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CUTANEOUS PHOTOBIOLOGY: PAST, PRESENT AND FUTURE

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The history and origin of the science of photobiology are reviewed. Interest in the biologic effects of light gradually increased, beginning with the discovery of ultraviolet and infrared radiation early in the 19th century. The basis of experimental photobiology was laid by the studies of Raab and Tappeiner on photodynamic action and the early uses of phototherapy by Finsen and Dorno.

The discovery of the association of porphyrins with some light-related skin diseases and of the capability of chemical agents such as coal tar and bergamot to induce phototoxic contact dermatitis resulted in a flurry of clinical investigations leading to better understanding of the processes of phototoxicity and photoallergy. The early epidemiologic studies of Unna and Dubreuilh relating solar radiation exposure to the formation of actinic keratoses and non-melanoma skin cancer were experimentally confirmed in animals by Findlay, Roffo, and Blum.

In the most recent quarter century (1950–1975), cellular and molecular photobiology has been refined. The studies on photochemistry of nucleic acid and of damage and repair mechanisms in DNA have set the stage for understanding the basic processes of biologic effects of light and promise the development of useful applications of specifically directed phototherapy and prevention of such light-induced diseases as skin cancer.

"And God said, 'Let there be light': and there was light." In just such timeless prose the ancient Hebrews described the origin of all creation and added that "God divided the light from the darkness" [1]. They saw light spectacularly divided into its component parts as a "bow in the clouds" [2]. Countless millenia passed before nature's awesome spectacle became a laboratory spectrum, generated by Sir Isaac Newton's prism [3]. Spectral radiations outside the narrow band of visible light were discovered 125 years later by Sir William Herschel, who in 1800 found that a thermometer registered a higher temperature beyond the visible red end of the spectrum than within it [4], and by Ritter who in 1801 showed a stronger chemical action on silver chloride beyond the visible violet end of the spectrum [5]. That light has harmful as well as salutory effects has been known since antiquity. Xenophon, describing the sufferings of Cyrus's soldiers in the snow, says: "Such of the soldiers . . . as had lost their sight from the effects of the snow . . . were left behind. It was found to be a relief to the eyes against the snow, if the soldiers kept something black before them on their march . . ." [6].

The years between 1950 and 1975 have witnessed a phenomenal growth in the very young science of photobiology. But the maturation of this discipline cannot be fully appreciated until something of its origins, beginning with the discovery of ultraviolet light, is known.

THE FIRST CENTURY: FROM RITTER TO RAAB

The discovery of ultraviolet radiation in 1801 by Ritter [5] did not make much of a stir in medical circles. In 1798 Willan had described sensitivity to light under the term eczema solare [7], a condition with which Rayer was also acquainted [8], but it was not until the latter part of the 19th century that their reports began to attract attention.

The experimental observation that some component of sunlight other than heat affects the skin was first made in 1820 by an English physician, Sir Everard Home [9]. His interest had been aroused by the President of the Royal Society of Medicine, who told him that one hot summer he had observed a silver fish whose back had been so badly exposed to the sun's rays that it was scorched and the surface, which looked as if it had been burned, rose above the scales of the surrounding skin. Exposing one of his own hands to the sun and covering the other with a black cloth, Home showed that the skin of the exposed hand, unlike that of the other,

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Abbreviations:
UV: ultraviolet
UVA: ultraviolet A (320–400 nm)
UVB: ultraviolet B (280–320 nm)
UVC: ultraviolet C (200–280 nm)

became "scorched" even though a thermometer registered 4° to 10° higher on the hand under the black cloth. To demonstrate the protective effect of pigmentation, he exposed the back of a Negro's hand to the same sun and the same temperature without eliciting an effect. Without knowing of Home's work, Finsen [10] in 1900 repeated the "black cloth" experiment under nearly identical conditions.

Home's experiments were confirmed in 1829 by Davy [11], who tried unsuccessfully to discover whether the different rays of the solar spectrum produce different effects.

Charcot [12], working with electric arcs, was the first to determine that ultraviolet radiation causes conjunctivitis and skin erythema. In 1860, Bazin [13] described three types of bullous lesions which he grouped under the term hydroa, one of which, hydroa vacciniforme, appeared to be induced by light. Kaposi described xeroderma pigmentosum in 1870 [14] but did not refer to its relation to light, a fact discovered by Unna in 1894 [15]. Hutchinson discovered prurigo aestivalis in 1878 [16], and nine years later [17] Veiel described eczema solare, which probably corresponded to Rasch's eczema-like polymorphic light eruption [18].

Most of the early attempts to classify these diseases were based on the appearance of the lesions; usually the only evidence that light was an etiologic factor was the fact that the eruptions were confined to those parts of the body not protected by clothing. When sunburn of normal skin was shown to be induced by ultraviolet (UV) radiation [12,19,20], workers tended to attribute all abnormal effects to "chemical" (i.e., UV) radiation.

In 1898, Anderson [21] discovered porphyrinuria in two of his patients, and it was soon recognized in other patients.

While studying the toxicity of the dye acridine for paramecia during the winter of 1897–98, Raab [22], a student in Tappeiner's laboratory in Munich, found that the death of these organisms depended not only on the concentration of the dye but also on the intensity of the light in the laboratory. Apparently the dye rendered the organisms sensitive to light in somewhat the same way as the photographic plate is sensitized. Raab's findings led to a long series of studies, principally by Tappeiner and Jodlbauer in the Munich laboratories [23], and to the formulation of the theory of photodynamic action. That this was a catalytic effect was shown by Straub in 1904 [24].

THE PERIOD OF DISCOVERY (1900–1925)

Within a relatively short time, the numerous intensive studies triggered by Raab's serendipitous observation led to the discovery that many dyes and pigments, such as eosin and chlorophyll, can sensitize various organisms and tissues, including human skin, to light [23,25–28]. All this came at a time of intense interest in the biologic effects of light and after the pioneer work of Finsen, whose successful phototherapy and other photobiologic studies had aroused widespread interest among biologists and physicians [29].

After Finsen's work and Downes and Blount's [30] discovery of the bactericidal action of uv radiation in 1877, heliotherapeutic institutes were established in 1902 in Denmark for skin tuberculosis and in Switzerland for bone and gastrointestinal tuberculosis. Four years later, almost coincidentally, Küch [31] built the first workable enclosed UV lamp, a mercury vapor arc, in Hanau, Germany, and by 1911 improved versions began to be used for medical purposes by Nagelschmidt [32].

The First Studies of the Action Spectra for Erythema and Pigmentation of Human Skin

During World War I, while working near the battlefronts to keep the first mobile x-ray units in operation, the chief radiation physicist for Siemens-Halske AG, Karl Hausser, contracted pulmonary tuberculosis and was sent to the heliotherapeutic sanitarium at Davos, Switzerland, then under the direction of Professor C. Dorno, another of the early medical photobiologists. When his health permitted, Hausser, an astute observer of nature, took long hikes into the mountains where he observed that, during the afternoon hours, a long hike on a glacier under the burning sun had had almost no effect whereas "a brief sojourn on snow at noontime resulted in a severe sunburn" [33]. Being an experienced radiation physicist with considerable knowledge of the composition of natural solar radiation and of its changes with the angle of the sun, Hausser proceeded to investigate these observations. The results were the first detailed studies of action spectra for erythema and pigmentation of the human skin. These studies were performed so meticulously and with such attention to minute details that to this day the proposed action spectra have only been refined but not radically altered. Very briefly, Hausser and Vahle [33] showed that skin erythema and pigmentation depend on the wavelengths of UV radiation; that the effect is limited mainly to wavelengths shorter than 320 nm; that the erythema produced by various wavelengths differs qualitatively as does the time course of the reaction; and that the marked variations in the erythema-producing capacity of sunlight, which are related to season and time of day, are due to the fact that the steep rise in erythema effectiveness lies in a narrow band of wavelengths around which the UV end of the sun's rays varies.

The Role of Light in the Pathogenesis of Skin Diseases

Changes in normal skin because of chronic insolation. That sunlight can cause acute and chronic changes in apparently normal skin has been known since antiquity. " . . . I am swarthy, because the sun has scorched me" [34]. Charcot [12] determined that acute erythema was due to UV radiation but Unna was the first to prove that

pigmentation could be induced by UV radiation [15]. It soon became apparent that the skin's tendency to react to light by pigmenting varies widely, not only among different races but also among individuals of similar ancestry. Hausser and Vahle [33] had shown that the longer UV wavelengths are more effective in producing pigmentation than the more erythemogenic shorter wavelengths. Later, Bloch performed his classical experiments on the mechanism of melanin formation in human skin, discovered dopa-oxidase, and laid the groundwork for the development of skin histochemistry [35]. Hammer [19] and later Ehrman [36] had shown that freckling is a dominant hereditary trait; decades later, this observation was shown to be related to a predisposition to skin carcinogenesis.

Changes in the stratum corneum, epidermis, and dermis as a result of chronic light exposure were first associated with UV radiation by Unna [15], who observed a thickening and brownish discoloration of the stratum corneum of light-exposed areas of skin and hyperplasia of the epidermis. With [37] was the first to report that the thickening of the stratum corneum provides some protection against further UV injury; later Guillaume [38] and then Miescher [39] documented this fact in detail. Miescher also showed that, eventually, a peculiar degeneration of the elastica and collagen of the skin develops, almost always on the most exposed areas of the skin of old persons constantly exposed to the sun [39].

From antiquity, the face and hands have been observed to be a warmer red and to have more marked pigmentation. As Finsen first observed [10], this persistent erythema is principally due to UV light. He also reported that skin intensively exposed to UV radiation continues to react to minor mechanical or thermal irritation many months after both the early erythema and pigmentation have disappeared. In other words, a single dose of UV radiation is sufficient to cause permanent damage to the blood vessels [10]). Chronic insolation also causes permanent vasodilation, e.g., the "dermatose du triangle sterno-claviculaire" of Brocq, which occurs in the V of the neck area of women.

The first intimation that skin cancer might be due to prolonged and repeated exposure to light came almost simultaneously from two sources. Unna associated the severe degenerative changes on the exposed areas of the skin of sailors with the development of skin cancer, which he diagnosed with astonishing regularity in his clinic in Hamburg, an old seaport town [15]. The same year (1894), Dubreuilh, studying skin diseases in the Bordeaux region of France, observed the frequent incidence of keratoses and skin cancer in the workers in the vineyards, but only occasionally in the city dwellers nearby [40]. These observations were later confirmed by Shield [41], Hyde [42], Paul [43], and others, who observed a high incidence of skin cancer among country people in the USA and Australia, where light exposure is much more intense than in Central Europe. In 1922, Bruusgaard [44] reported that the frequent incidence of skin cancer among sailors was due to a combination of sunlight and coal tar, to which sailors were heavily exposed in those days.

Effect of light on abnormally photosensitive skin. Anderson [21] was the first to suggest the association of porphyrins with hydroa aestivale. In 1908, Hausmann [45] had found that hematoporphyrin is a photosensitizer of the photodynamic type. A year later Ehrman [46] had connected this with the occurrence of porphyrinuria in hydroa and had suggested that the lesions result from the sensitization of the skin to light by porphyrins. In 1912, Günther [47] correlated porhyrinuria with hydroa and described four types, in only two of which light sensitivity was associated with porphyrin excretion. Finally, Meyer-Betz [48] sensitized himself to light by intravenous injections of hematoporphyrin; remaining sensitive to light for two months, he proved that man becomes sensitive to light in the presence of porphyrins.

The discovery that porphyrinuria is related to at least some photodermatoses was exciting, but it soon became apparent that in some clinically classical photodermatoses no abnormality of porphyrin metabolism could be demonstrated. Of greatest importance were the delineation of chronic polymorphic light eruption by Rasch [49] and Haxthausen and Hausmann [50] and the time-honored observation of light-induced hyperpigmentation in pellagra.

Sensitization of skin by chemical agents. That topically applied agents can photosensitize skin was first reported by Lewin in 1913 [51], who observed erythema and burning and itching of exposed skin sites in workers using coal tar pitch. He rightly ascribed this to a photodynamic reaction. In retrospect, the observation that topical agents could photosentize skin was not new. Reference to the use of a plant extract for the production of pigmentation had been made in the Atharva Veda (ca. 1400 B.C. [52]) and to the phototoxic effect of the psoralens by the Arabic physician, Ibn El-Bitar (ca. 1250 A.D. [53]). In 1916, Freund [54] observed cutaneous phototoxic reactions to eau de cologne and correctly concluded that the active ingredient was probably oil of bergamot. This phototoxic effect of cologne was independently rediscovered in 1925 by Hoffman and Schmitz [55], and eight years earlier Oppenheim had described a photodermatosis that was due to contact with field plants (dermatitis striae praetensis) [56].

In 1929, Haxthausen and Hausmann [50] had shown that the administration of various drugs and chemicals by mouth or parenterally causes photosensitization. During therapy with diamino methyl acridine (trypaflavin) for gonorrhea, Jausion and Pagès [57] observed "coup de lumière acridinique," and Haxtausen and Hausmann associated luminal administration with a light-induced eruption as a result of the induction of porphyria [50].

Early investigation of phototherapy. The use of extract of the plant *Ammi majus* Linn for phototherapeutic treatment of vitiligo goes back to antiquity. It is referred to in the holy Indian writings [52] and documented in detail by Arab physicians of the Middle Ages [53]. This time-honored therapy did not come to the attention of Western physicians until the early 1950s, but in 1925 Axman, using eau de cologne containing bergamot [58], had accidentally rediscovered this use of plant extracts.

Palm [59] was the first to indicate that light might be of therapeutic value in rickets. Huldschinsky's [60] incidental discovery of the effect of irradiation, with the mercury vapor arc, on the radiographic manifestation of rickets started the train of events which stimulated many investigations on the effects of UV radiation and finally led to Steenbock and Daniels's [61] discovery of vitamin D and its activation in the skin.

The pioneer of modern phototherapy in dermatology was Finsen, whose extensive and elegant experiments on the treatment of skin tuberculosis with natural and artificial UV radiation stimulated the current interest in cutaneous photobiology [29]. The first medical use of chemically enhanced phototherapy (other than for the restoration of pigmentation) was reported by Jesionek and Tappeiner in 1905 [62]. These pioneers in the study of photodynamic action treated five basal cell carcinomas by injecting eosin into the tumor and exposing it to light; three cures were reported. Tappeiner and Jodlbauer showed that bacteria, fungi, and various parasites can be killed by photodynamically active agents [23]. On the basis of the phototoxic reaction to acridine observed in man, Jausion and his co-workers extensively investigated its use in various skin diseases, particularly in alopecia areata, but met with indifferent success [57]. Finally, in 1925, Goeckerman [63] successfully used the phototoxic effects of coal tar described by Lewin [51], together with UV radiation, to treat psoriasis.

THE PERIOD OF CONSOLIDATION (1926–1950)

During the first quarter of the 20th century, photobiologists had concentrated on learning the effects of various UV wavelengths on cells and tissues, exploring the principles of photodynamic action, and describing and studying the pathogenesis of light-induced skin diseases. Since the variable effects of natural sunlight had long been known, most of this work was done with artificial light sources, none of which really simulated the spectral composition of sunlight. During the second quarter of the century, serious attempts were made to quantify previous observations and build on the accumulated knowledge.

Instrumentation

During this period, better instruments for measuring the spectral composition of light were developed, incorporating diffraction gratings and electronic photocells. The meteorologic physicists had by then measured the spectral composition of sunlight, and the absorption characteristics of ozone and its presence in the stratosphere had been well documented [64].

Correlating field measurements of solar ultraviolet B (UVB 280–320 nm) with the development of skin erythema had shown that at least half of UVB reaches the ground from scattered sky radiation rather than directly from the sun [65]. The amount and composition of UVB at ground level were reported to be greatly affected by the ozone concentration in the stratosphere, by albedo, and by the angle of the sun (i.e., time of day, latitude, and season). Other variables include contamination of the atmosphere by scattering particles (dust, aerosols, haze, clouds). The principles behind natural protective devices were advanced about this time [65,66].

Immunologic Photosensitivity Reactions

That skin disturbances caused by light may be due to an allergic (immunologic) mechanism was discovered after the concept of "allergy" had been formulated. Merklen [67] and Ward [68] established solar urticaria as a clinical entity. Epstein [69] reviewed comprehensive studies on this subject, and Rajka [70] used serum passive transfer to demonstrate specific antibody. Blum, Allington, and West [71,72] showed that the symptoms of urticaria solare could be elicited by different wavelength ranges in different patients, an indication that more than one photochemical reaction could cause this clinical manifestation, which should thus be regarded as more than one disease.

In addition to this immediate type of solar urticaria, Epstein [69] induced a delayed, eczematous type of photoallergic reaction by the intradermal administration of sulfanilamide, and Burckhardt [73] confirmed the presence of delayed photoeczematous dermatitis and introduced the photopatch test. The elegant and detailed studies on the immunologic reactions taking place in these disorders were to come in the future.

Photocarcinogenesis

After Unna [15], Dubreuilh [40], and others made the clinical association of chronic sunlight exposure to skin cancer, dermatologists debated whether this association is found in all white-skinned people, or, as Haxthausen and Hausmann had proposed [50], only in those carrying a forme fruste trait of xeroderma pigmentosum. This latter view began to change when, in 1928, Findlay [74] found that daily irradiation of mice with UV from a mercury arc induced skin cancer. Findlay had also observed that when mice are treated with tar before exposure to UV radiation, the time needed to induce skin cancer is reduced. In 1933, he produced skin cancer in rats with UV light [75]; his findings were soon corroborated by Putschar and

Holtz [76]. Sarcomas of the eyes of rats were produced with UV radiation by Huldschinsky in 1933 [77].

The individual most responsible for calling attention to the causal relation between solar and artificial UV radiation and skin cancer in man and experimental animals was Roffo [75]. In a series of studies between 1930 and 1936, Roffo showed that skin cancer could be induced in rats with natural sunlight as well as with mercury arc radiation, and he carried out the first real epidemiologic study on skin cancer in man [78]. Like Dubreuilh, he emphasized that the skin areas most likely to develop skin cancer also showed a strong tendency to produce hyperkeratoses, which he considered to be premalignant lesions. Finally, Roffo carried out the first action spectrum studies of skin photocarcinogenesis where he showed that clear window glass is sufficient to prevent the production of skin cancer by both natural sunlight and mercury arc radiation and thus set an approximate limit of less than 320 nm for effective UV radiation [79].

In 1941–1944 Blum, Grady, and Kirby-Smith at the National Cancer Institute performed a comprehensive series of experiments on UV carcinogenesis in mice [80,81]. Taking advantage of a stable photoelectric cell developed by Rentschler of Westinghouse and an integrating meter devised by Kuper, Brochett, and Eichen at the National Institutes of Health, Blum and his associates, confident of the reproducibility of the dosage from day to day, repeatedly exposed albino mice to UV radiation and finally obtained highly reproducible cancers. Variability was reduced by using only male animals and a genetically homogeneous strain (strain A) and by limiting the quantitative observations to only one part of the body, the ear. For details of these elegant experiments, Blum's classic work, *Carcinogenesis by Ultraviolet Light*, should be consulted [81].

Blum reported several important observations on tumor induction:

1. A single dose of UV light did not induce tumors during the lifetime of these animals.

2. A useful measure for tumor induction was the "development time," i.e., the time lapse between the first UV dose and the appearance of a tumor of a certain volume. Within an identically treated population of mice, this was distributed in a consistently regular fashion (Fig. 1).

3. Differences in dose, intensity, or interval between doses did not alter the shape or the slope of the dose–time relation but only moved their relative position along the dose axis (Fig. 2).

4. The incidence of skin cancer was well distributed in the mouse population when plotted against the logarithm of the square of the number of doses [82].

5. Reciprocity held until the dose became too small to produce tumors in the lifetime of the animal.

Chemically pure phenanthrene compounds which produced skin cancer in rodents had been isolated in the early 1930s. Findlay [74] had already reported that an application of coal tar, followed by UV radiation, increased the probability of skin carcinogenesis and shortened the development time of the tumors. In 1935, Lewis [83] had observed that "When certain cancer-producing hydrocarbons were added to cultures of chick embryo tissue, the cells developed photosensitivity to the electric light used for the study of cells in tissue cultures. The photodynamic action caused definite changes in the state of the cell protoplasm, which were often accompanied by inhibited cell division. This brought about a later occurrence of abnormalities of mitosis that duplicated many of the types of abnormal mitosis characteristic of malignant growth."

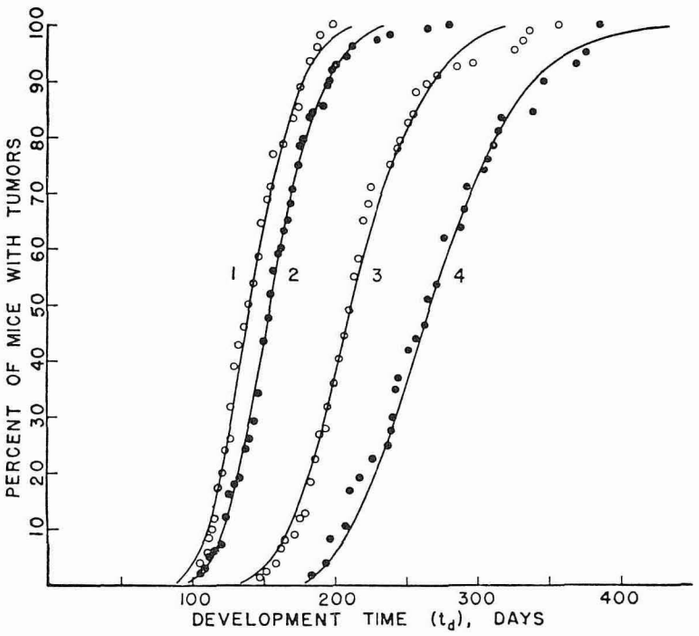

FIG. 1. Plot of percentage of mice with tumors against the development time t_d under different conditions of dosage. *Curve 1:* Single dose 2×10^7 ergs·cm^{-2}, dose rate 4.3 ergs·cm^{-2}·sec^{-1}. *Curve 2:* 2.6×10^7 ergs·cm^{-2}, dose rate 4.3 ergs·cm^{-2}·sec^{-1}. *Curve 3:* 1.8×10^7 ergs·cm^{-2}, dose rate 3.3 ergs·cm^{-2}·sec^{-1}. *Curve 4:* 1.8×10^7 ergs·cm^{-2}, dose rate 0.18 ergs·cm^{-2}·sec^{-1}. (From Blum [81])

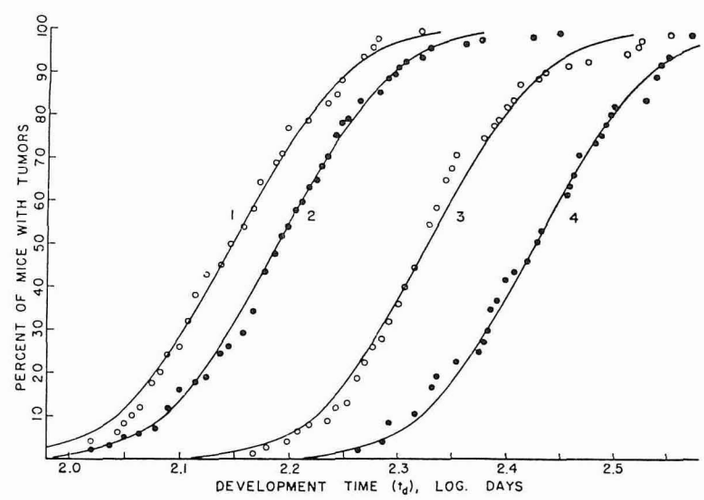

FIG. 2. The same data apply as for Figure 1, but they are plotted in terms of the logarithm of the development time. (From Blum [81])

Mottram and Doniach [84], who compared the carcinogenic and photodynamic activity of various hydrocarbons as well as of tar, soot, and shale oil, found a strong correlation between the two activities. When experimental studies in animals were performed, however, various investigators found either potentiation or even protection during simultaneous carcinogen and UV radiation exposures [85,86]. It was not until decades later that the explanation for these discrepancies became apparent, namely, that not only are the carcinogenic phenanthrenes photodynamically active, but they can be photochemically decomposed to noncarcinogenic photoproducts as well (see below).*

International Cooperation in Photobiology

Today photobiology has become an interdisciplinary study of great importance. Mankind is entirely dependent on solar radiation, and the interactions between light and matter are the subject of intensive investigations by physicists, chemists, biologists, and medical scientists throughout the world. Organized photobiology had its beginning in 1928. The need for international cooperation was first recognized by dermatologists who were studying erythema and other effects of light on human skin. Among the organizers of the first international meeting were the dermatologists Saidman and Jausion from France. The first international committee (Comité International de la Lumière) was organized with Axel Reyn of Sweden as the president. The First International Congress of Light was held in Paris in 1929, with Saidman as president. The Second Congress in 1932 counted among its 42 members such giants as Bernhard, Miescher, Hausser, Jesionek, Lomholt, and Reyn. The subjects for general discussion were a standard unit for biologically effective UV radiation (which to this date does not exist!), the therapeutic effect of general "light" baths, and helioclimatologic research in relation to public health [87].

In 1951, the name of the group was changed to Comité Internationale de Photobiologie. Two of the Finsen medals were given to cutaneous photobiologists: H. Jausion in 1951 for his studies of phototherapy and P. B. Rottier in 1960 for fundamental studies of the basic phenomena underlying the formation of erythema of the human skin by UV radiation [87].

In the United States, the American Society of Photobiology was founded in 1972 as the official national member of the Comité Internationale de Photobiologie, with a dermatologist as a member of the charter councilors.

THE PERIOD OF MOLECULAR PHOTOBIOLOGY (1950–1975)

Advances in Instrumentation

Light sources. Until the third quarter of the 20th century, photobiologic studies were carried out mainly with two kinds of light sources: the low-pressure mercury arc, which emitted practically only a single wavelength (253.7 nm), and various medium-pressure and high-pressure mercury arcs, which emitted mixtures of resonance lines. Because of their instability and unreliability, carbon arcs had almost disappeared.

Interest in the technology of light production, stimulated by industrial, military, and space application needs, gave rise to new and medically useful light sources. The use of UV-emitting phosphors in fluorescent lamps resulted in relatively inexpensive light sources with defined spectra which could simultaneously irradiate large areas (Fig. 3). Particularly in recent years, phosphor technology has advanced to the point where tailoring output spectra to specific photobiologic uses is possible, e.g., "bilirubin blue" lamps for phototherapy of hyperbilirubinemia, high-intensity ultraviolet A (UVA 320–400 nm) phosphors for psoriasis therapy, etc. A veritable arsenal of phosphors and techniques is available from lamp manufacturers.

As knowledge of photochemistry deepened, it became apparent that the chromophores in photochemical reactions could be defined from their action spectra. For such purposes, monochromatic light sources were needed, and thus high-transmission, small monochromators which were relatively free of stray light were developed. Improvement in diffraction gratings, discovery and use of Fabry etalons, and development of narrow-band, high-transmission, thin film filters all made for less dependence on the cumbersome and expensive

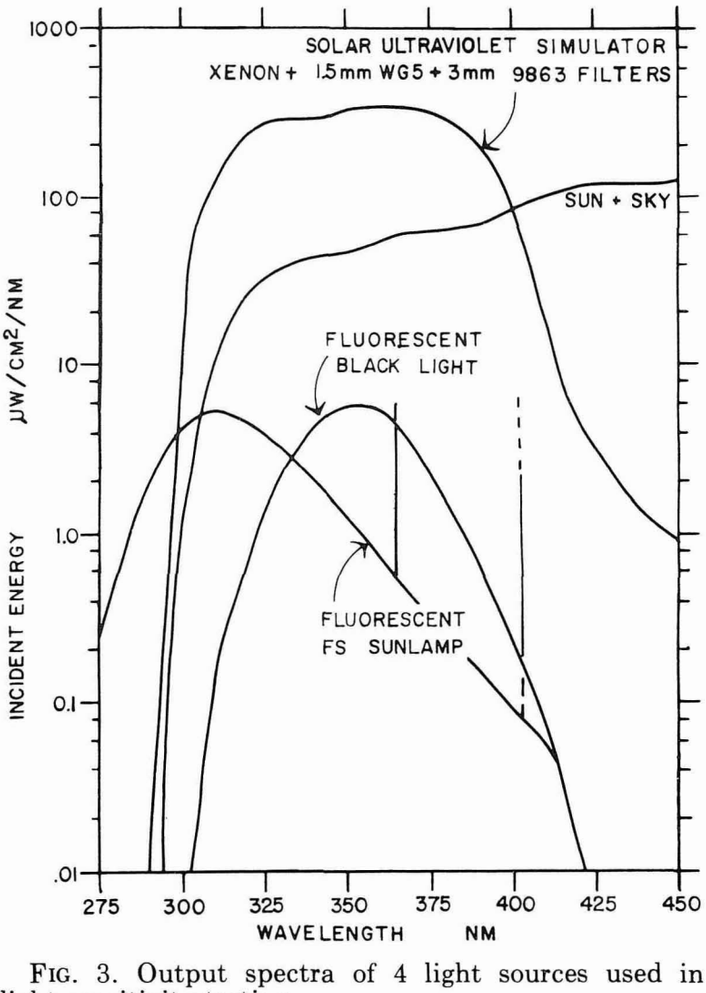

FIG. 3. Output spectra of 4 light sources used in light-sensitivity testing.

*Davies RE, Dodge HA, Austin WA: Carcinogenicity of DMBA under various light sources. Abstract #347, Proceedings of the VI International Congress of Photobiology, Bochum, Germany, 1972.

quartz prisms of earlier days [88]. Although valuable single wavelength studies have been conducted with lasers, a continuously tunable UV laser is not yet available. When developed, such lasers will greatly advance the study of action spectra.

The needs of space research and cutaneous photobiology stimulated the development of solar simulators. The combination of high-powered xenon arcs with continuous spectra, improvement in the design and construction of quartz lens systems, and the design of high-efficiency power supplies have enabled us to construct light sources whose spectrum resembles that of natural sunlight but whose UV intensity, augmented by up to an order of magnitude over the solar constant, significantly reduces exposure time [89].

Light-measuring devices. For modern photobiologic studies, it is necessary not only to control the spectral composition and intensity of the light beam used but also to produce accurate and reproducible measurements. In the past two decades, much more sensitive thermopiles, reliable and stable amplifiers, photomultiplier vacuum tubes with various spectral characteristics, and silicon photodetectors sensitive in the UVB spectrum have been developed. With the highly stable DC amplifiers, available since the advent of parametric operational amplifiers, accurate observations can be made simply. However, spectroradiometric measurements of light sources with line or continuous spectra are still difficult procedures, and the rapidly varying shape of the action spectra of many biologic phenomena prompted the search for analog detectors, with a spectral response similar to that of the biologic system to be investigated.

Cadmium cathodes were used in Potsdam and Davos as early as 1910. The first integrating analog meter was designed by Rentschler who used a zirconium photodiode in the mid-1930s. These photodiodes, however, suffered from individual variability, temperature sensitivity, and the unavailability of good amplifiers. In the mid-1950s, Robertson developed a UVB detector based on a magnesium tungstate fluorescent phosphor and used an unusually stable cold cathode thyratron to amplify the weak detector output [90]. This system had spectral characteristics closely simulating those of the skin erythema action spectrum and was useful for continuous measurements of natural solar erythemal UVB in the field (Fig. 4). In 1972–1973, Robertson and Berger redesigned this detector, and continuous measurements of solar erythemal UVB are now being made in 22 locations in North America, Australia, Hawaii, and Europe [91] (Fig. 5).

Although these instruments can be used for rate or flux measurements, they are generally operated as integrating "dosimeters." The values obtained are proportional to the total UVB input and are weighted at each wavelength by the characteristic excitation spectrum of the phosphor. These integral values cannot be resolved into wavelength-specific components without independent information concerning the spectral composition of the source. In practice, the integral values are regarded as analogs of the erythemogenic potency of the total UV dose because the excitation spectrum resembles the generally accepted erythemogenic action spectrum. The inherent assumption is that an action spectrum can be multiplied, wavelength by wavelength, by the input spectrum, and that the components of the resultant effectiveness spectrum can be summed to give an effective dose; this, however, is true only if each wavelength acts independently and additively. The further extrapolation of relating such "doses" to biologic responses with different or unknown action spectra becomes increasingly tenuous as the differences between the phosphor excitation spectrum and the biologic response spectrum increase [92].

Action spectra. A defined photobiologic response can be characterized in terms of its action spectrum. This is a measure of either the magnitude of response to a given amount of each effective wavelength or (more commonly) the amount of each wavelength required to produce a defined magnitude of response (usually expressed in normalized inverse form). Determinations of action spectra are beset with problems, both practical and theoretical. The relative effectiveness of different wavelengths may differ by orders of magnitude; experimental and equipment limitations usually dictate that their effects be studied at greatly different intensities. Such comparisons require close adherence to the Bunsen–Roscoe law of dose–time reciprocity which may be difficult to

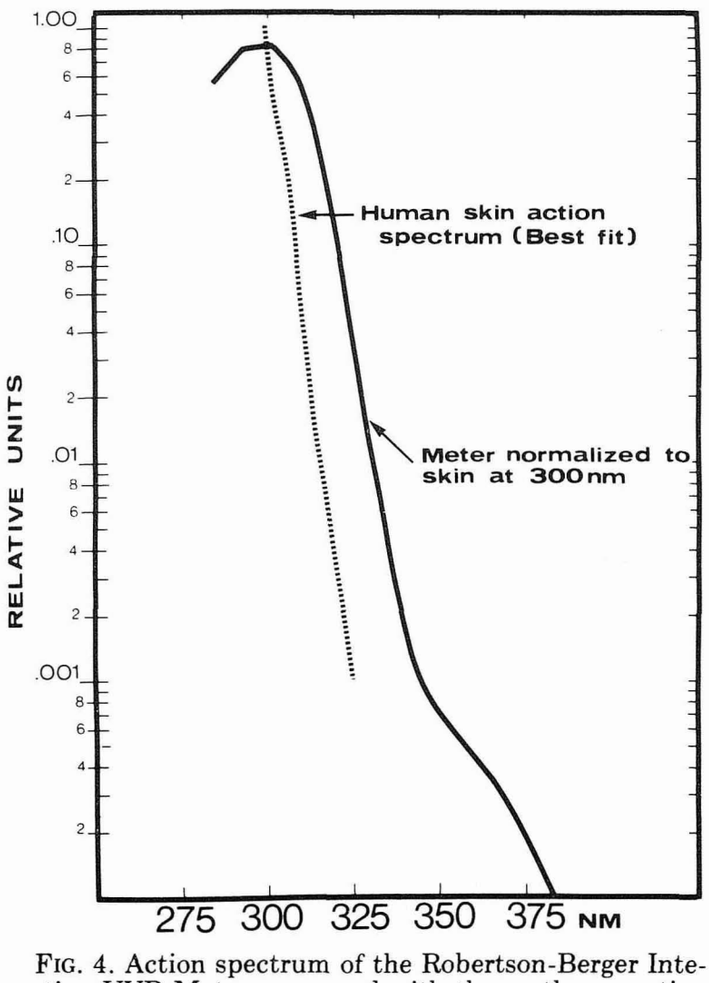

FIG. 4. Action spectrum of the Robertson-Berger Integrating UVB Meter compared with the erythema action spectrum of human skin [141].

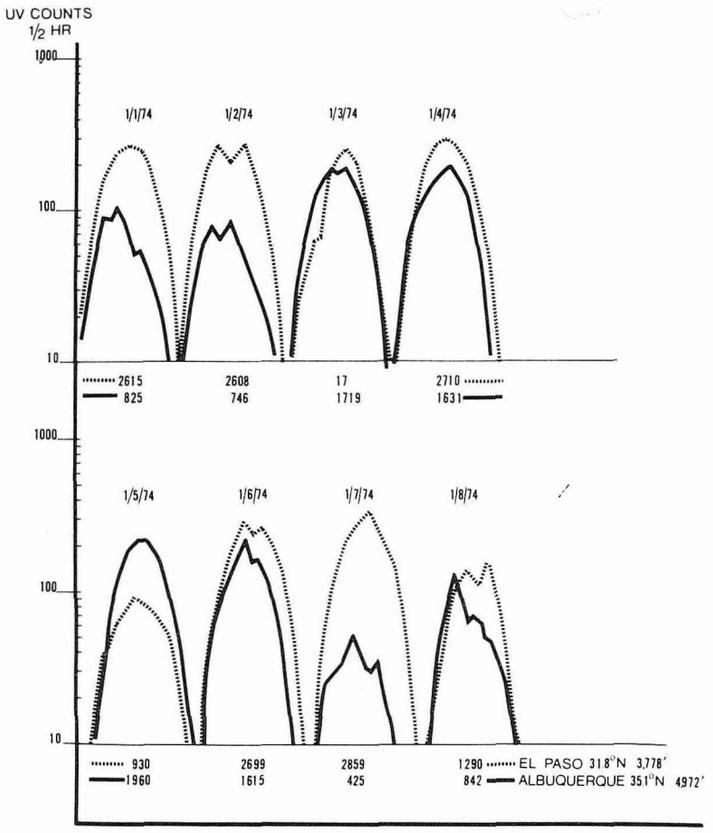

FIG. 5. Half-hourly readings of erythemal UV light taken from Robertson-Berger meters in Albuquerque, New Mexico, and Tallahassee, Florida, in January, 1974. Note the marked effect of cloud cover at Albuquerque compared with the almost daily clear weather in El Paso [141].

demonstrate experimentally. Moreover, since dose, delivery time, and flux (intensity) are interrelated variables, only two of which can be varied independently, even the limits of reciprocity can be difficult to define. For these and other reasons, few biologic action spectra are known in detail.

As monochromators became more available and more refined in terms of stray light rejection and intensity of primary light sources, additional details of the action spectra for cutaneous erythema, pigmentation, and several photodermatoses were described. The most intensive studies of this type were carried out first by Paul Rottier, beginning in 1953. He demonstrated that, although the absolute sensitivity of skin to any one wavelength differs greatly, the realtive sensitivity, particularly of the peaks (260 and 300 nm), is constant and that such ratios of sensitivity can be used to determine abnormal reactions, particularly those that are due to "foreign" substances sensitizing the skin [93].

In 1959, Magnus [94] in London and Wiskemann and Wulf [95] in Hamburg began systematically to study the action spectra for skin erythema in normal and diseased skin. Currently, information is available about the action spectra for various phototoxic agents (tar, pitch, 8-methyoxypsoralen, chlorpromazine) and photodermatoses (solar urticaria, porphyria cutanea tarda, chronic polymorphic light eruption). A new disorder, erythropoietic protoporphyria, was discovered by Magnus and co-workers, who used the action spectrum as a guide [96].

The disagreements which developed during the 1960s over the shape of the action spectrum for "normal" skin erythema were due to differences in the time lapse from irradiation to determination of erythema, i.e., a prblem of clear description and definition of end point [96] (Fig. 6). Only in the past few years has it been shown conclusively that skin erythema can be reproducibly induced by wavelengths in the 330 to 380 nm range and that the energy required is 1000 to 2000 times greater than that needed at 300 nm.

Skin cancer has long been known to be induced by UVB and UVC (200–280 nm) [81], but the precise shape of the action spectrum for skin photocarcinogenesis is not known. Roffo [79] and Funding, Henriques, and Rekling [97] showed that wavelengths longer than 320 nm did not produce skin cancer; under conditions resembling natural human exposure, this long wavelength limit still appears to be correct. However, chronic continuous irradiation of hairless mice with erythemogenic doses of UVA also produced skin cancer [98]. The lack of detailed information on the shape of the carcinogenesis action spectrum makes any prediction about the biologic consequences of modifying the stratosphere uncertain (see below).

Cellular and Molecular Photobiology

The widely varied effects of UV radiation on many cell types and organisms have been reported

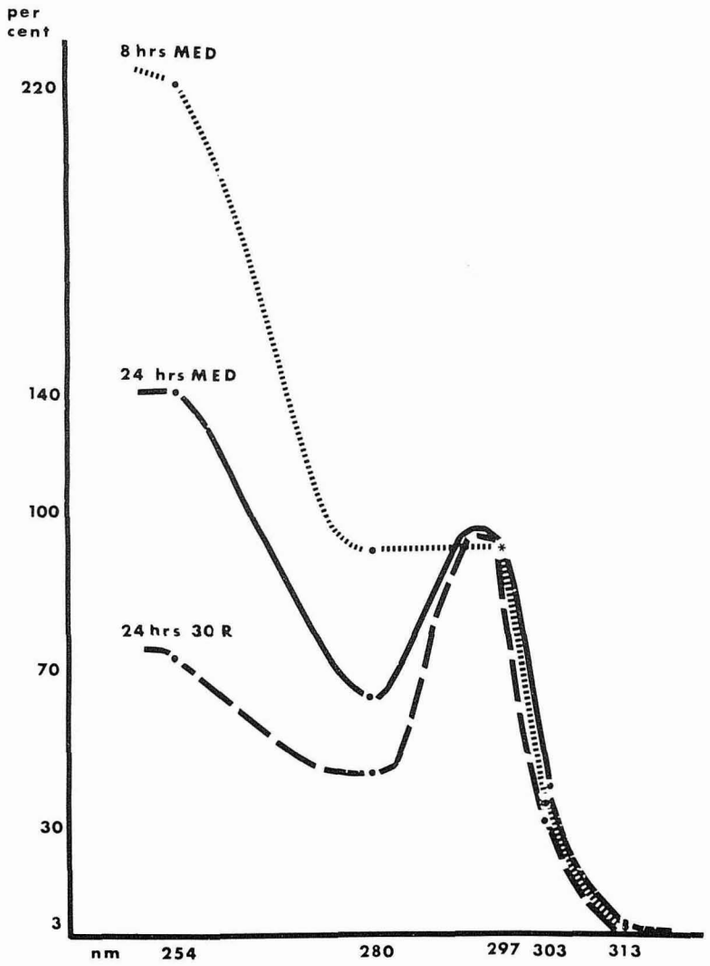

FIG. 6. Erythema action spectra for normal human skin. Note great similarity for wavelengths from 297 to 313 nm, and marked differences for minimal erythema dose (*MED*) read at 8 hr, 24 hr, and a curve constructed by using values for moderate erythema (24 hr, 30 r). (From Berger et al [88])

over the past 100 years, but this early work failed to appreciate both the need to control the wavelengths of the light and the importance of the physiologic state of the biologic system before, during, and after the radiation. In 1929, Gates had discovered that the relative effectiveness of different wavelengths in killing bacteria paralleled the absorption spectrum of nucleic acid [99], but the chemical basis for some of the deleterious effects of UV radiation on nucleic acids did not become evident until the late 1940s. More recently, the discovery by Beukers and Berents of UV-induced thymine dimers in DNA stimulated an interest in molecular UV photobiology [100]. We now know that many other types of photoproducts besides thymine dimers are formed in the nucleic acid of cells, some of which have been isolated and characterized [101]. In several, their relative biologic importance has also been determined.

Photochemistry of Nucleic Acids

Some of the biologic effects of UV radiation can now be explained in terms of specific chemical and physical changes produced in DNA. DNA can be structurally damaged by chemical mutagens and radiation and repaired by cellular enzyme systems; thus it serves as the substrate for repair enzymes (see below). How many such structural changes can be induced, we still do not know, but it may be useful to discuss briefly the most frequently formed products whose actions are best understood. Some structural defects disrupt the continuity of the molecule, others interfere with replication or transcription by changing hydrogen bonding. Single-strand breaks and DNA–DNA cross-links are induced by UV radiation, but usually at such high doses that their practical importance is questionable [102]. Pyrimidine hydrates are apparently not formed efficiently in double-stranded DNA but in single-stranded DNA and may be important in the induction of mutations. The cyclobutane type dimers formed by pyrimidines (separately and as mixed dimers) are chemically the most stable and well-defined lesions produced by UV radiation in DNA [100,101]. Dimers can also be formed either between thymine and cytosine or between cytosine pairs alone [103]. Their formation involves linking the 5,6-unsaturated bonds to form a cyclobutane ring and must distort the phosphodiester backbone of the double helix in the vicinity of each dimer. In bacteria, a UV dose of 1 erg/mm^2 produces about 6 pyrimidine dimers in a DNA molecule containing 10^7 nucleotides. This is the approximate number of nucleotides in the genome of *Escherichia coli* [104]. The biologic importance of this type of dimer has been demonstrated in certain situations [105]; but since this type of photoproduct is not formed in DNA under all conditions, other types of photoproducts must also be significant. Under certain conditions, DNA cross-links with protein [102]. One chemical mechanism for this cross-linking may involve the attachment of amino acid residues through their SH or OH groups to the 5- and 6-carbon of cytosine and thymine. The sensitivity of DNA to alteration by UV radiation can be changed by various factors, especially by changes in the environment or physical state or in the base composition.

Finally, the biologic importance of any given photochemical alteration of nucleic acid depends on whether or not it is formed under a particular set of biologic conditions, and, if so formed, whether the biologic system can repair the lesion [101].

DNA Repair

Since biologically important amounts of UV radiation reach the earth and must have done so since the beginning of organic evolution, mechanisms must have arisen very early in biologic time to aid in the recovery from the damage done by photons.

In recent years, three kinds of recovery have been described: (1) The damaged molecule or part of a molecule can be restored to its functional state in situ either by an enzymatic mechanism or by "decay" of the damage to some innocuous form. (2) The damaged part can be removed and replaced with undamaged material to restore normal function. (3) The cell may either bypass or ignore the unrepaired damage.

Because the sequence of events needed for appropriate biologic replication and normal function of DNA molecules is important, conditions favorable to the survival of a cell usually require that any successful molecular repair process must be completed within some narrowly defined period of time. Furthermore, the type as well as the extent of recovery depends on the nature of the damaged molecule.

Several different repair mechanisms have already been described, and other kinds are being discovered with increasing frequency as new methods for photoinjury and analysis of repair are developed. Excellent reviews of several of these repair mechanisms can be found in Smith and Hanawalt [101] and in the proceedings of a symposium on molecular and cellular repair processes [106]. Here only the most important and best known will be described.

Enzyme-catalyzed photoreactivation. This best-known form of in situ repair uses illumination with light to facilitate the direct repair in situ of photoproducts produced by absorption of UV photons in DNA. Most nonmammalian cells contain an enzyme system which splits pyrimidine dimers and thus restores a normal DNA strand in situ. The enzyme binds specifically to UV-irradiated DNA to form a complex that is stable in the dark. When this complex is illuminated with long-wavelength UV (330 nm or longer) or visible light, it separates into the active enzyme and a repaired DNA which can no longer bind to the enzyme. Illuminating the enzyme or the damaged DNA before the complex is formed has no effect on UV damage repair [107]. This photoreactivation mech-

nism is most important for the survival of plants and small animals (such as insects) in the field and for such organisms to survive UV damage in tropical and mountainous areas.

The studies of Setlow [108] provided the first experimental evidence which led to a model for dark repair of UV damage. He postulated a repair mechanism in which defective regions in one of the two DNA strands could be excised and later replaced with normal nucleotides by utilizing the complementary base-pairing information in the intact strand. This mechansim, which is known as "cut and patch," is important for the repair of various structural defects of DNA.

Excision repair involves the following steps [101]:

1. Recognition—This system can recognize different structural defects in DNA, including those which do not involve pyrimidines and those which are not due to UV effects (usually caused by alkylating agents, etc.). The details of this recognition mechanism are not precisely known.

2. Incision—After DNA damage has been recognized, a single-strand break near the damage point must be produced, probably by an enzymatic process.

3. Excision and repair replication—These processes may occur separately or concurrently. The known enzymes exonuclease III and DNA polymerase may be responsible for these steps.

4. Rejoining—The repair process is completed only when the repaired segment is rejoined to the continuous DNA strand. Polynucleotide ligase may well be responsible for this step.

Evidence for excision repair mechanisms has been found in microorganisms, viruses, and mammalian cells and in various tissues [109] (Fig. 7).

Recombination repair. The observation of Howard-Flanders [110] that double mutant strains of *E. coli*, deficient in both excision and recombination, were more sensitive to UV radiation than either of the single mutant strains alone suggested another dark repair mechanism besides "cut and patch." The nature of DNA synthesis on unrepaired templates is not yet clear, but studies in various mutant strains of bacteria indicate that there is at least one and perhaps more than one dark repair system in addition to the excision repair mode. The DNA repair systems in bacteria are genetically controlled, and genetic loci control the extent of DNA degradation and may control the gene products needed for the correct functioning of the repair enzymes. The finding by Cleaver and Carter [111] that excision repair in xeroderma pigmentosum in man is genetically defective and the fact that variants of this disorder involve different abilities to repair UV damage to the cells support the hypothesis that heritable characteristics are involved in cancer production in man.

Light-Associated Diseases

Several national and international conferences have dealt specifically with medical problems related to light. For details of advances in these fields, the monographs edited by Urbach [112] and by Pathak et al [113] and the proceedings of the meetings of the American Society for Photobiology contain much information.

Phototoxicity and photoallergy. Epstein first clearly separated phototoxic from photoallergic skin disorders in 1939 [69]. Both types of photosensitized response can be elicited by certain chemical agents, but as the name implies, "photoallergy" can develop only when immune recognition of the agent is present. During the past decade, the prevalence of photoallergic disorders has increased dramatically, especially of photoallergic contact dermatitis caused by antimicrobial agents introduced into personal care products. The mechanisms of these types of photoallergic contact dermatitides have been described by Wilkinson [114], Magnus [115], Wiskemann [116], Kligman [117], and others. The discovery that these agents caused sensitization to wavelengths longer than the usual skin erythema spectrum, i.e., UVA, is especially important. The use of these photosensitizing antimicrobial agents was abruptly curtailed in the 1970s, but many of the affected users (persistent light reactors) continue to be plagued by an inconvenient and sometimes incapacitating hypersensitization to sunlight many years after their contact with those agents.

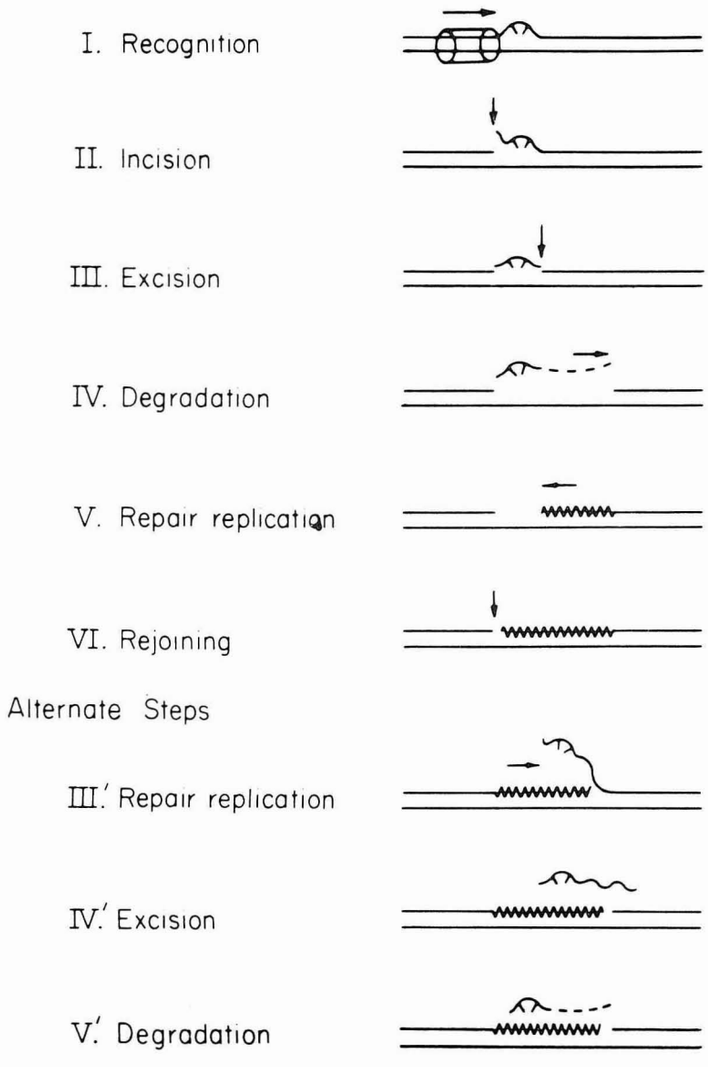

FIG. 7. Schematic representation of the postulated steps in the excision repair of damaged DNA. (From Smith and Hanawalt [101])

The pathogenetic mechanism of UV radiation carcinogenesis on the cellular level remains obscure. Basic data about the molecular effect of UV radiation on DNA were of no help until recent demonstrations of pyrimidine dimer formation and excision and repair by unscheduled DNA replication in mammalian cells in vitro [118] and in vivo [119] and in cultured cells from cancer-prone skin [105]. This last observation resulted in a flurry of research activity because the possibility that unrepaired DNA damage might be involved in cancer production hit a responsive chord—a "Zeitgeist" phenomenon. However, xeroderma pigmentosum variants, in which excision repair systems were apparently normal, were soon discovered; the patients, however, were as cancer prone as those with little or no DNA repair [111].

Excision repair occurs after damage by both carcinogenic and noncarcinogenic agents [120] to the skin of man and mice [121], rat liver and kidney, rabbit brain, UV-induced squamous cell carcinoma in hairless mouse skin [109], and human tumor cell suspensions [122]. Thus a wide variety of mammalian cells and at least some malignant cells are amenable to excision repair.

In addition to the well-documented capability of UV radiation to induce cancer of the skin in man and mice, Setlow and Hart have shown that fish liver cells, UV-irradiated in vitro and reinjected into isogeneic recipients, give rise to tumors [123]. The tumor induction was UV radiation dose dependent, and illumination of the irradiated cells with visible light before injection markedly reduced tumor production. Since fish cells possess the photoreactivating enzymes, these data imply that pyrimidine dimers induced in cellular DNA by UV radiation are related to the development of the tumors.

Current evidence suggests that injury to DNA is somehow related to carcinogenesis, a tenable assumption in view of the evidence that DNA damage encourages mutagenesis in cells. However, in mouse skin and in most cancer patients, the DNA repair systems apparently can repair UV damage; thus the absence of DNA repair cannot be the basis of most skin cancers. In an elegant experiment, which suggests an explanation for this dilemma, Zajdela and Latarjet [124] painted a solution of caffeine, a potent inhibitor of postreplication DNA repair, on the skin of mice during irradiation with UV and found that the caffeine-treated skin developed fewer skin cancers than an unpainted control area on the same animal.

Epstein et al [121] and Zajdela and Latarjet [124] suggest that production of skin cancer by UV radiation is initiated by DNA repair which enables the cell to survive and yet leaves in place or even favors subsequent errors in DNA replication and results in a greater likelihood of malignant change. Further experiments are needed to sort out the mechanisms involved and the relative contribution of DNA damage and DNA repair to carcinogenesis.

Chemically Enhanced Photocarcinogenesis

The relation between light and chemicals and carcinogenesis, first reported by Findlay in 1928 [74], has become increasingly important and significant. The earliest observations, including Findlay's studies with tar and mercury arc lights, dealt with interactions of light and carcinogenic chemicals. Despite mixed results, correlations between carcinogenic and phototoxic activity were postulated and observed. Among the repeated attempts to relate the photophysical and photobiologic properties of compounds to their carcinogenic activity, the most ambitious have been those of Santamaria [125] and his associates and of Epstein et al [126]. Within a given series of compounds, correlations with physical phenomena have not been sufficiently good to be of predictive value. With some exceptions, qualitative correlations with photobiologic processes appear to be quite good.

Several investigators have studied whether UV-induced and chemically induced skin carcinogenesis are additive [125,127,128]. Adequate date indicate that photodecomposition of carcinogens in situ may occur at various light intensities; in at least some cases, the photoproducts have had little carcinogenic activity.† Another type of light–chemical interaction in carcinogenesis was first described by Büngeler [129], who showed that some photoactive compounds not inherently carcinogenic could nevertheless enhance the carcinogenicity of light. Except for psoralens and aromatic hydrocarbons, however, such compounds administered topically to mammals were apparently not phototoxic [130]. The relation between phototoxicity and photocarcinogenicity is somewhat ambiguous: topical 8-methoxypsoralen consistently enhances photocarcinogenicity in hairless mice, whereas under conditions of minimal chronic phototoxicity, topical anthracene does not [131]. The fact that 8-methoxypsoralen is phototoxic both topically and orally and that trimethylpsoralen is phototoxic only topically suggests a further complication. Although it is highly important to know whether newly introduced chemicals and drugs have phototoxic activity, it is even more important to know whether such activity is associated with enhanced photocarcinogenicity.

UV light, potentially carcinogenic, has been reported to act as an initiator of chemically promotable tumors [132] and a promoter of chemically initiated tumors [133]. Carcinogen effectiveness is reportedly enhanced by pretreating mice with UV light. Moreover, a single acute phototoxic event, such as a severe UVB insult, can cause tumor production without either promotion or other treatment [134]. Thus, light plus chemical interaction can include any or all of the following: direct

†Davies RE, Dodge HA: Modification of chemical carcinogenesis by phototoxicity and photochemical decomposition of carcinogen, Proceedings of the 1st Annual Meeting, American Society of Photobiology, Sarasota, Florida, June 1972.

carcinogenic effect of light or chemical; chemical, light-induced, or phototoxic trauma; photochemical alteration of the chemical agent; and modulation of tissue response to one agent by pretreatment or post-treatment of the other.

Photoprotection

During this past quarter of a century, efforts have been renewed to afford the skin some protection against the harmful effects of light. Armed with the knowledge that the protective material should be tailored to the specific part of the spectrum responsible for damage, workers have developed several effective and cosmetically acceptable sunscreens. In particular, paraaminobenzoic acid and its derivatives have helped to prevent acute sun damage [135]. Skin staining with dihydroxyacetone-lawsone and ingestion of beta carotene have been used effectively for certain disorders [136]. The latter, which is effective in some other way than simply in terms of physical optics, points towards the development of a new class of protective agents.

Phototherapy

Astute clinical observations over a period of many years have suggested that deliberate exposure to sunlight and other sources of UV light has a beneficial effect on certain skin disorders. The best documented are acne vulgaris, psoriasis, atopic dermatitis, and perhaps mycosis fungoides. Chemically enhanced phototherapy also originated long ago; in ancient India, crude psoralen preparations were used for phototherapy of vitiligo.

Improvement in light sources and dosimetry has reawakened interest in phototherapy. Goeckerman [63] showed that coal tar plus UV radiation caused significant, if temporary, improvement in psoriasis, and El Mofty was the first to treat a large series of vitiliginous patients with pure 8-methoxypsoralen [137].

Utilization of the tissue-destructive effect of photodynamic agents is being reevaluated, particularly in tumor phototherapy.‡ The results of the photodynamic destruction of herpes virus, which can be reliably produced in tissue culture, are being applied to human viral infections [138], but it is too soon to ascertain how effective such therapy is. Perhaps the most exciting use of phototherapy has been the treatment of neonatal hyperbilirubinemia, a sometimes fatal, sometimes crippling disorder of infants. Discovery that bilirubin is photolabile and can easily be destroyed in vivo by irradiating the skin of infants with blue light has revolutionized the therapy for this disease [139].

Finally, the experimental use of intensive UVA phototherapy, chemically enhanced with 8-methoxypsoralen for the treatment of psoriasis has been reported by Parrish, Fitzpatrick, Tanenbaum, and Pathak [140]. Early results are impressive, but whether long-term complications will arise if such therapy is carried out for many years is still not known.

Environmental Impacts

Although cutaneous photobiology is still not exactly a household word, it recently achieved recognition as an indirect result of man's passion for speed and comfort. Both jet engines and fluorocarbon research have the dubious distinction of being able to deplete the UV-absorbing ozone in the stratosphere. Such a depletion would inevitably increase the amount of UVB reaching the earth's level and among other effects, would increase the risk of each UVB-related disease. What direction the change will take has caused little dispute, but the magnitude of uncertainty in each step in the multiorder series of equation and models for gas photochemistry, UV transmission, and biologic responses remains an area of controversy and concern [141].

Even if accurate predictions, supported by measurments, could establish the relation between a specific change in a stratospheric component and the resulting change in the quantity and quality of earth-level UV radiation, the further extrapolation to biologic consequences will be difficult. Three principal difficulties remain: (1) relating the earth-level dose to the dose actually received by the target, (2) establishing the relative effectiveness of the various spectral components (action spectrum) for producing a particular response, (3) establishing the nature of the dose-response reciprocity under conditions of annual, diurnal, and random changes in the intensity of each component wavelength.

Illustrative of this type of problem is whether the incidence of skin cancer in man will change with alterations in the stratospheric ozone [143]. The qualitative action spectrum for UV carcinogenesis in mice is known very crudely; it is assumed to be similar for man. Something is known about reciprocity for uniform doses of constant spectra in mice. There is qualitative evidence in man that the response is related to the dose and intensity of UV radiation (which cannot be distinguished in available data), but the nature and limits of the reciprocity between dose and effect responses are not known. The behavioral component in relating potential dose to received dose is major even in restricted experimental animals; in man, it is undoubtedly much greater.

One relatively simple part of this problem is contained in the following question: What effect will a defined change in ozone content have on the potentially carcinogenic component of a constant source spectrum? The optical properties of ozone are well enough known to enable us to calculate the

‡ Tomson SH, Emmett EA, Fox SH: Photodestruction of mouse epithelial tumors after oral acridine orange and Argon laser, Proceedings of the 2nd Annual Meeting of the American Society of Photobiology, Vancouver, Washington, July 1974.

attenuation of the source spectrum. The problem is to match such predicted changes experimentally. Since glass filters provide only an approximate match and since it is impossible without a known action spectrum to predict how well an approximate match represents reality, the use of such filters is of only qualitative value.

QUO VADIMUS?

As we enter the last quarter of the 20th century, photobiology has attained scientific respectability, and cutaneous biologists can be proud of their role in this achievement.

We have no wish to share in the fate of phophets but we can point to some directions that research in photobiology will almost certainly take without predicting the results.

1. The biologically significant knowledge we have acquired about the interaction between photons and molecules will be consolidated, expanded, and clarified. This may lead to a better understanding of the mechanisms of DNA repair and perhaps to useful applications of a more specifically directed phototherapy.

2. Having acquired a better understanding of the photochemical events that take place when chromophore and photon interact, we can determine the mechanisms underlying some of the photodermatoses and can devise more specific therapeutic intervention.

3. As we come to understand and measure photobiologic effects better, we will find new biologic uses for light of all wavelengths, not only for UV radiation.

4. The introduction of new and the growing use of old chemicals (including drugs and therapeutic compounds) increase the probability of adverse side effects. However, as the environmental impact of light interacting with man-made chemicals becomes better known and the awareness of such ubiquitous problems increases, episodes such as the epidemic of photoallergic contact dermatitis during the 1960s should become preventable.

5. Given the tools already available, increased knowledge of time-dose, reciprocity, and other effects, and the development of more effective and easily usable sunscreens, we believe that in the foreseeable future most types of skin cancer can be prevented.

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