0022-202X/81/7701-0002$02.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 77:2–7, 1981

Vol. 77, No. 1
Printed in U.S.A.

REPORTS

Photobiology and Photomedicine: The Future Is Bright

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Important events since 1966 that have helped to advance photobiology in general and photomedicine in particular are reviewed. More formal courses on photobiology are needed so that future photobiologists and photodermatologists will not have to be self-taught about the properties and action of light. The effectiveness of current phototherapies and their future improvement are discussed. Some of the areas of photobiology that will impact on photomedicine in the years to come are ultraviolet (UV) radiation effects on the immune system, the light activation of enzymes as a potential new type of phototherapy, the development of new photosensitizers for phototherapy, the effects of near-UV radiation on cellular membranes, and, of course, the role of DNA damage and repair in mutagenesis and carcinogenesis. The future is bright for photomedicine.

I will begin my history of cutaneous photobiology in 1966 (the earlier history has been reviewed [1]), because that was the year when the photochemistry of deoxyribonucleic acid (DNA) and its enzymatic repair were formally introduced to photodermatology. I refer to the international meeting on The Biologic Effects of Ultraviolet Radiation (with emphasis on the skin) that was held in Philadelphia in 1966 [2]. Although invited lectures on DNA photochemistry and DNA repair were presented, the importance of DNA to the future of photodermatology was clearly not appreciated by the majority of the audience in 1966. In the first place, the action spectra for erythema did not seem to implicate DNA (however, see below), and secondly, even today many scientists still seem not to fully appreciate the unique role that DNA plays in cells. However, in 1968 Cleaver [3] reported that skin fibroblasts from patients with the heritable disease xeroderma pigmentosum were deficient in their capacity to perform DNA repair. (N.B., These patients are abnormally photosensitive, and develop skin cancer in sun-exposed sites at an early age.) This and subsequent related studies demonstrated quite conclusively that DNA damage and repair are very important topics for photomedicine, as the program for this symposium clearly confirms.

Although the conference in 1966 pointed the way, it was several years before molecular photomedicine became established. In addition to the general expansion of knowledge and development of new techniques and equipment in molecular biology and medicine, a major stimulus to photomedicine has been the growing awareness by the public that sunlight does more than permit plants to grow and animals to see. The first event to awaken general interest in the effects of sunlight on man and his environment was the concern over the possibility that high flying supersonic transports (SST's) might pollute the stratosphere with engine exhausts, and thereby destroy the ozone layer that protects the earth by greatly attenuating the solar ultraviolet (UV) radiation (especially those wavelengths shorter than about 320 nm). As a consequence, reports were written on the "Biological Impacts of Increased Intensities of Solar Ultraviolet Radiation" [4], and in 1971 the Department of Transportation initiated a 4-yr study on the possibility of ozone depletion by SST's and its possible biological consequences [5, 6].

Following close on the heels of concern over the possible depletion of the ozone layer by high flying aircraft, were concerns over the possible destruction of the ozone layer by nuclear weapons testing [7], and an even more significant threat to the ozone layer by the chlorofluoromethanes that are used in refrigeration and in many types of spray cans [8, 9]. Publicity about these various reports not only made the general public aware that sunlight might have detrimental effects on man, but it also helped to extract some money out of various agencies to support some badly needed research on the effects of solar UV radiation on man and other organisms.

Two important events in 1972 that helped to stimulate photomedicine were an international conference on photosensitization and photoprotection held in Tokyo [10], and the formation of the American Society for Photobiology [11].

The proceedings of the Tokyo meeting, published under the title of "Sunlight and Man" [10], summarized the advances in the field of photodermatology 8 yr after the initial conference in Philadelphia, and is still the most current summary of the field. A treatise on photomedicine, however, is in press [12].

Although other countries have had societies for photobiology for some years, it was not until 1972 that the then members of the U.S. National Committee on Photobiology (NAS/NRC) plunged ahead and established the American Society for Photobiology. The Society is composed of 14 subdisciplines, one of which is photomedicine.

The first meeting of the American Society for Photobiology in 1973 probably catalyzed a quantum jump in the advancement of photomedicine. The meeting was small, and there were not enough scientific papers in each of the 14 subspecialties of photobiology to keep each specialist busy in his/her specialty. As a consequence, there was a lot of session hopping and a lot of camaraderie on the beach; physicians talked to chemists, biologists, and physicists, and vice versa. Physicians were introduced to the techniques and conceptual approaches used in research by the plant and bacterial photobiologists. Physicists, chemists, and engineers obtained a better understanding of the problems confronting physicians and biologists. The solutions to some of these problems were already available, and only awaited the establishment of an appropriate line of communication. Friendships and interdisciplinary scientific collaborations were begun at this meeting that continue today.

PHOTOTHERAPIES

The recent development and modernization of several types of phototherapies have also greatly stimulated interest in photomedicine. The first of these phototherapies was the treatment

This work was supported by grants CA-02896 and CA-06437 from the National Cancer Institute, DHEW.

Keynote Address, presented at the 30th Symposium on the Biology of Skin: Photobiology and Photomedicine. Salishan Lodge, Gleneden Beach, Oregon, October 12–16, 1980.

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Abbreviations:

3-CPs: 3-carbethoxypsoralen

8-MOP: 8-methoxypsoralen

of neonatal jaundice with light. It was introduced by Cremer, Perryman, and Richards [13] in 1958, and in 1969 the National Foundation sponsored a symposium on the phototherapy of jaundice in newborn infants [reviewed in reference 14]. Although this therapy is highly successful in lowering the serum levels of bilirubin in newborn infants, and is widely used, the U.S. National Committee on Photobiology (NAS/NRC) became concerned that physicians were using light as if it were a drug, but some were not taking the same precautions that they would normally take with a new drug. As a consequence of this concern, the U.S. National Academy of Sciences established a committee to review possible problems related to the phototherapy of jaundice in newborn infants, and to suggest solutions and areas of needed research. Two reports were published in 1974 [15, 16]. A more recent review on this subject has appeared [17].

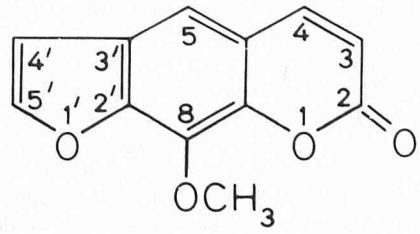
A second phototherapy was introduced in 1972 [18]. It was really a photochemotherapy (although this terminology was not introduced until later [19]), because a photosensitizing drug was added prior to irradiation. This treatment was used against herpes virus in experimental keratitis in rabbits. The photosensitizing chemical was proflavine, and the radiation was from a 150-w incandescent lamp [18]. Subsequently, neutral red and a cool-white fluorescent lamp were used to treat herpes simplex infections in humans [20]. In 1975, the Bureau of Radiological Health published an evaluation of the benefits and risks of the photodynamic therapy for herpes simplex [21]. The major problem stemmed from the fact that the phototherapy as then practiced was not successful, and some cells treated *in vitro* under the conditions used in the therapy became transformed, i.e., subsequent injection of these transformed cells into newborn animals led to the development of tumors. These results led to the concern that this mode of therapy might be carcinogenic in humans. As a photobiologist, one of my concerns was that such a negative (although correct) evaluation of this treatment might discourage others from approaching this type of therapy in a more systematic manner, or worse still, that phototherapy might be abandoned altogether.

There are thousands of photosensitizing chemicals. Some are most reactive with DNA, some work on the cytoplasm, and others are specific for cell membranes [22]. Before "phototherapy" is discounted as a failure for the treatment of herpes simplex, photosensitizers that are more specific for the virus or for virus infected cells should be searched for. One such study that seems promising used photosensitizers that appear to work primarily on membranes rather than on DNA [23].

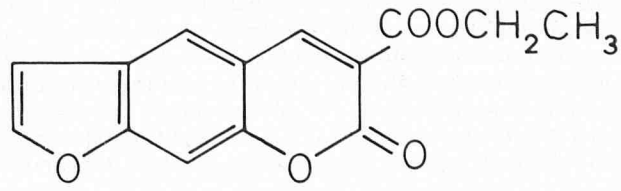
The second program of photochemotherapy was initiated in 1974 [19] for the treatment of psoriasis. The photosensitizing drug 8-methoxypsoralen (8-MOP) (Fig 1) was taken orally, and the patients were subsequently treated with fluorescent lamps emitting in the UV-A region (320–400 nm) of the near-UV spectrum. The use of the drug psoralen plus UV-A radiation led to the acronym of "PUVA" for this type of therapy. While this therapy has proved to be very beneficial for most patients, other patients have received little benefit, and some have been harmed by it [24]. However, the same can probably be said about all types of therapies, even one as simple as the taking of aspirin. As with all types of therapy, it is a matter of the proper evaluation of the risks versus the benefits. In any case, the PUVA studies have attracted the attention of both clinicians and basic scientists, and have stimulated greater interest in the concepts and potential of photomedicine.

While the results of the first clinical trials on PUVA therapy with 8-MOP are being evaluated [e.g., 24], several laboratories, especially in France [25, 26] and Italy [27], are actively trying to develop new drugs that may be even more effective than 8-MOP in the treatment of psoriasis, but which may have less detrimental side effects.

Another type of photochemotherapy that looks promising is the treatment of tumors with a photosensitizer and light [reviewed in reference 28]. In this case the photosensitizer most often used is a derivative of hematoporphyrin, and more recently, a laser has been used along with fiber optics to achieve an efficient delivery of the light energy to the tumor.



8-METHOXYPSORALEN



3-CARBETHOXYPSORALEN

FIG 1. Chemical structures of 8-methoxypsoralen and 3-carbethoxypsoralen.

An exciting new approach to photochemotherapy, which is still in its developmental stage, is to use a drug that is effective in the treatment of a disease state (e.g., methotrexate in the treatment of psoriasis) but that has been inactivated by the addition of a photochemically labile blocking group. The inactivated drug should show little systemic toxicity, but should express its therapeutic potential when activated in the target area by irradiation with light of the proper wavelength. This new approach has recently been patented by J. J. Voorhees and W. Wierenga (U.S. Patent Serial No. 787320, April 13, 1977, University of Michigan).

BASIC PHOTOBIOLOGY

One major factor that is holding back progress not only in photomedicine, but also in other areas of photobiology, is that few current photobiologists are formally trained in the basics of photochemistry and photobiology. This is due to the fact that most were trained in other disciplines, and then only became interested in the chemical and/or biological effects of nonionizing radiation later in their careers.

A basic problem among many "self-taught" photobiologists is a lack of understanding of the first law of photochemistry, which states that *light must be absorbed before photochemistry can occur*. Since photobiological responses are the result of chemical and/or physical changes induced in biological systems

by nonionizing radiation, it is clear that light must first be absorbed in the biological system to cause the chemistry that causes the biological response.

If this simple but very powerful law of photochemistry were to be remembered and put into use by all photobiologists, then the science of photobiology would advance even faster. For example, a famous photodermatologist stated at a recent meeting that visible light is less "photochemically reactive" than is UV radiation. The first law of photochemistry would immediately tell one that this statement is not true. It is correct that, in general, visible light has less of a detrimental effect on biological systems than does UV radiation, but this is not due to some unique property of visible light. Rather, it is due to the fact that, in cells, there are many fewer chromophores of biological importance that are able to absorb visible light, as may be confirmed by an absorption spectrum of a cell lysate. However, whenever visible light is absorbed within a cell, photochemistry can and does occur. Unfortunately, many other common misconceptions about the properties of light still exist [29, 30].

Some problems in photodermatology have had to do with interpreting action spectra, and using action spectra data properly when the chromophore is subsequently exposed to polychromatic light. Because only certain of the effective wavelengths of light in the action spectrum for erythema are present in sunlight, and each of these wavelengths is present to different extents, the concept of the *effectiveness spectrum* was introduced to photodermatology [31]. The effectiveness spectrum is the product of the action spectrum for the biological effect and the emission spectrum of the polychromatic light source (Fig 2*a*). The effectiveness spectrum for sunlight-induced erythema peaks at longer wavelengths (~310 nm) than does the action spectrum (~297 nm) [31, 32]. This result has great significance to those who are developing sun screens.

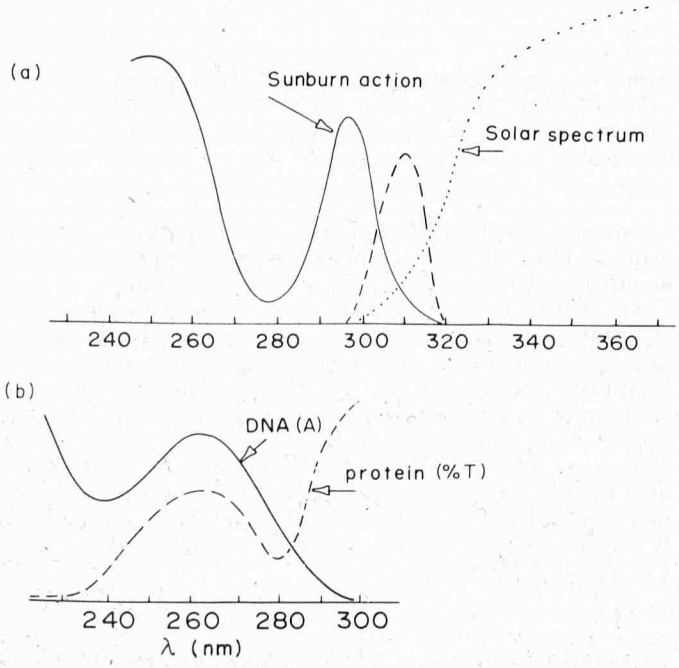


FIG 2. *a*, The action spectrum for the production of sunburn (*solid line*), a typical spectrum of sunlight at the earth's surface (*dotted line*), and the product of the 2 spectra, i.e., the *effectiveness spectrum* (*dashed line*). (*b*) The absorption spectrum of DNA (*solid line*), and the *transmission* spectrum of a protein that contains aromatic amino acids (*dashed line*). Note that proteins filter out much less of the longer wavelengths of light that are absorbed by DNA. The product of these 2 spectra should be the action spectrum for DNA damage in the case where a layer of protein lies between the light source and the DNA. This product spectrum (not shown) is similar to the sunburn action spectrum in Fig 2*a* [32].

Many of the problems of interpreting action spectra for skin reactions have resulted from not taking proper account of the shielding of the inner layers of the skin by the outer layers. These outer layers (composed mostly of proteins) absorb certain wavelengths of light from the light source, and therefore effectively alter the spectral distribution of the light that reaches the inner layers of skin (Fig 2*b*). Thus, it has been demonstrated that the product of the transmission spectrum of protein and the absorption spectrum of DNA yields a curve that is very similar to the action spectrum for erythema [32]. Therefore, it is not improbable that the chromophore for erythema might be DNA.

Still another problem is that action spectra are determined with essentially monochromatic radiation. Very frequently, the response of an organism will not follow the response predicted from the action spectrum, when exposed to polychromatic radiation. This is due, in part, to the fact that many biological systems respond to the different wavelengths of light in a nonadditive way, i.e., the responses can be either synergistic or antagonistic. Many examples of radiation antagonism and synergism exist [33].

A related problem is the development of photochemotherapeutic drugs in the laboratory using monochromatic or narrowband radiation [e.g., 34], and then using them in the clinic with broad-band radiation [e.g., 27]. Frequently, different photochemistry is obtained with a compound, depending upon the wavelengths of radiation used. This is particularly true for nonsymmetrical compounds that have 2 photochemically reactive sites, as is the case for compounds like 8-methoxypsoralen [35].

It is obvious that the science of photobiology will progress as the knowledge and expertise of photobiologists progress. To speed up this process, what is needed is the introduction of more formal courses and training programs on photobiology. One important step in this direction was the 2-week College Faculty Conference on Photobiology and Radiation Biology (July 1980) sponsored by the National Science Foundation and administered by the American Institute of Biological Sciences. It is hoped that the college teachers who participated as students in this course will now incorporate more topics on photobiology in their existing courses, and one day may give a whole course on photobiology.

THE FUTURE OF PHOTOMEDICINE

The future progress of photomedicine, as in every other discipline in science and medicine, depends upon the rate of development of new techniques and instrumentation, of breakthroughs in basic research, and on the creative application of these techniques, instrumentation, and information to the problems that face mankind. There are several areas of photobiology that should be very important to the progress of photomedicine in the near future.

Phototechnology

Recently, there have been significant advances in the design and manufacture of light sources, monochromators, and filters that are helping all of photobiology. The new light source that has caught the imagination of many people is the laser. However, headlines, both in the lay and scientific press, promise more magic from lasers than they can possibly deliver. After all, the radiation from a laser must still obey the laws of photochemistry. Although scientists and engineers throughout the world are trying to find unique applications for lasers in medicine, only a few breakthroughs have been made [28]. Perhaps more applications will be found in the future [36].

Photoimmunology

A new area of research that has had a very stimulating effect on photomedicine is photoimmunology, especially the immunobiology of UV radiation-induced tumors [reviewed in reference 37]. If UV radiation-induced tumors are generally so antigenic that they cannot be transplanted to syngeneic hosts, the obvious question to ask is what permits the tumor to grow in the first place. The answer is that chronic UV irradiation produces a systemic alteration in the animal that prevents the immunologic rejection of these primary tumors, or prevents the rejection of UV radiation-induced tumors transplanted from another animal of the same strain [37]. Determining the molecular and cellular bases of this phenomenon should greatly expand our knowledge of the immune system.

In addition, this immunological response to UV radiation may help to solve the riddle of why solar radiation appears to be involved in the development of melanomas, even though the site of irradiation does not always correlate with the site of appearance of the melanomas [38]. One hypothesis is that the mutagenic lesion leading to some melanomas may be produced by some agent other than solar radiation (either an endogenous or an exogenous agent), but the immunological environment favorable for the growth of a melanoma is produced systemically by exposure to solar radiation.

The obvious implications of these and other immunological effects of UV radiation on animals and man to be discussed at this conference should help to reinforce our concern about the excessive exposure of people to sunlight.

Light Activation of Enzymes

Another area of research that is expanding rapidly, and one that I feel may eventually have a big impact on photomedicine stems from the observation that many enzymes are activated by light [39, 40]. Plants and animals perceive light by numerous photoreceptors other than true eyes [41, 42]. A sensitive photoreceptor must be able to receive a few photons of light, and then be able to amplify this signal and thereby initiate a photobiological response. From theoretical considerations, enzymes would be a good choice as a signal amplifier. In theory, one photon can activate one enzyme molecule, which can then process thousands of substrate molecules per minute. The products of the first enzymatic reaction may then trigger a second enzymatic reaction, giving a further amplification of the initial light signal. One example of the light activation of enzymes that is currently receiving much attention relates to the problem of visual transduction. This process begins with the absorption of light by rhodopsin in the rod outer segment, which results in the activation of the enzymes GTPase and cyclic GMP phosphodiesterase, and ends with the hyperpolarization of the cell. The bleaching of one molecule of rhodopsin leads to the hydrolysis of 1000–2000 molecules of cyclic GMP within 100–300 ms [reviewed in reference 40]. As more information is gained about the photoactivation of enzymes, this may lead to the development of new types of phototherapies for patients who are either overproducers or underproducers of certain metabolites, or who may have been exposed to excessive levels of some toxic agent.

Photosensitization

I have already mentioned my concern over the past usage of photochemotherapy for the treatment of herpes simplex. Since there exists a considerable base of knowledge on the selective action of photosensitizers [22, 43], there is no longer the need to choose a photosensitizer at random for use in phototherapy. In principle, photosensitizers can be tailored to do specific jobs.

Currently several laboratories [25–27] are trying to develop new photosensitizers that may be even more effective than 8-MOP in the treatment of psoriasis, but which may have less detrimental side effects. One outcome of this search for new drugs for PUVA therapy has me very excited. While 8-MOP (Fig 1) is effective against psoriasis, it also elicits a tanning reaction. The new drug 3-carbethoxypsoralen (3-CPs) (Fig 1) is also effective against psoriasis, but produces no erythema [25]. This suggests that the effectiveness of a sensitizer against psoriasis may be unrelated to the production of erythema, and that the screening of drugs for the production of erythema as a way of finding good drugs for treating psoriasis may be counterproductive. It also suggests that if one could find out why 8-MOP produces erythema and 3-CPs does not, exciting progress will be made toward understanding the age old problem in dermatology of what causes radiation-induced erythema.

Effects of Near-UV Radiation on Cell Membranes

In 1966, photodermatologists were much more concerned with the effects of near-UV radiation on the membranes of cells and organelles than they were on its effects on DNA [2]. As more information became available concerning the importance of DNA damage to cell lethality, the pendulum then began to swing over to the concept that most of the lethal effects of near-UV radiation on cells were through its action on DNA [44]. More recently, however, it has been demonstrated that a significant amount of the lethal effects of UV-A radiation on bacterial cells is through membrane damage [45]. This damage was not generally observed in the past because the then usual methods of growing and plating cells (i.e., using complex growth media) prevented the expression of this membrane damage. The response of cells in minimal growth medium to the membrane damage produced by near-UV radiation is similar to their response to heat. If this near-UV radiation effect on membranes can be confirmed in mammalian cells, then it will open a new area of concern in terms of the overexposure of people to UV-A radiation. For example, people heavily exposed to UV-A radiation might be more sensitive to toxic environmental agents because their cells may be more permeable to these toxic agents. The study of the effects of near-UV radiation on cellular membranes should be an exciting area for research in the coming years.

DNA Repair, Mutagenesis and Carcinogenesis

Largely through work on the molecular defect in xeroderma pigmentosum and other heritable diseases that render patients photosensitive, and studies on the photochemical reactivity of the furocoumarins used in the treatment of psoriasis, the study of DNA repair has become a major topic in photomedicine. Many biochemical mechanisms are now known for the repair of damaged DNA [46, 47], and probably new ones still remain to be discovered. Although many pathways of DNA repair have been described, they are still not well understood, even those in simple bacteria. Understanding the multiple mechanisms of DNA repair will remain an exciting challenge in the years to come.

The fact that mutagenesis is largely the result of errors made during the repair of damaged DNA [48], and that most chemical carcinogens have now been shown to be mutagens [49], suggests that the first step toward carcinogenesis may be an error made during the repair (or replication) of damaged DNA. Therefore, the study of the molecular basis of UV radiation mutagenesis will continue to be an important area of interest to photodermatology. This prediction is reinforced by the observation that skin cells from patients with xeroderma pigmentosum are more easily mutated *in vitro* by UV radiation than are cells from normal controls [e.g., 50]. In addition, it has been shown recently that there are multiple mechanisms for producing UV radiation mutagenesis [51, 52], and the implications of this result need to be explored.

It is now known that even spontaneous mutagenesis is largely under the control of the same DNA repair genes that control UV radiation mutagenesis [53]. This suggests that spontaneous mutagenesis arises largely through the metabolic production of

lesions in DNA. Clearly, these results have relevance to the spontaneous induction of cancer [54].

The genetic predisposition to spontaneous carcinogenesis, by virtue of having a high spontaneous mutation rate, can occur at many levels. (1) A person could metabolically overproduce agents that are detrimental for DNA, such as the superoxide radical or hydrogen peroxide, both of which are normal by-products of enzyme reactions in cells [reviewed in reference 55]. (2) The person could be an underproducer of the enzymes that are the first line of defense against such normal but detrimental species (e.g., superoxide dismutase, peroxidase, catalase, etc.). (3) If their DNA is damaged, a person may be deficient in error-free DNA repair, or be too efficient in error-prone DNA repair. (4) Once a transformed cell is produced, it may not be recognized by a defective immune system, and may develop into a cancer. This hypothesis is diagramed in Fig 3. Therefore, patients that are predisposed to skin cancer, and even those sensitive to sunlight, may not necessarily all be deficient in DNA repair. It is possible, for example, that a person's DNA repair capacity could be normal, but he produces so much metabolic damage to his DNA that the added exposure to UV radiation saturates the capacity of his cells to perform DNA repair effectively and/or accurately, leading both to enhanced lethality and/or enhanced mutagenesis.

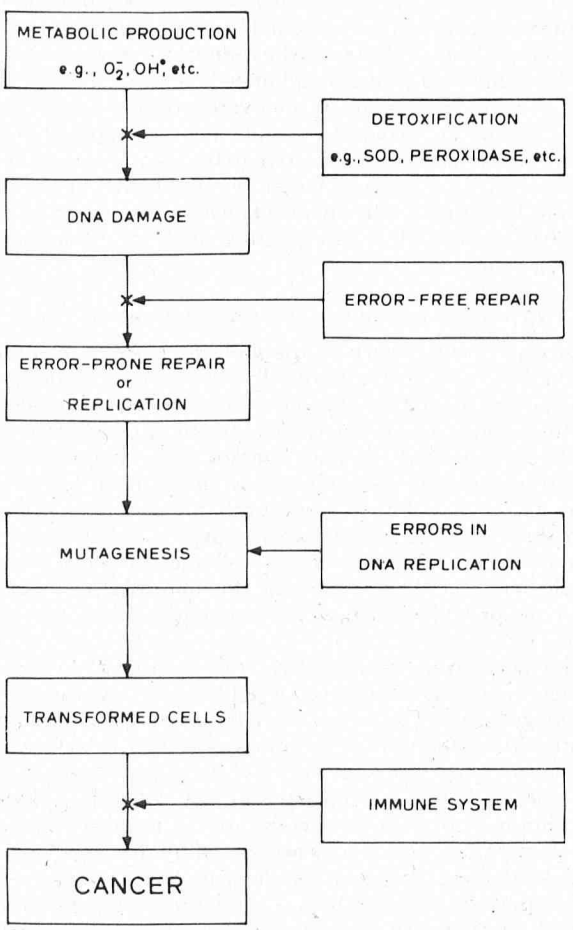


FIG 3. The probable steps leading to spontaneous carcinogenesis. A person may be an overproducer of metabolites that are toxic to DNA, or an underproducer of the enzymes that detoxify these agents. If DNA is damaged and then repaired or replicated in an error-prone manner (e.g., due to a genetic defect in error-free repair) then mutations will be produced that may lead to cellular transformation. A defective immune system may not recognize these transformed cells, and a cancer may develop.

CONCLUSIONS

The science of photobiology has been both "legitimized" and greatly stimulated in the U.S.A. by the formation of the American Society for Photobiology, and the Society continues to prosper. There is a more general awareness by the public that light has both beneficial and detrimental effects [56], but many misconceptions about the properties of light still abound, even among highly educated people. Physicians are stimulating more basic scientists to do research in the areas of photobiology that directly impact on clinical problems. There is a growing sophistication among clinicians about the pathologies produced by light, and a concerted effort is underway to refine old phototherapies and to develop new ones. A great deal of progress has occurred in photobiology and photomedicine since 1966, and the future is bright.

I wish to express my appreciation to Drs. M. A. Karasek, J. A. Parrish, N. J. Sargentini and T. V. Wang for their critical reading of an early draft of this paper.

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