The Effects of Light on the Human Body

Sunlight tans skin, stimulates the formation of vitamin D and sets biological rhythms. Light is also used in the treatment of disease. Such effects now raise questions about the role of artificial light

by Richard J. Wurtman

Since life evolved under the influence of sunlight, it is not surprising that many animals, including man, have developed a variety of physiological responses to the spectral characteristics of solar radiation and to its daily and seasonal variations. With the coming of summer in the Northern Hemisphere millions of people living in the North Temperate Zone will take the opportunity to darken the shade of their skin, even at the risk of being painfully burned. Coincidentally the sunbathers will replenish their body's store of vitamin D, the vitamin that is essential for the proper metabolism of calcium. Skin-tanning and subcutaneous synthesis of vitamin D from its precursors, however, are only the best-known consequences of exposure to sunlight.

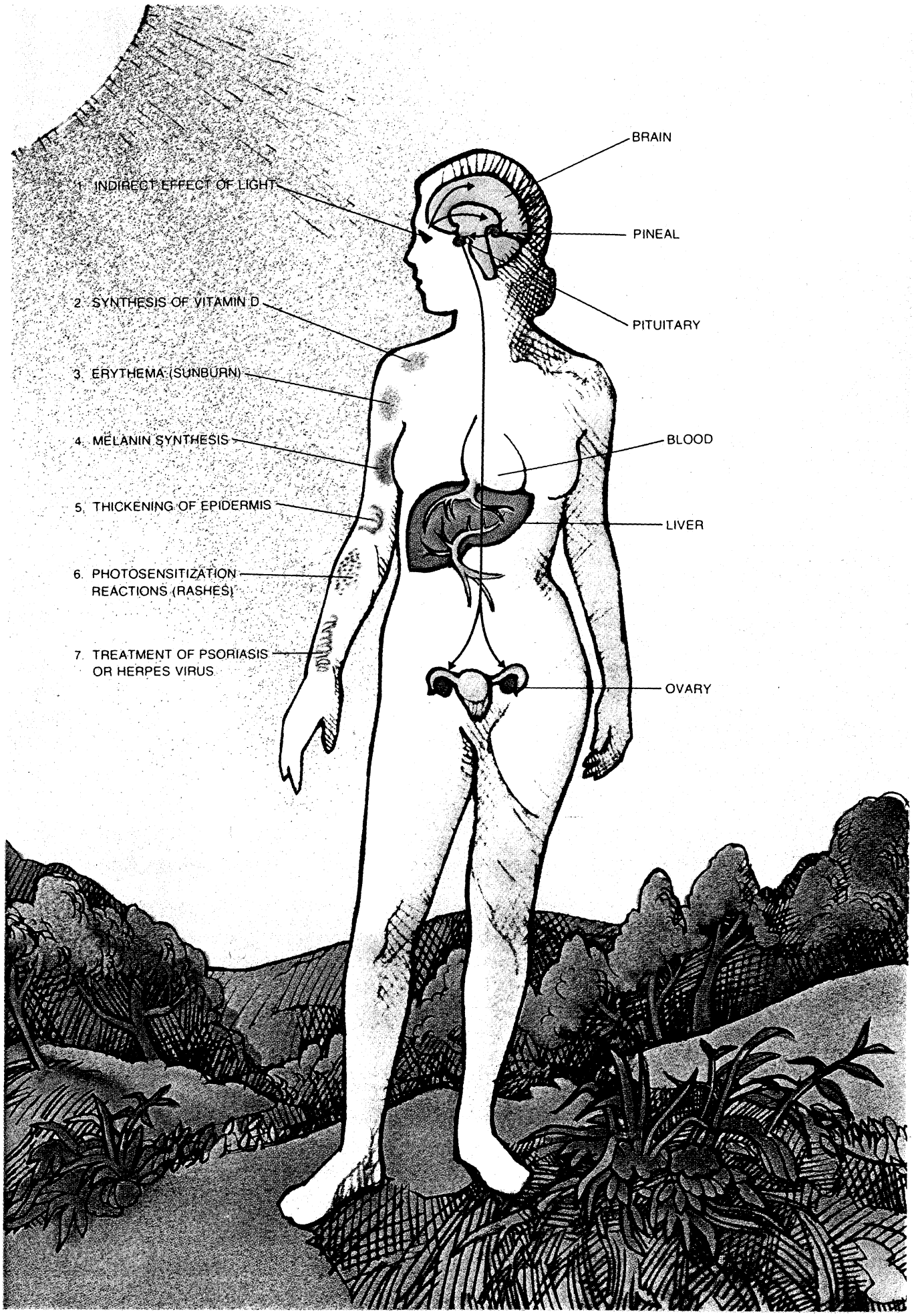
Investigators are slowly uncovering subtler physiological and biochemical responses of the human body to solar radiation or its artificial equivalent. Within the past few years, for example, light has been introduced as the standard method of treatment for neonatal jaundice, a sometimes fatal disease that is common among premature infants. More recently light, in conjunction with a sensitizing drug, has proved highly effective in the treatment of the common skin inflammation psoriasis. It seems safe to predict that other therapeutic uses for light will be found.

At least equally significant for human well-being is the growing evidence that fundamental biochemical and hormonal rhythms of the body are synchronized, directly or indirectly, by the daily cycle of light and dark. For example, my coworkers at the Massachusetts Institute of Technology and I have recently discovered a pronounced daily rhythm in the rate at which normal human subjects excrete melatonin, a hormone synthesized by the pineal organ of the brain. In experimental animals melatonin induces sleep, inhibits ovulation and modifies the secretion of other hormones. In man the amount of the adrenocortical hormone cortisol in the blood varies with a 24-hour rhythm. Although seasonal rhythms associated with changes in the length of the day have not yet been unequivocally demonstrated in human physiology, they are well known in other animals, and it would be surprising if they were absent in man. The findings already in hand suggest that light has an important influence on human health, and that our exposure to artificial light may have harmful effects of which we are not aware.

The wavelengths of radiation whose physiological effects I shall discuss here are essentially those supplied by the sun after its rays have been filtered by the atmosphere, including the tenuous high-altitude layer of ozone, which removes virtually all ultraviolet radiation with a wavelength shorter than 290 nanometers. The solar radiation that reaches the earth's surface consists chiefly of the ultraviolet (from 290 to 380 nanometers), the visible spectrum (from 380 to 770 nanometers) and the near infrared (from 770 to 1,000 nanometers). About 20 percent of the solar energy that reaches the earth has a wavelength longer than 1,000 nanometers.

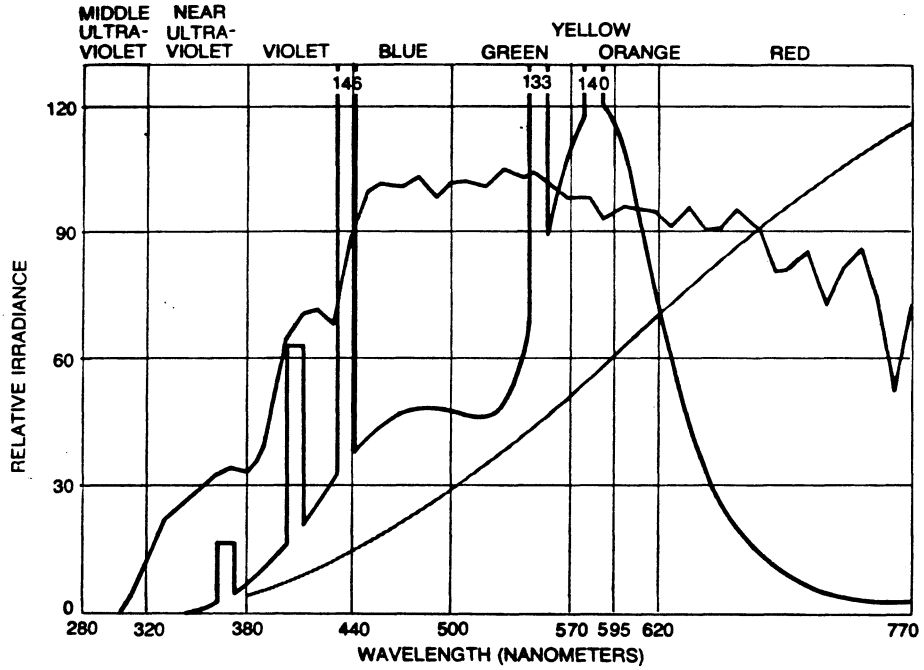
The visible spectrum of natural sunlight at sea level is about the same as the spectrum of an ideal incandescent source radiating at a temperature of 5,600 degrees Kelvin (degrees Celsius above absolute zero). The solar spectrum is essentially continuous, lacking only certain narrow wavelengths absorbed by elements in the sun's atmosphere, and at midday it has a peak intensity in the blue-green region from 450 to 500 nanometers [*see upper illustration on next page*]. The amount of ultraviolet radiation that penetrates the atmosphere varies markedly with the season: in the northern third of the U.S. the total amount of erythemal (skin-inflaming) radiation that reaches the ground in December is only about a fifteenth of the amount present in June. Otherwise there is little seasonal change in the spectral composition of the sunlight reaching the ground. The actual number of daylight hours, of course, can vary greatly, depending on the season and the distance north or south of the Equator.

SOME DIRECT AND INDIRECT EFFECTS OF LIGHT on the human body are outlined in the drawing on the opposite page. Indirect effects include the production or entrainment (synchronization) of biological rhythms. Such effects are evidently mediated by photoreceptors in the eye (*1*) and involve the brain and neuroendocrine organs. For example, excretion of melatonin, a hormone produced by the pineal organ, follows a daily rhythm. In animals melatonin synthesis is regulated by light. The hormone, acting on the pituitary, plays a role in the maturation and the cyclic activity of the sex glands. Ultraviolet radiation acts on the skin to synthesize vitamin D (*2*). Erythema, or reddening of the skin (*3*), is caused by ultraviolet wavelengths between 290 and 320 nanometers. In response melanocytes increase their synthesis of melanin (*4*), a pigment that darkens the skin. Simultaneously the epidermis thickens (*5*), offering further protection. In some people the interaction of light with photosensitizers circulating in the blood causes a rash (*6*). In conjunction with selected photosensitizers light can be used to treat psoriasis and other skin disorders (*7*). In infants with neonatal jaundice light is also used therapeutically to lower the amount of bilirubin circulating in the blood until infant's liver is mature enough to excrete the substance. The therapy prevents the bilirubin from concentrating in the brain and destroying brain tissue.

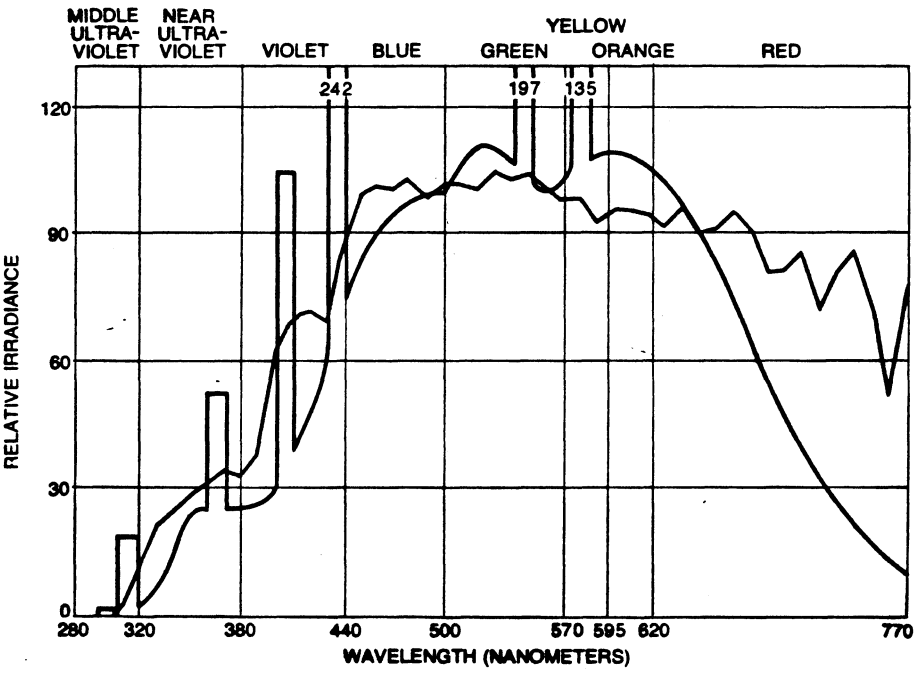

1. INDIRECT EFFECT OF LIGHT
2. SYNTHESIS OF VITAMIN D
3. ERYTHEMA (SUNBURN)
4. MELANIN SYNTHESIS
5. THICKENING OF EPIDERMIS
6. PHOTOSENSITIZATION REACTIONS (RASHES)
7. TREATMENT OF PSORIASIS OR HERPES VIRUS
BRAIN
PINEAL
PITUITARY
BLOOD
LIVER
OVARY

The most familiar type of artificial light is the incandescent lamp, in which the radiant source is a hot filament of tungsten. The incandescent filament in a typical 100-watt lamp has a temperature of only about 2,850 degrees K., so that its radiation is strongly shifted to the red, or long-wavelength, end of the spectrum. Indeed, about 90 percent of the total emission of an incandescent lamp lies in the infrared.

Fluorescent lamps, unlike the sun and incandescent lamps, generate visible light by a nonthermal mechanism. Within the glass tube of a fluorescent lamp ultraviolet photons are generated by a mercury-vapor arc; the inner surface of the tube is coated with phosphors, luminescent compounds that emit visible radiations of characteristic colors when they are bombarded with ultraviolet photons. The standard "cool white" fluorescent lamp has been designed to achieve maximum brightness for a given energy consumption. Brightness, of course, is a subjective phenomenon that depends on the response of the photoreceptive cells in the retina. Since the photoreceptors are most sensitive to yellow-green light of 555 nanometers, most fluorescent lamps are designed to concentrate much of their output in that wavelength region. It is possible, however, to make fluorescent lamps whose spectral output closely matches that of sunlight [*see lower illustration on this page*].



SPECTRUM OF SUN at sea level (*color*) is compared with the spectra of a typical incandescent lamp (*gray curve*) and of a standard "cool white" fluorescent lamp (*black curve*). The visible spectrum lies between the wavelengths of 380 and 770 nanometers. The peak of the sun's radiant energy falls in the blue-green region between 450 and 500 nanometers. Cool-white fluorescent lamps are notably deficient precisely where the sun's emission is strongest. Incandescent lamps are extremely weak in the entire blue-green half of the visible spectrum.



BROAD-SPECTRUM FLUORESCENT LAMP known as Vita-Lite (*black curve*) closely approximates spectral characteristics of sunlight (*color*). Wavelengths emitted by fluorescent lamps can be adjusted by selecting phosphors with which inner surface of lamp is coated.

Since fluorescent lamps are the most widely used light source in offices, factories and schools, most people in industrial societies spend many of their waking hours bathed in light whose spectral characteristics differ markedly from those of sunlight. Architects and lighting engineers tend to assume that the only significant role of light is to provide adequate illumination for working and reading. The illumination provided at eye level in artificially lighted rooms is commonly from 50 to 100 footcandles, or less than 10 percent of the light normally available outdoors in the shade of a tree on a sunny day.

The decision that 100 footcandles or less is appropriate for indoor purposes seems to be based on economic and technological considerations rather than on any knowledge of man's biological needs. Fluorescent lamps could provide higher light intensities without excessive heat production, but the cost of the electric power needed for substantially higher light levels would probably be prohibitive. Nevertheless, the total amount of light to which a resident of Boston, say, is exposed in a conventionally lighted indoor environment for 16 hours a day is considerably less than would impinge on him if he spent a single hour each day outdoors. If future studies indicate that significant health benefits (for example better bone mineralization) might accrue from increasing the levels of indoor lighting, our society might, in a period of energy shortages, be faced with hard new choices.

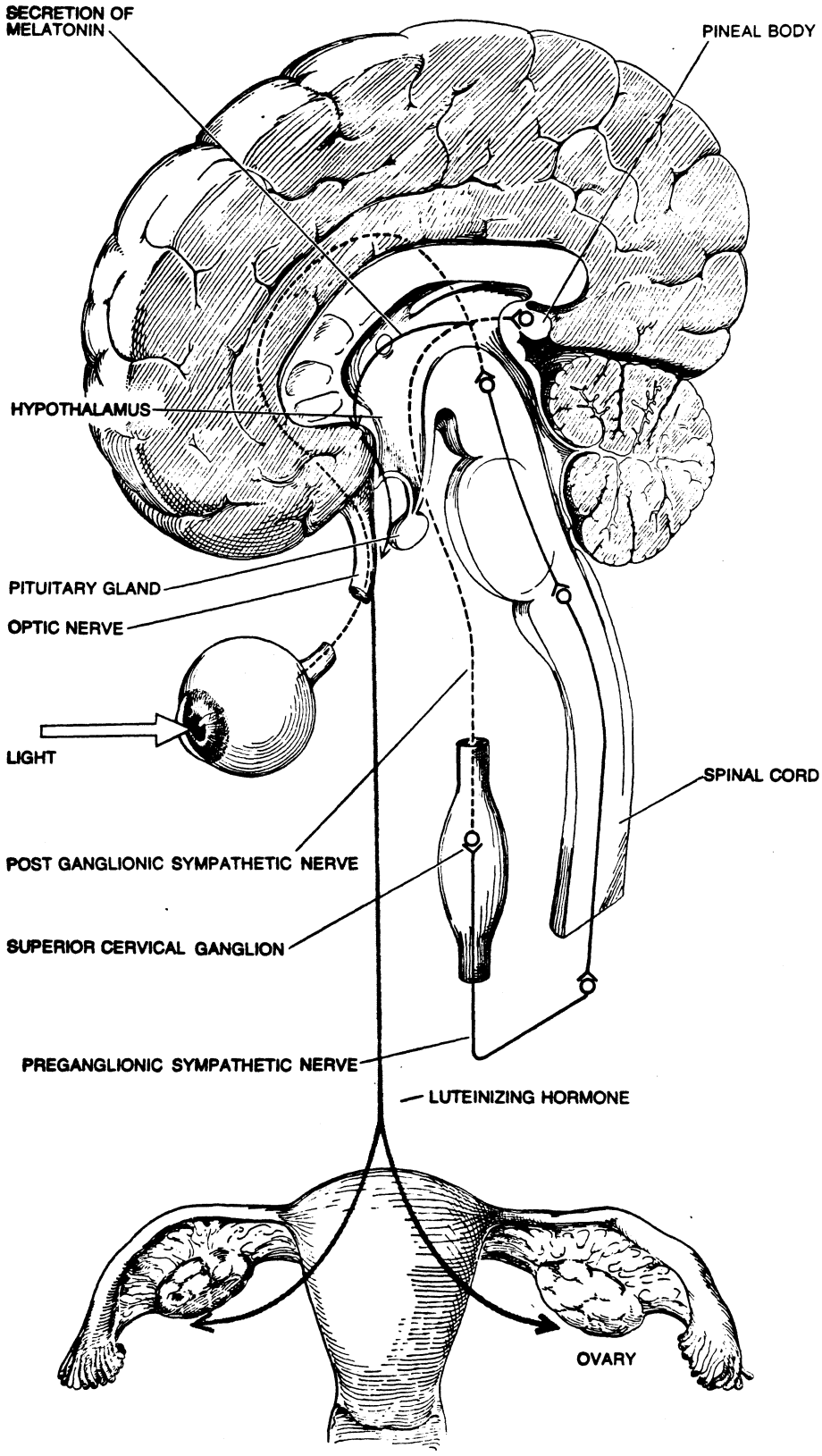
Each of the various effects of light on mammalian tissues can be classified as direct or indirect, depending on whether the immediate cause is a photochemical reaction within the tissue or a neural or neuroendocrine signal generat-

ed by a photoreceptor cell. When the effect is direct, the molecule that changes may or may not be the one that actually absorbs the photon. For example, certain molecules can act as photosensitizers: when they are raised to transient high-energy states by the absorption of radiation, they are able to catalyze the oxidation of numerous other compounds before they return to the ground state. Photosensitizers sometimes present in human tissues include constituents of foods and drugs and of toxins produced in excess by some diseases.

In order to prove that a particular chemical change in a tissue is a direct response to light one must show that light energy of the required wavelength does in fact penetrate the body to reach the affected tissue. In addition the photoenergetic and chemical characteristics of the reaction must be fully specified, first in the test tube, then in experimental animals or human beings, by charting the reaction's "action spectrum" (the relative effectiveness of different spectral bands in producing the reaction) and by identifying all its chemical intermediates and products. Visible light is apparently able to penetrate all mammalian tissues to a considerable depth; it has even been detected within the brain of a living sheep.

Ultraviolet radiation, which is far more energetic than visible wavelengths, penetrates tissues less effectively, so that erythemal radiations barely reach the capillaries in the skin. The identification of action spectra for the effects of light on entire organisms presents major technical problems: few action spectra have been defined for chemical responses in tissues other than the skin and the eyes.

The indirect responses of a tissue to light result not from the absorption of light within the tissue but from the actions of chemical signals liberated by neurons or the actions of chemical messengers (hormones) delivered by circulation of the blood. These signals in turn are ultimately the result of the same process as the one that initiates vision: the activation by light of specialized photoreceptive cells. The photoreceptor transduces the incident-light energy to a neural signal, which is then transmitted over neural, or combined neural-endocrine, pathways to the tissue in which the indirect effect is observed. For example, when young rats are kept continuously under light, photoreceptive cells in their retina release neurotransmitters that activate brain neurons; these neurons in turn transmit signals over complex neuroendocrine pathways that reach the anterior pituitary gland,



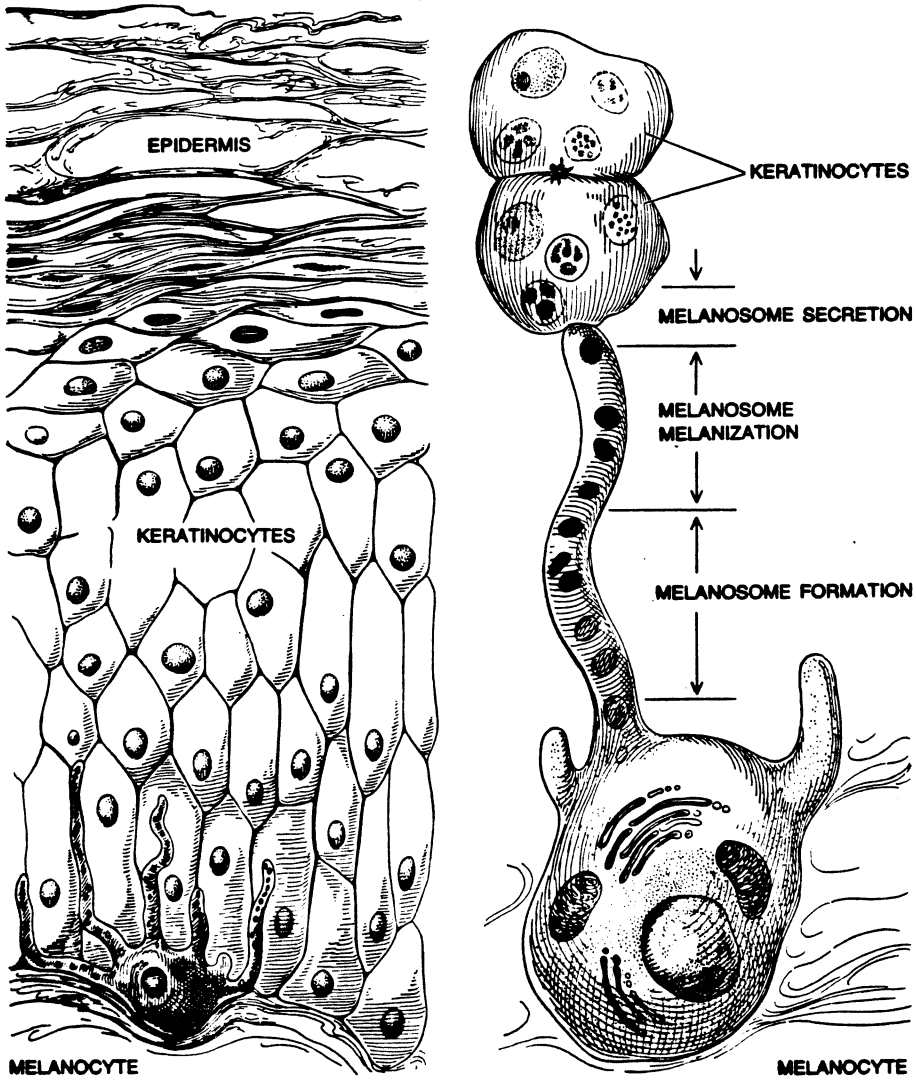
INDIRECT EFFECT OF LIGHT ON OVARIES OF RATS is shown schematically. Light activates receptors in the retina, giving rise to nerve impulses that travel via a chain of synapses through the brain, the brain stem and the spinal cord, ultimately decreasing the activity of neurons running to the superior cervical ganglion (in the neck) and of the sympathetic nerves that reenter the cranium and travel to the pineal organ. There the decrease in activity reduces both the synthesis and the secretion of melatonin. With less melatonin in blood or cerebrospinal fluid, less reaches brain centers (probably in hypothalamus) on which melatonin acts to suppress secretion of luteinizing hormone from anterior pituitary. Thus more hormone is released, facilitating ovarian growth and presumably ovulation.

where they stimulate the secretion of the gonadotropic hormones that accelerate the maturation of the ovaries [*see illustration on preceding page*].

That the ovaries are not responding directly to light can be shown by removing the eyes or the pituitary gland of the rat before exposing it to continuous light. After either procedure light no longer has any influence on ovarian growth or function. Various studies confirm that the effect of light on the ovaries is mediated by photoreceptive cells in the retina. It has not been possible to show, however, which of the photoreceptors in the eye release the neurotransmitters that ultimately affect the pituitary gland.

Natural sunlight acts directly on the cells of the skin and subcutaneous tissues to generate both pathological and protective responses. The most familiar example of a pathological response is sunburn; in susceptible individuals exposed over many years sunlight also causes a particular variety of skin cancer. The chief protective response is tanning. Ultraviolet wavelengths in the narrow band from 290 to 320 nanometers cause the skin to redden within a few hours of exposure. Investigators generally agree that the inflammatory reaction, which may persist for several days, results either from a direct action of ultraviolet photons on small blood vessels or from the release of toxic compounds from damaged epidermal cells. The toxins presumably diffuse into the dermis, where they damage the capillaries and cause reddening, heat, swelling and pain. A number of compounds have been proposed as the offending toxins, including serotonin, histamine and bradykinin. Sunburn is largely an affliction of industrial civilization. If people were to expose themselves to sunlight for one or two hours every day, weather permitting, their skin's reaction to the gradual increase in erythemal solar radiation that occurs during late winter and spring would provide them with a protective layer of pigmentation for withstanding ultraviolet radiation of summer intensities.

Immediately after exposure to sunlight the amount of pigment in the skin increases, and the skin remains darker for a few hours. The immediate darkening probably results from the photooxidation of a colorless melanin precursor and is evidently caused by all the wavelengths in sunlight. After a day or two, when the initial response to sunlight has subsided, melanocytes in the epidermis begin to divide and to increase their synthesis of melanin granules, which are then extruded and taken up into the adjacent keratinocytes, or skin cells [*see illustration at left*]. Concurrently accelerated cell division thickens the ultraviolet-absorbing layers of the epidermis. The skin remains tan for several weeks and offers considerable protection against further tissue damage by sunlight. Eventually the keratinocytes slough off and the tan slowly fades. (In the U.S.S.R. coal miners are given suberythemal doses of ultraviolet light every day on the theory that the radiation provides protection against the development of black-lung disease. The mechanism of the supposed protective effect is not known.)



MECHANISM OF SUN-TANNING is an extension of the mechanism responsible for skin pigmentation. After exposure to the sun melanocytes begin to divide and increase their output of melanin granules, produced in the tiny intracellular bodies called melanosomes. The melanosomes are secreted into the adjacent keratinocytes, or skin cells, where the melanin causes the skin to take on a darker appearance. The tan fades as the keratinocytes slough off.

In addition to causing sunburn and tanning, sunlight or its equivalent initiates photochemical and photosensitization reactions that affect compounds present in the blood, in the fluid space between the cells or in the cells themselves. A number of widely prescribed drugs (such as the tetracyclines) and constituents of foods (such as riboflavins) are potential photosensitizers. When they are activated within the body by light, they may produce transient intermediates that can damage the tissues in sensitive individuals. A typical response is the appearance of a rash on the parts of the body that are exposed to the sun.

In individuals with the congenital disease known as erythropoietic protoporphyria unusually large amounts of porphyrins (a family of photosensitizing chemicals) are released into the bloodstream as a result of a biochemical ab-

normality. The porphyrins absorb visible radiations and give rise to intermediates that are toxic to tissues. Patients with the disease complain at first of a burning sensation in areas of the skin that are exposed to sunlight; reddening and swelling soon follow.

Investigators can easily induce these typical symptoms without serious consequences in patients suffering from mild forms of erythropoietic protoporphyria, so that the disease is one of the few of its kind where the action spectrum for a direct effect of light has been studied in detail. The skin damage is caused by a fairly narrow band of wavelengths in the region of 400 nanometers. This band has also been shown to coincide with one of the absorption peaks of abnormal porphyrins. The symptoms of the disease can be ameliorated by administering photoprotective agents such as carotenoids, which quench the excited states of oxygen produced as intermediates in the photosensitization reactions.

In the past few years physicians have treated several skin diseases by deliberately inducing photosensitization reactions on the surface of the body or within particular tissues. The intent is to cause selective damage to invading organisms (such as the herpes virus), to excessively proliferating cells (as in psoriasis) or to certain types of malignant cells. The activated photosensitizers appear to be capable of inactivating the DNA in the viruses or in the unwanted cells. In treating herpes infections the photosensitizer (usually a dye, neutral red) is applied directly to the skin or to the mucous membrane under the ruptured blister; the area is then exposed to low-intensity white fluorescent light.

The treatment for psoriasis was devised by John A. Parrish, Thomas B. Fitzpatrick and their colleagues at the Massachusetts General Hospital. They administer a special photosensitizer (8-methoxypsoralen, or methoxalen) by mouth and two hours later expose the afflicted skin areas for about 10 minutes to the radiation from special lamps that emit strongly in the long-wave ultraviolet at about 365 nanometers. The sensitizing agent is present in small amounts in carrots, parsley and limes. It is derived commercially from an Egyptian plant (*Ammi majus* Linn.) that was used in ancient times to treat skin ailments. Scores of patients have responded successfully to the new light treatment, which will soon be generally available.

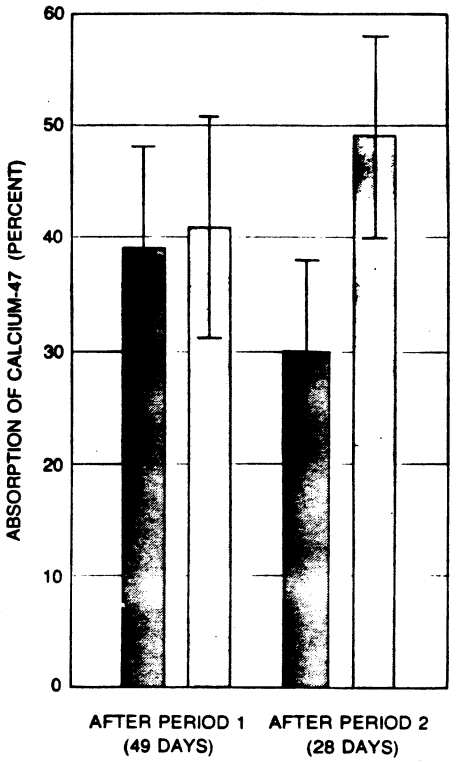
The formation of vitamin D_3, or cholecalciferol, in the skin and subcutaneous tissue is the most important of the beneficial effects known to follow exposure to sunlight. Vitamin D_3 is formed when ultraviolet radiation is absorbed by a precursor, 7-dehydrocholesterol. A related biologically active compound, vitamin D_2, can be obtained by consuming milk and other foods in which ergosterol, a natural plant sterol, has been converted to vitamin D_2 by exposure to ultraviolet radiation. Although vitamin D_2 can cure rickets in children who are deficient in vitamin D_3, it has not been demonstrated that vitamin D_2 is biologically as effective as the vitamin D_3 formed in the skin.

In a population of normal white adults living in St. Louis, studied by John G. Haddad, Jr., and Theodore J. Hahn of the Washington University School of Medicine, some 70 to 90 percent of the vitamin D activity in blood samples was found to be accountable to vitamin D_3 or its derivatives. The investigators concluded that sunlight was vastly more important than food as a source of vitamin D. (Although vitamin D_3 is also found in fish, seafood is not an important source in most diets.) In Britain and several other European countries the fortification of foods with vitamin D_2 has now been sharply curtailed because of evidence that in large amounts vitamin D_2 can be toxic, causing general weakness, kidney damage and elevated blood levels of calcium and cholesterol.

A direct study of the influence of light on the human body's ability to absorb calcium was undertaken a few years ago by Robert Neer and me and our coworkers. The study, conducted among elderly, apparently normal men at the Chelsea Soldiers' Home near Boston, suggests that a lack of adequate exposure to ultraviolet radiation during the long winter months significantly impairs the body's utilization of calcium, even when there is an adequate supply in the diet. The calcium absorption of a control group and an experimental group was followed for 11 consecutive weeks from the onset of winter to mid-March.

During the first period of seven weeks, representing the severest part of the winter, all the subjects agreed to remain indoors during the hours of daylight. Thus both groups were exposed more or less equally to a typical low level of mixed incandescent and fluorescent lighting (from 10 to 50 footcandles). At the end of the seven weeks the men in both groups were found to absorb only about 40 percent of the calcium they ingested. During the next four-week period, from mid-February to mid-March, the lighting was left unchanged for the control subjects, and their ability to absorb calcium fell by about 25 percent. The men in the experimental group, however, were exposed for eight hours per day to 500 footcandles of light from special fluorescent (Vita-Lite) lamps, which simulate the solar spectrum in the visible and near-ultraviolet regions. In contrast with the control subjects' loss of 25 percent of their capacity to absorb calcium, the experimental group exhibited an increase of about 15 percent [*see illustration above*]. The additional amount of ultraviolet radiation received by the experimental subects was actually quite small: roughly equivalent to what they would get during a 15-minute lunchtime walk in the summer.

Our study indicates that a certain amount of ultraviolet radiation, whether it is from the sun or from an artificial



CALCIUM ABSORPTION was increased by a daily eight-hour exposure to broad-spectrum artificial light in a study made by the author and his colleagues at a veterans' home. During the first seven weeks after the beginning of winter, control subjects (*gray bars*) and experimental subjects (*colored bars*) were equally exposed to the same low levels of typical indoor lighting. The bars at the left show their ability to absorb calcium at the end of the initial period. During the next four-week period conditions for the control subjects were unchanged; their ability to absorb calcium fell about 25 percent. The experimental subjects, who were exposed to 500 footcandles of broad-spectrum fluorescent light for eight hours per day for four weeks, showed an average increase of about 15 percent in their calcium absorption.

source, is necessary for adequate calcium metabolism. This hypothesis receives support from a recent study conducted by Jean Aaron of the Mineral Metabolism Unit at the General Infirmary at Leeds in England, who found that undermineralization (osteomalacia) is far more prevalent in autopsy samples collected in England during the winter months than it is in samples collected during the summer. Thus it seems likely that properly designed indoor lighting environments could serve as an important public-health measure to prevent the undermineralization of bones among the elderly and others with limited access to natural sunlight.

Perhaps 25,000 premature American infants were sucessfully treated with light last year as the sole therapy for neonatal jaundice. The rationale for this remarkable treatment is as follows. When red blood cells die, they release hemoglobin, which soon degrades into the yellow compound bilirubin. An increase in the concentration of bilirubin in the blood, due to excessive production of the compound or to failure of the liver to remove it, gives the skin its characteristic jaundiced color.

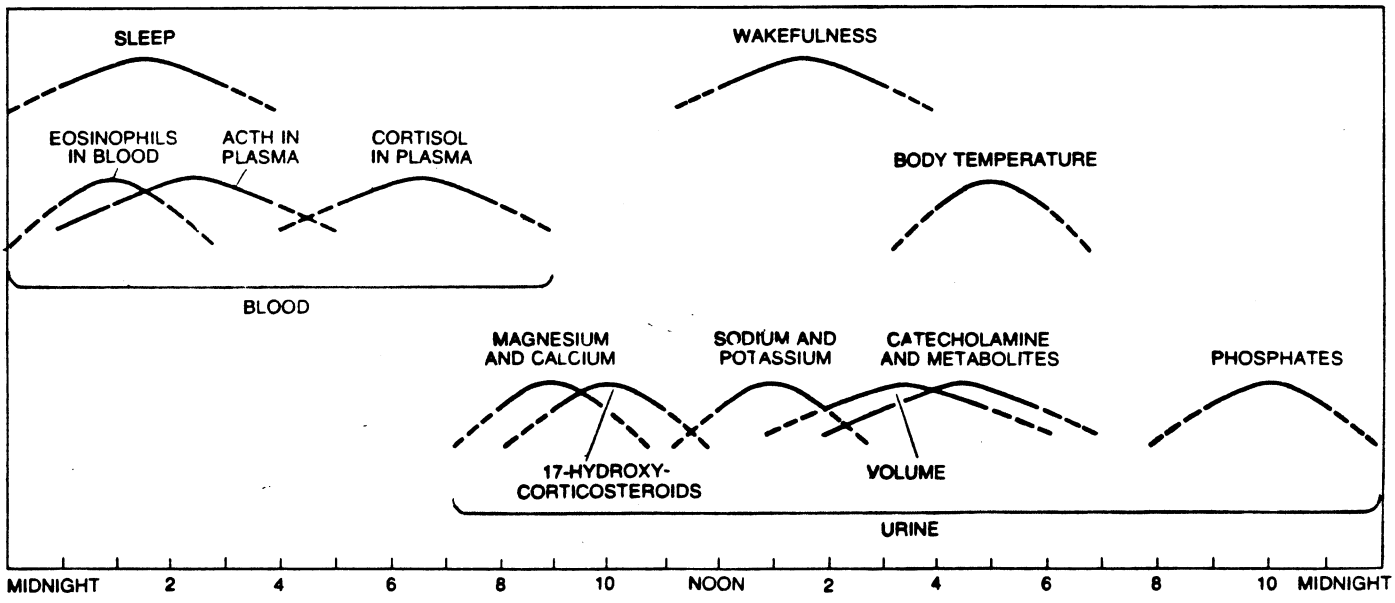
A potentially dangerous form of hyperbilirubinemia afflicts from 15 to 20 percent of premature infants because their liver is physiologically immature; in some cases the amounts of bilirubin released into the bloodstream are also increased as a result of blood-type incompatibility or concurrent infections. In such infants the bilirubin, which is soluble in fat, becomes concentrated in certain parts of the brain, where it can destroy neurons, producing the clinical syndrome kernicterus (yellow nuclei). The toxicity of bilirubin is aggravated by other factors, such as anoxia, acidosis, low body temperature, low blood sugar, low blood protein and infection. The brain damage resulting from kernicterus is often irreversible; it can cause various degrees of motor and mental retardation, leading to cerebral palsy and even death.

All current therapies for neonatal hyperbilirubinemia are based on the hope that if the level of bilirubin in the blood plasma can be kept from reaching between 10 and 15 milligrams per 100 milliliters until the maturing liver is able to remove the offending substance, there will be no brain damage. One widely used therapy involves exchange transfusions, in which jaundiced blood from the infant is completely replaced with normal blood from the donor.

Some years ago it was discovered that bilirubin in solution could be bleached by light and thus destroyed; the nature of the photodecomposition products remains unknown. This observation prompted R. J. Cremer, P. W. Perryman and D. H. Richards, who were then working at the General Hospital at Rockford in England, to see if light might be effective in lowering the plasma bilirubin in infants suffering from hyperbilirubinemia. That possibility was supported by informal observations that newborn infants whose crib had been placed near an open window tended to show less evidence of jaundice than infants whose crib was less exposed to light. Perhaps sunlight was accelerating the destruction of bilirubin. If it was, it should be possible to reproduce the effect with artificial light.

The efficacy of light therapy was fully confirmed in a controlled study conducted by Jerold F. Lucey of the University of Vermont College of Medicine. The treatment consists in exposing jaundiced infants to light for three or four days, or until their liver is able to metabolize bilirubin. Although it was initially assumed that the light converted the bilirubin into nontoxic products that could be excreted, it now turns out that a major fraction of the excreted material is unchanged bilirubin itself. Hence it is at least conceivable that phototherapy has a direct beneficial effect on the liver and the kidneys.

Many questions remain concerning the mechanism of phototherapy for hyperbilirubinemia and the long-term effectiveness of that therapy in protecting infants against brain damage. Blue light is the most effective in decomposing pure solutions of bilirubin. In clinical tests, however, full-spectrum white light in almost any reasonable dosage (continuous, intermittent or in brief strong pulses) has proved effective in lowering plasma-bilirubin levels, regardless of the fraction of the radiant energy that falls in the blue region of the spectrum. Thus the mechanism by which light destroys bilirubin in infants may differ from the simple photochemical reaction that takes place in a test tube. For example, a photosensitization reaction, perhaps mediated by circulating riboflavin, may underlie the desirable effect. Another possibility is that the light may act on the



DAILY RHYTHMS are characteristic of many human physiological functions. Whether these 24-hour rhythms are produced by the daily light-dark cycle or are simply entrained by that cycle remains to be unequivocally established. Each curve represents the typical daily peak for a physiological state or for the levels of particular substances that circulate in the blood or are excreted in the urine.

plasma albumin to which most of the circulating bilirubin is bound. Alternatively the physiologically effective wavelength may be not in the blue region at all but in some other region of the spectrum, still to be identified, that is present in all the white-light sources.

The observation that ordinary sunlight or artificial light sources can drastically alter the plasma level of even one body compound (in this case bilirubin) opens a Pandora's box for the student of human biology. It presents the strong possibility that the plasma or tissue levels of many additional compounds are similarly affected by light. Some such responses must be physiologically advantageous, but some may not be.

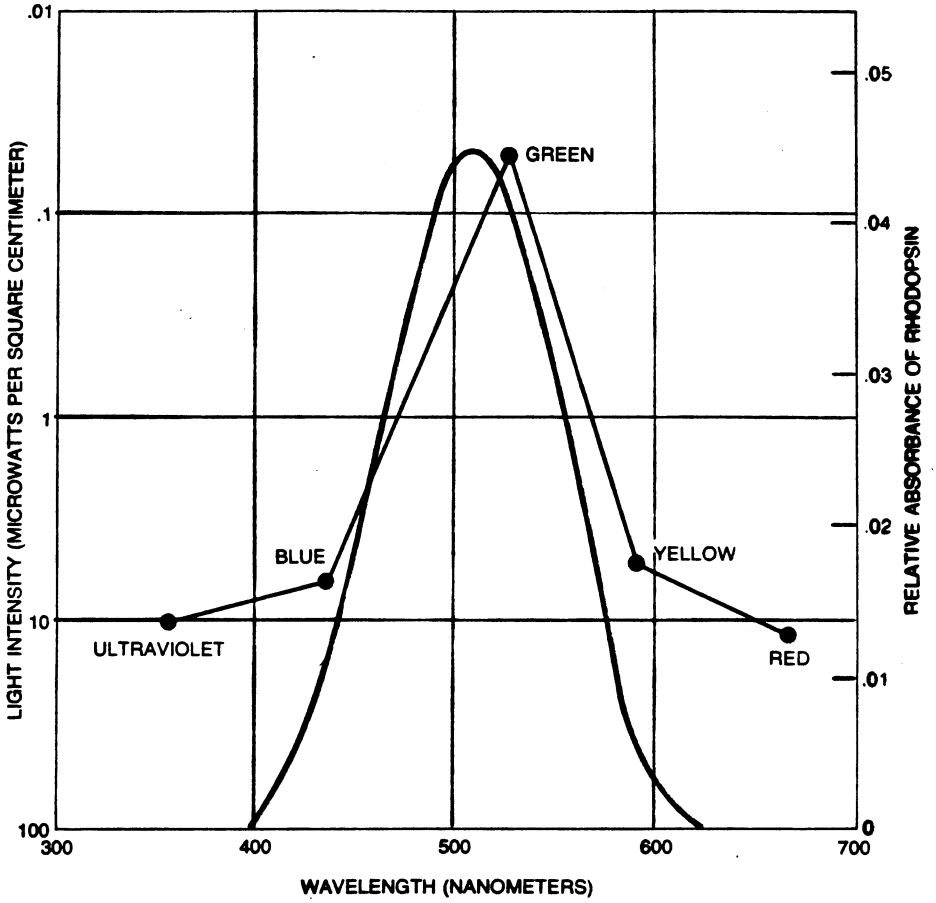
Let us turn now to the indirect effects of light, those associated in one way or another with biological rhythms. The amount of time that all mammals are exposed to light varies with two cycles: the 24-hour cycle of day and night and the annual cycle of changing day length. (Even at the Equator there are small seasonal variations in the light-dark cycle.) These light cycles appear to be associated with many rhythmic changes in mammalian biological functions. Physical activity, sleep, food consumption, water intake, body temperature and the rates at which many glands secrete hormones all vary with periods that approximate 24 hours.

In human beings, for example, the concentration of cortisol, one of the principal hormones produced by the adrenal cortex, varies with a 24-hour rhythm [*see illustration on opposite page*]. The level is at a maximum in the morning hours, soon after waking, and drops to a minimum in the evening. When people reverse their activity cycle, by working at night and sleeping during the day, the plasma-cortisol rhythm takes from five to 10 days to adapt to the new conditions. When the cortisol level is studied in rats, it is found that the rhythm persists in animals that are blinded but not in animals kept under continuous illumination. Blindness in human beings seems to upset the rhythm, so that the times of the daily peaks and valleys are out of phase with the normal pattern and may even vary from day to day.

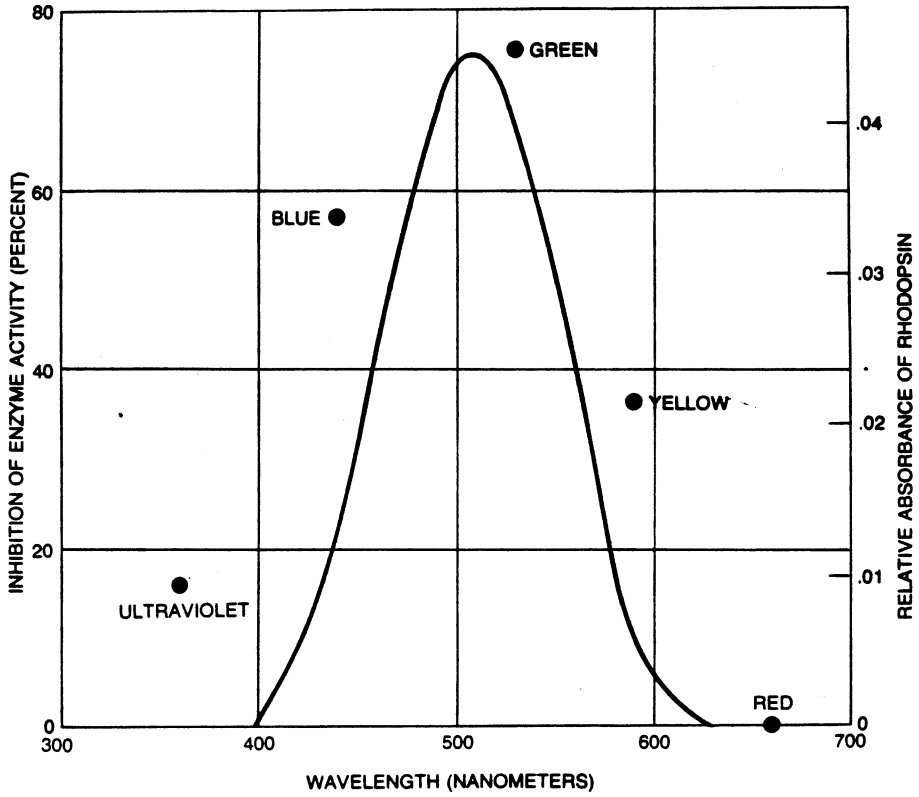
Among the rhythmic functions that can be closely studied in one and the same animal (specifically rhythms in sleep, physical activity and food consumption) it has been shown that in the absence of cyclic exposure to light the rhythms become "circadian" (that is, their periods become approximately 24 hours in length rather than exactly). The fact that such rhythms can "free-run" suggests that they are not simply reflex responses to 24-hour cycles of light or some other environmental component. The factors responsible for the rhythms are not yet known; they might include other cyclic inputs such as the consumption of food or the intake of water, which also free-run in the absence of light. Some investigators are convinced that the rhythms are generated by intrinsic oscillators, commonly called biological clocks.

Little is known about the action spectra or the light intensities needed either to generate or to "entrain" (synchronize) daily rhythms in mammals. There is strong presumptive evidence, however, that in most mammals light exerts its effects indirectly through photoreceptors in the eye. It is not known whether the photoreceptors are the same ones (the rods and the cones) that mediate vision, discharging into nonvisual pathways, or whether they are a distinct family of photoreceptors with their own neural network.

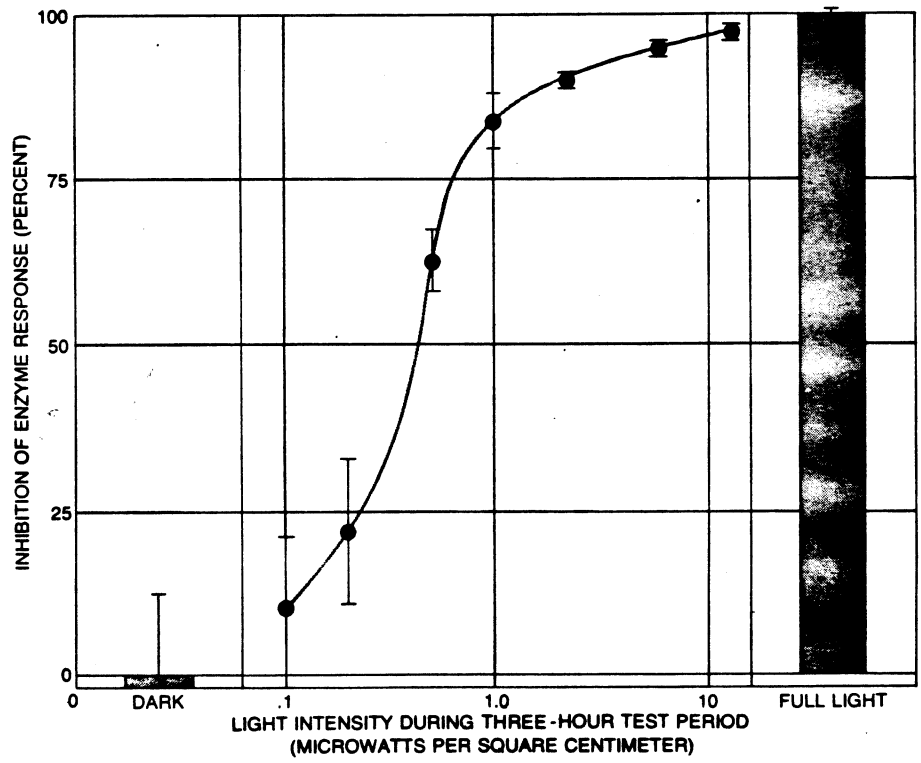
In our laboratory at M.I.T. we have investigated the daily rhythmicity in the body temperature of rats to see what colors of light are most effective in inducing a change in rhythm to a new light-dark cycle and what intensities are needed. The body temperature of rats normally rises by one or two degrees C. at the onset of darkness and falls again at daybreak. We found that green light is the most potent in changing the phase of the temperature cycle and that ultraviolet and red wavelengths are the least potent. The action spectrum plotted from these results closely follows the absorption spectrum for rhodopsin, the photosensitive pigment in the rods of the retina [*see illustration above*]. In separate studies a similar action spectrum, peaking in the green, was found for the wavelengths of light that are most effective in inhibiting the function



BODY-TEMPERATURE RHYTHM IN RATS, which follows a 24-hour cycle, can be altered by shifting the hours of the light-dark cycle. The author and his colleagues have found that green light is much more effective in establishing a new rhythm than radiation of other wavelengths (red, yellow, blue or ultraviolet). Black curve estimates the wavelength and intensity needed to establish a new 24-hour rhythm in half of an experimental group of rats. It closely follows the relative sensitivity of rhodopsin from rat retinas (*curve in color*).



PINEAL ACTIVITY OF RATS can be suppressed by exposing the animals continuously to light. As in the case of the daily temperature rhythm, green light is more effective than light of other spectral colors in suppressing the organ's enzyme activity, as is shown by the labeled dots. The enzyme that is measured is the melatonin-forming enzyme hydroxyindole-O-methyltransferase. Presumably the suppression is mediated by rhodopsin (*curve in color*).



GRADATION IN LIGHT INTENSITY leads to proportional inhibition in the activity of the rat's pineal gland, indicating that light controls synthesis of the pineal hormone, melatonin. Rats that had been kept in constant light for 48 hours were exposed to various light intensities for the next three hours. Their pineals were then analyzed for serotonin-N-acetyltransferase, an enzyme that participates in melatonin synthesis, with the results plotted here.

of the pineal gland of rats [*see top illustration at left*].

Cycles in environmental lighting can interact with biological rhythms in two ways. The light cycle may directly induce the rhythm, in which case either continuous light or darkness should rapidly abolish it, or the cycle may simply entrain the biological rhythm so that all animals of a given species exhibit maximums or minimums at about the same time of day or night. In the latter case the rhythmicity itself may be generated by a cyclic input other than light, either exogenous (for example food intake) or endogenous (a biological clock). If the cycle is simply entrained by light, an environment of continuous light or darkness might not extinguish it. In human beings psychosocial factors are probably of greater importance than light cycles in generating or synchronizing biological rhythms. The biological utility of even so dramatic a rhythm as that of sleep and wakefulness, for example, remains to be discovered.

Annual rhythms in sexual activity, hibernation and migratory behavior are widespread among animals. The rhythms enable members of a species to synchronize their activities with respect to one another and to the exigencies of the environment. For example, sheep ovulate and can be fertilized only in the fall, thus anticipating the spring by many months, when food will be available to the mother for nursing the newborn. In man no annual rhythms have been firmly established, except, of course, those (such as in sun-tanning and vitamin D_3 levels) that are directly correlated with exposure to summer sunlight.

The best-characterized indirect effect of light on any process other than vision is probably the inhibition of melatonin synthesis by the pineal organ of mammals. Although melatonin seems to be the major pineal hormone, its precise role has not yet been established. When melatonin is administered experimentally, it has several effects on the brain: it induces sleep, modifies the electroencephalogram and raises the levels of serotonin, a neurotransmitter. In addition melatonin inhibits ovulation and modifies the secretion of other hormones from such organs as the pituitary, the gonads and the adrenals, probably by acting on neuroendocrine control centers in the brain.

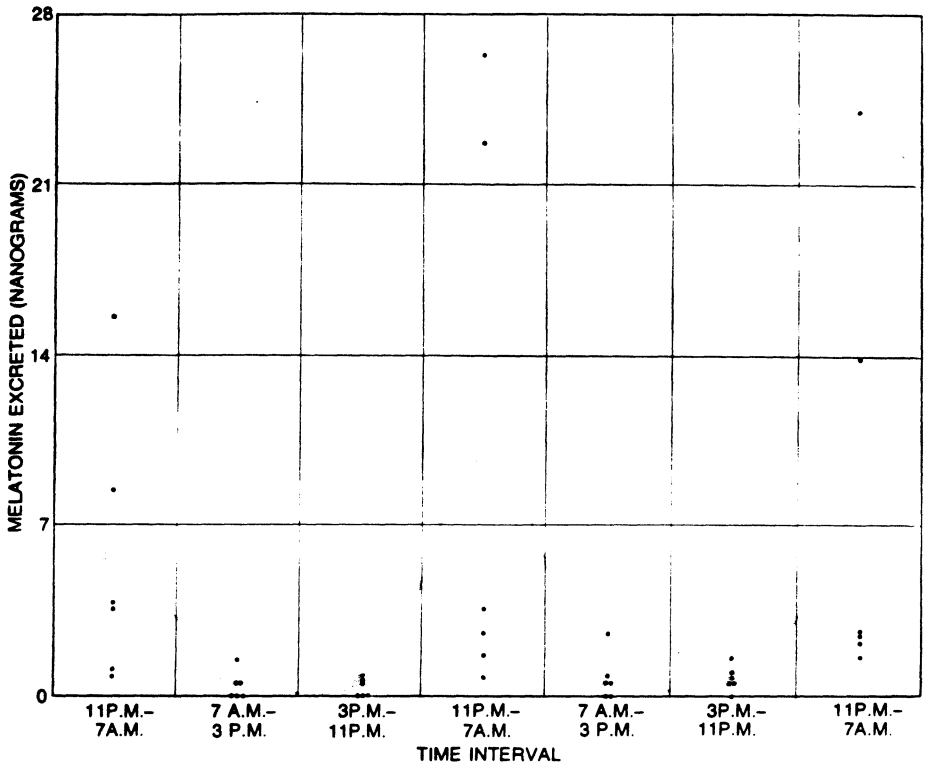
Experiments performed on rats and other small mammals during the past decade provide compelling evidence that the synthesis of melatonin is suppressed by nerve impulses that reach the pineal

over pathways of the sympathetic nervous system. These impulses in turn vary inversely with the amount of visible light impinging on the retina. In rats the pineal function is depressed to half its maximum level when the animals are subjected to an amount of white light only slightly greater than that shed by the full moon on a clear night [*see bottom illustration on opposite page*]. A multisynaptic neuronal system mediates the effects of light on the pineal. The pathway involved, which is apparently unique to mammals, differs from the route taken by the nerve impulses responsible for vision.

Quite recently Harry Lynch, Michael Moskowitz and I have found a daily rhythm in the rate at which normal human subjects excrete melatonin. During the third of the day corresponding to the bedtime hours, 11:00 P.M. to 7:00 A.M., the level of melatonin in the urine is much higher than it is in any other eight-hour period [*see illustration at right*]. It remains to be determined whether the rhythm in melatonin excretion in humans is induced by light or is simply entrained by it.

In some birds and reptiles the pineal responds directly to light, thereby serving as a photoreceptive "third eye" that sends messages about light levels to the brain. In the pineal organ of mammals any trace of a direct response to light is lost. Evidently photoreceptors in the retina mediate the control of the pineal by light. Since, as I have noted, the function of the pineal in rats is influenced most strongly by green light, corresponding to the peak sensitivity of the rod pigment rhodopsin, the retinal photoreceptor would seem to be a rod cell, at least in this species.

Light levels and rhythms influence the maturation and subsequent cyclic activity in the gonads of all mammals and birds examined so far. The particular response of each species to light seems to depend on whether the species is monestrous or polyestrous, that is, on whether it normally ovulates once a year (in the spring or fall) or at regular intervals throughout the year. Examples of polyestrous species are rats (ovulation every four or five days), guinea pigs (every 12 to 14 days) and humans (every 21 to 40 days). The gonadal responses also seem to depend on whether the members of the species are physically active during the daylight hours or during the night. Recently Leona Zacharias and I had the opportunity to examine more than a score of girls and women (members of a diurnally active polyestrous species) who had become blind in the first year of life. We observed that gonadal maturation had in general occurred earlier in this group than in normal girls. In contrast, in rats (a polyestrous species that is active at night) blindness delays maturation, and continuous illumination accelerates the maturation of weanlings with normal vision.



RHYTHM IN MELATONIN SECRETION in human beings has been found by the author and his colleagues. The black dots show the melatonin content of urine samples from six subjects during consecutive eight-hour periods. The colored circles and broken curve correspond to the mean values. High values that were recorded for the 11:00-P.M.-to-7:00-A.M. samples suggest that synthesis of melatonin in man, as in rats, increases with onset of darkness.

The gonads of most birds and of most diurnally active, monestrous animals (the ferret, for instance) mature in the spring, in response to the gradual increase in day length. Ovulation can be accelerated in such animals by exposing them to artificially long days. The annual gonadal activity in domestic sheep, on the other hand, occurs in the fall, in response to the decrease in day length. The mechanisms that cause some species to be monestrous and others polyestrous, or that cause some animals to sleep by day and others by night, are entirely unknown, as are the factors that cause the gonadal responses of various species to light to vary as widely as they do.

The multiple and disparate effects of light I have described support the view that the design of light environments should incorporate considerations of human health as well as visual and aesthetic concerns. We have learned that the chemical constituents of the environment in the form of food, drugs and pollutants must be monitored and regulated by agencies with suitable powers of enforcement. A major part of their responsibility is to see that nothing harmful is put into food or drugs and that nothing essential is left out of food. The food and drug industries, for their part, look to public and private research organizations, including their own laboratories, for intellectual guidance in creating wholesome and beneficial (as well as profitable) products.

In contrast, only minuscule sums have been expended to characterize and exploit the biological effects of light, and very little has been done to protect citizens against potentially harmful or biologically inadequate lighting environments. Both government and industry have been satisfied to allow people who buy electric lamps—first the incandescent ones and now the fluorescent—to serve as the unwitting subjects in a long-term experiment on the effects of artificial lighting environments on human health. We have been lucky, perhaps, in that so far the experiment has had no demonstrably baneful effects. One hopes that this casual attitude will change. Light is potentially too useful an agency of human health not to be more effectively examined and exploited.