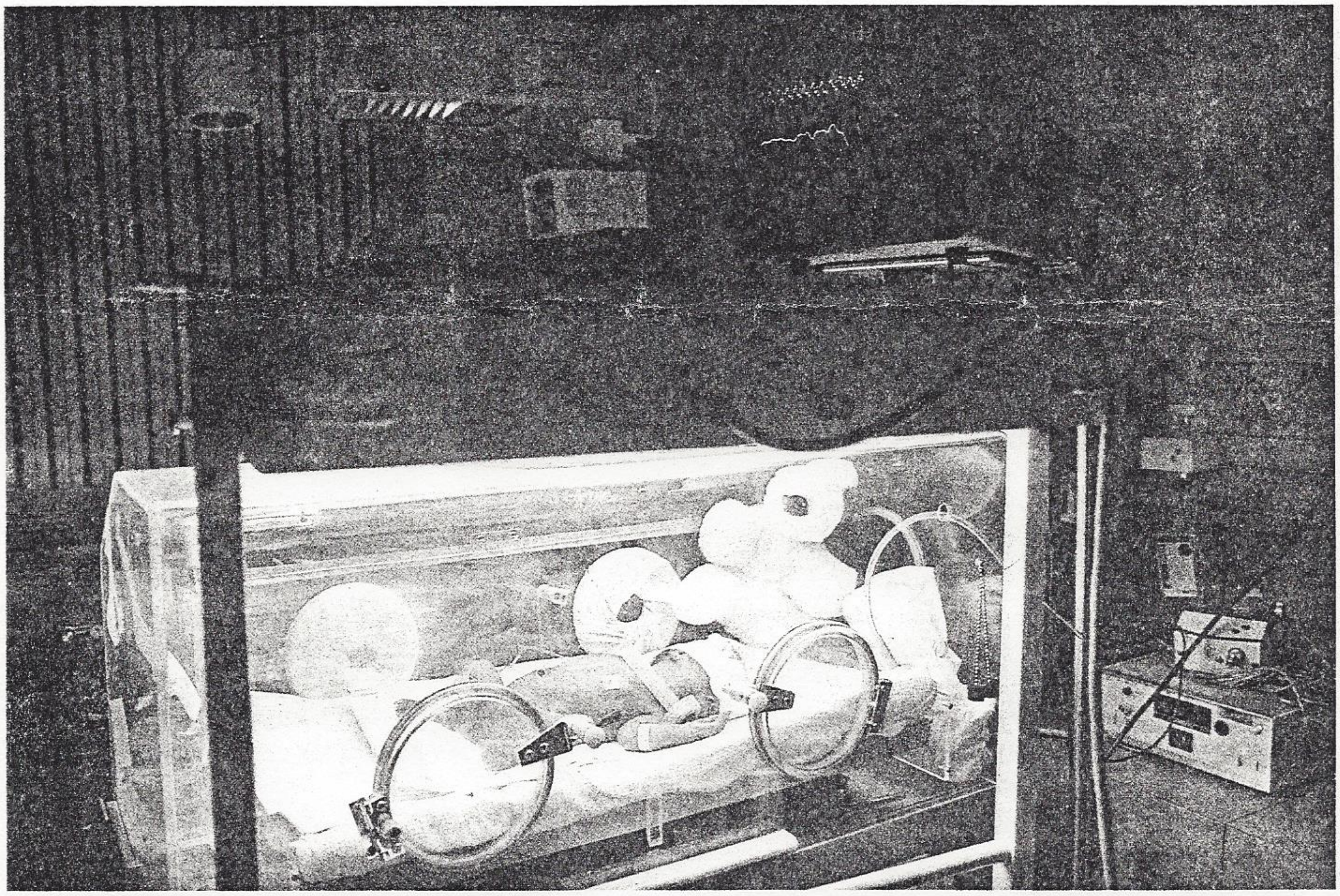

Prism

Newborns suffering from jaundice due to dangerous levels of bilirubin are bathed in high-intensity blue light. Depending on the severity of their jaundice, infants remain under the lights from a day to a week and are brought out only for feedings. Bandages protect eyes from possible damage. After a week babies' livers usually fully develop and can dispose of bilirubin in the bile.

baby was not. That triangular shape matched the corner of a blanket that had fallen across the baby's stomach. It seemed the sun had bleached out the jaundice.

The basis for this remarkable effect is just now being understood, largely due to the research of chemist Antony McDonagh and coworkers at San Francisco Medical Center. In the liver, bilirubin normally hooks up to a second chemical and is then shipped out in the bile—like hooking a garbage scow to a tug to be led out for dumping. It is this hookup system that is deficient in newborns' livers. Without it bilirubin is too insoluble to be transported into bile and so starts to accumulate in the body. The bilirubin begins to circulate near the surface of the skin, where light can filter through to it. When a photon of blue light energy enters a bilirubin molecule, it acts like a sudden blow to the molecule's midsection, causing the molecule to double over on itself. This contorted form of bilirubin is itself soluble in bile and after transport back to the liver can be directly excreted. The blue light, in a sense, acts as an artificial liver until the baby's liver can function alone.

It is a matter of luck that, in the case of hyperbilirubinemia, there is a molecule present in the body capable of responding to light with beneficial consequences. There are, however, great limitations to a technique that must await such a propitious combination of circumstances before it can be used. A more versatile use of light energy in curing disease involves the deliberate introduction of light-responsive chemicals into the body.

One sort of light-activated chemicals are the porphyrins, which are essential to almost all life-forms on Earth. When the porphyrins combine with magnesium, they form chlorophyll; in combination with iron they become the oxygen-carrying heme of hemoglobin. But when porphyrins are inadequately metabolized and build up to excessive levels in the body, as in the porphyria diseases, these life-giving chemicals can kill. When a concen-

A werewolf story

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Although light is often an agent of cure, it can also be an accomplice to disease, as in the light-aggravated porphyria disorders. Some of the stranger manifestations of this disease might begin to explain the persistent and nearly universal stories about the creatures we call werewolves.

Almost 2,000 years before Lon Chaney Jr., Ovid recounted what may be the first werewolf story: "In vain he attempted to speak; from that very instant His jaws were besputtered with foam, and only he thirsted for blood, as he raged amongst flocks and panted for slaughter. His vesture was changed into hair, his limbs became crooked; A wolf, he retains yet large traces of his former expression, Hoary he is as afore, his countenance rabid, His eyes glitter rabidly, the picture of fury."

Such stories of lycanthropy, the changing of men into wolves, are found in international literature and folklore. Our werewolf, from the Latin *vir* for man, literally man-wolf, is in Russia the *oborot*, in Portugal the *lobis-homen*, in France the *loup-garou*, and in Scandinavia the *vagr*. In medieval days suspected werewolves were sometimes flayed alive in the search for the dreaded wolf skin hidden beneath their human one. While other man-into-beast stories certainly exist, like the frenzied bear-shirters, or *ber-serkrs*, of Scandinavian origin, there are far more accounts of people being changed into wolves. It is mentioned by Herodotus and Pliny, and there is even a section of the 11th-century treatise *De-creta* dealing with werewolves who seek absolution. King James VI of Scotland gives an unusually sensitive account of the *war-woolfe* in his *Demonologie* of 1597, calling it "a naturall superabundance of melancholie."

In 1964, Lee Illis published a paper in the *Proceedings of the Royal Society of Medicine* entitled "On Porphyria and the Aetiology of Werewolves." In it he considered whether the great prevalence of lycanthropy accounts might not be indicative of some real, if highly romanticized, disorder. Porphyria, with the build-up in the body of the naturally occurring porphyrins and the attendant severe pathological reactions to light, was Illis' most likely candidate.

In porphyria, porphyrins absorb the energy from light and pass it on to nearby oxygen molecules, converting the oxygen into the devastatingly reactive "singlet" form. Singlet oxygen can instantly destroy any soft tissues in which it is produced, leading to festering wounds, extensive inflammatory reactions, and progressive tissue deterioration. Porphyrins have the additional quality of fluorescing under any wavelength of light —though the most spectacular effects are produced by ultraviolet and blue light. The deep, lurid, blood-red fluorescence can be seen when ultraviolet light is shone upon porphyrin-containing eggshells, such as those of brown chicken eggs. The fluorescence may also be seen in the teeth of porphyria sufferers who have deposits of excess porphyrins there.

Porphyrins are naturally found in the skins of certain marine worms, acting like behavioral implants to ensure that they will remain burrowing, light-shy creatures. Some porphyria sufferers may have a similar lifestyle imposed upon them. They would come out only at night, the lurid red glowing from their teeth becoming perhaps more pronounced in the bluish light of a full moon. This effect would be even more grotesque with the progressive deterioration of the gums and other surrounding soft tissues, making the teeth seem enlarged and misshapen. Compound this with the excessive growth of body hair that frequently and inexplicably accompanies the disease, and one is left with an appearance that medieval peasantry might not have passed off as just peculiar. In fact, without knowledge of the modern concepts of photochemistry, it would be hard to come up with a better or more convincing explanation than—a werewolf. —*M.S.*

tration of porphyrins is activated by light, massive damage can be done to the surrounding tissues. But suppose this destructive effect could be limited to tissues that one wanted to destroy? Porphyrins could act like planted grenades carrying light-triggered fuses, awaiting only a burst of light to set them off.

This concept is now being tried in the treatment of some cancers. The procedure is being developed by Thomas Dougherty, a radiation biologist at the Roswell Park Memorial Institute in Buffalo, New York.

The porphyrin derivatives used in the procedure are absorbed and retained by cancerous tissue in far greater amounts than they are by normal tissue. Doctors inject a cancer patient with the chemicals and then wait a few days for them to clear from the body's healthy tissues. The tumor area retains high levels of the chemicals and is then doused with a red-wavelength light, which penetrates tissue better than other wavelengths, leading to the selective destruction of the cancerous growth. Interior tumors—in the bladder, lung, or esophagus, for instance—can be reached by thin, flexible optic fibers linked to red-light lasers.

Although photoradiation therapy is still in its early days, extremely promising results have already been achieved in more than 300 patients. Cases have included advanced lung carcinomas, blad-

courtesy A. M. McDonagh, UCSF

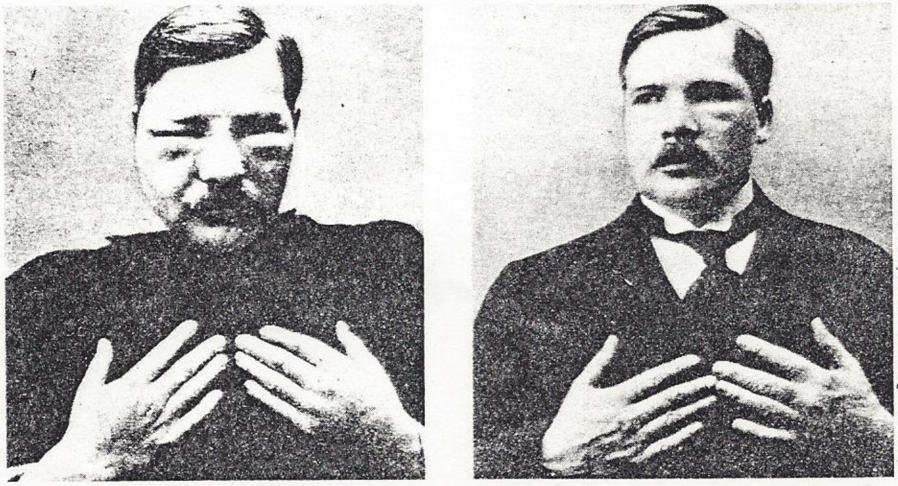
Patients with tubercular skin disease were treated with sun in 1900 at the Finsen Institute in Copenhagen. Special lenses concentrate light on affected areas without causing thermal burns. The treatment became obsolete after the discovery of antibiotics.

der cancers, and head and neck tumors. Experiments are continuing for adapting the technique to other malignancies, such as tumors of the eye. Since porphyrins have the additional property of fluorescing bright red under ultraviolet light, the derivatives are also being developed as probes for detecting cancerous tissue within the body. It is entirely possible that within the next few years, light therapy will find a place alongside surgery, chemotherapy, and radiation as a major cancer treatment.

These developments are among the first cautious steps physicians have taken toward exploiting the healing power of light. Though as venerable as God's first biblical decree, light has a long history of being viewed by the medical profession with a rather skeptical eye. From the use of gems in ancient times for focusing and condensing the healing powers of light to fads using colored lights to treat various maladies in the 1900s, approaches to light therapy have not evoked enthusiasm from the medical community.

Light as an agent of cure was given legitimacy by a Nobel Prize at the turn of this century. The 1903 prize for medicine went to Niels Finsen of Denmark for his pioneering work in the application of light to the cure of disease. Finsen's inspiration was a blending of that primeval, sun-seeking urge so prevalent in our species with his desire to ameliorate his own progressively degenerative illness. Too ill to attend the 1903 Nobel reception, he sent a letter: " . . . the disease was

Friedrich Meyer-Betz, a German physician, injected himself with porphyrin in 1912 to test whether it made humans sensitive to light. The first photograph shows him four days later, after he took a walk on a sunny day. Most of the swelling subsided by the sixth day, second photograph, but he remained light-sensitive for several months.



courtesy A. M. McDonagh, UCSF (2)

Although light has connotations of innocence, it also has a darker side.

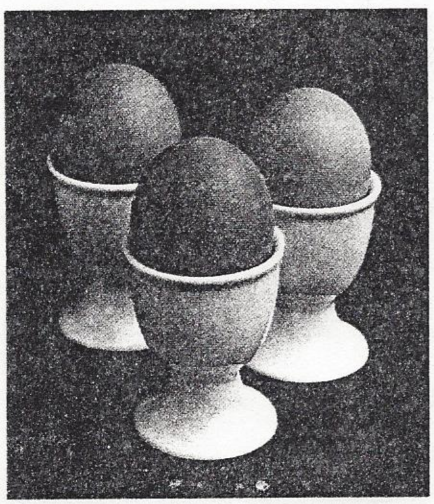
responsible for my starting investigations on light. I suffered from anemia and tiredness, and since I lived in a house facing the north, I began to believe that I might be helped if I received more sun. . . . I collected all possible observations about animals seeking the sun, and my conviction that the sun had a useful and important effect on the organism . . . became stronger and stronger."

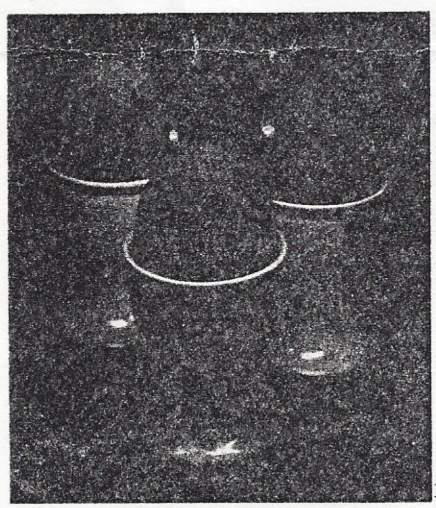
Finsen adapted light to the treatment of smallpox, greatly reducing its scarring, and to the cure of the then common tubercular skin infection *lupus vulgaris*. But light was not quite as effective in curtailing his own illness. He died at the age of 44, a year after receiving the Nobel Prize.

Science, of course, often finds elements of truth in folk remedies. In Cairo's street markets one can still buy a medicinal plant that has been in use for thousands of years. The Egyptians and some ancient Indian peoples used the ground-up black seeds of the Nile Valley weed *Ammi majus* to treat vitiligo. In this condition, patches of skin lose their pigmentation, like little islands of albinism. The oil of the plant, when stimulated by sunlight, restores these whitened patches to their natural hue.

Today *Ammi majus* plantations in the Nile Valley are the major world sources of the active chemical ingredient in this plant oil, a psoralen compound. Thanks to the original and creative developments of researchers like dermatologist John Parrish of Harvard Medical School, the uses of psoralen compounds have far surpassed those of the early vitiligo days. The therapy, known as PUVA for psoralen plus a kind of ultraviolet light known as UV-A, is now used for conditions ranging from eruptions of the skin caused by light to some forms of hives and an uncommon type of lymphoid cancer. The most prevalent use of PUVA, however, is in the highly effective treatment of the common affliction of psoriasis.

In psoriasis, underlying skin cells begin to multiply very rapidly, eventually supplanting the skin's usual outer layer. The resultant red, scaly, and rough surface may remain restricted to a local region, or it may cascade over the surface of the body. The grotesque effect can be devastating. As one patient described it, "Psoriasis doesn't end life—it just ends living." PUVA therapy, a series of treatments entailing taking a psoralen pill and lying under UV-A lamps, usually clears up the symptoms by decreasing cell replication. There is, however, a price to be paid.





Prism (2)

Porphyrins, which occur in everything from seashells to beer, make brown eggs fluoresce red under ultraviolet light.

Although light carries with it connotations of benevolence and innocence, one must take special care not to overlook its darker side. Psoralen plus UV-A turns out to make a highly carcinogenic mix that induces skin cancers in experimental animals and elevates risks of such malignancies in PUVA patients. While these skin cancers are generally curable, they are important indicators of the benefit/risk approach that every patient ought to bring to any therapy. Is it, for instance, worth the risk of skin cancer to repigment some vitiliginous skin areas? For some patients, perhaps, the answer is yes. One name for vitiligo in India translates as "white leprosy." On the other hand, the use of psoralens such as oil of bergamot for cosmetic purposes, as in some suntan lotions available in Europe, might not, given the risks, seem quite as compelling. Even the benign-looking blue light shone on newborns has some side effects—notably increased water loss and loose stools. But a follow-up study of thousands of treated infants, now in its seventh year, has found no long-term deleterious effects of the treatment.

The use of light as a "drug" to cure disease still is a developing concept. New applications may use other parts of the spectrum, employing visible light either as a direct treatment or as a secondary source to regulate the delivery and actions of other drugs within the body. This emphasis on the therapeutic properties of light is well stated by an old Italian proverb that even modern physicians are beginning to appreciate: "Go to the sun, not to the doctor." S

Michael Shodell is a contributing editor to Science 82.