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Environmental Health Criteria 14

ULTRAVIOLET RADIATION

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

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ENVIRONMENTAL HEALTH CRITERIA FOR ULTRAVIOLET RADIATION

A WHO Task Group on Environmental Health Criteria for Ultraviolet Radiation met in Geneva from 30 October to 3 November 1978. Dr V. Vouk, Manager, Health Criteria and Standards, Division of Environmental Health opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the third draft criteria document and made an evaluation of the health risks from exposure to ultraviolet radiation (UVR).

The first draft was prepared by Professor F. Urbach of the Temple University School of Medicine, Philadelphia, PA, USA on the basis of reviews prepared by Dr Y. Škreb of the Institute of Medical Research and Occupational Health, Zagreb, Yugoslavia, Professor F. Stenbäck of the Department of Pathology, University of Kuopio, Kuopio, Finland, and the Sysin Institute of General and Community Medicine, USSR. The second and third drafts were prepared taking into account comments received from the national focal points and from the United Nations Environmental Programme (UNEP), the International Labour Organisation (ILO), the World Meteorological Organization (WMO), and the International Atomic Energy Agency (IAEA).

The collaboration of these national institutions, international organizations, WHO collaborating centres, and individual experts is gratefully acknowledged. The Secretariat wishes to thank, in particular, Professor Urbach for his help in all phases of preparation of the document and Dr M. Faber of the Finsen Institute, Copenhagen, Denmark, who assisted the Secretariat in the final editing of the document.

This document is based primarily on original publications listed in the reference section together with several recent reviews of the health aspects of UVR including publications by Urbach (1969), Fitzpatrick et al. (1974), and Forbes et al. (1978).

Details of the WHO Environmental Health Criteria Programme including some of the terms frequently used in the documents may be found in the introduction to the Environmental Health Criteria Programme published together with the environmental health criteria document on mercury (Environmental Health Criteria 1 — Mercury, World Health Organization, Geneva, 1976), and now available as a reprint.

1. SUMMARY AND RECOMMENDATIONS FOR FURTHER STUDIES

1.1 Summary

Exposure to ultraviolet radiation (UVR) occurs from both natural and artificial sources. The sun is the principal natural source. The known effects of UVR on man may be beneficial or detrimental, depending on a number of circumstances.

Artificial UVR sources are widely used in industry and, because of the germicidal properties of certain portions of the UVR spectrum, they are also used in hospitals, biological laboratories, and schools. UVR is extensively used for therapeutic purposes, as in the prevention of vitamin D deficiency, the treatment of skin diseases, and for cosmetic purposes. Artificial UVR sources are available as consumer products.

The migration of people between areas of different UVR exposure, whether for occupational or recreational reasons gives rise to unforseen exposures.

UVR can be classified into UV-A, UV-B, and UV-C regions. Wavelengths in the UV-C region (200—280 nm) cause unpleasant, but usually not serious effects on the skin and eye. Although UV-C is very efficiently absorbed by nucleic acids, the overlying dead layers of skin absorb the radiation to such a degree that there is only mild erythema and, usually, no late sequelae, even after repeated exposures. Since solar UVR below 290 nm is effectively absorbed by stratospheric ozone, no such radiation reaches living organisms from natural sources.

Most observed biological effects of UV-B radiation (280—320 nm) are extremely detrimental to living organisms. However, living organisms are usually protected from excessive solar UV-B radiation by feathers, fur, or pigments that absorb the radiation before it reaches sensitive physiological targets. Other means of protection include behavioural patterns and the ability to tolerate certain UV-B radiation injury because of molecular and other repair mechanisms.

Much less is known about the biological effects of UV-A radiation (320—400 nm). It can augment the biological effects of UV-B, and doses of UV-A, which, alone, do not show any biological effect, can, in the presence of certain chemical agents, result in injury to tissues (phototoxicity, photoallergy, enhancement of photocarcinogenesis).

Beneficial effects: It is now generally acknowledged that a long period of UVR deficiency may have a harmful effect on the human body. The best known manifestation of "UVR deficiency" is the development of vitamin D deficiency and rickets in children because of a disturbance in the phosphorus and calcium metabolism. The

resultant effect on the bone-forming processes is accompanied by a sharp reduction in the defensive powers of the body, making it particularly vulnerable to many diseases. Appropriate measures to increase UV-B exposure by improving the architectural features of buildings (orientation of windows, use of UV-B transmitting window glass), the use of sun and sun-and-air bathing (solaria), and the development of artificial UVR sources and installations (photaria) have been shown to correct and prevent disease states due to UVR deficiency. In fair-skinned people, all the beneficial effects can be obtained with daily suberythemal doses.

Harmful effects: These may be acute or chronic, and involve primarily the eyes and skin. The acute effects of UVR on the eyes consist of the development of photokeratitis and photoconjunctivitis, which are unpleasant but usually reversible and easily prevented by appropriate eyewear. Acute effects on the skin consist of solar erythema, "sunburn", which, if severe enough, may result in blistering and destruction of the surface of the skin with secondary infection and systemic effects, similar to a first or second degree heat burn. The skin has natural, adaptive protective mechanisms consisting of increased production of the skin pigment melanin, and thickening of the outer horny layer.

Chronic effects on the eye consist of the development of pterygium and squamous cell cancer of the conjunctiva and perhaps cataracts. Chronic skin changes due to UVR consist of "aging" (solar elastosis) and the induction of premalignant changes (actinic keratoses) and malignant skin tumours (non-melanoma and melanoma skin cancers). The evidence for a causal association of UV-B radiation with these chronic changes, particularly with skin cancer induction, is reviewed in detail.

Additional harmful effects (phototoxicity, photoallergy, and enhanced photocarcinogenesis) are produced by the interaction of UVR and a variety of environmental and medicinal chemicals. This results in acute and chronic skin changes caused by UVR of wavelengths which are not normally of an injurious nature.

Ranges of exposure limits for solar UVR are described in section 7.1.

The following criteria for occupational exposure levels in work places have been proposed:

(*a*) for the UV spectral region of 315—400 nm, total irradiance on unprotected skin or eyes, based on either measurement or output data, should not exceed 10.0 W/m^2 for periods of more than 100 seconds, and, for exposure times of 1000 seconds or less, the total radiant energy should not exceed 1.0×10^4 J/m^2;

(*b*) for the UV spectral region of 200—315 nm, total irradiance incident on unprotected skin or eyes, based on either measurement or output data, should not exceed 1.0 W/m^2 of energy equivalent to

the effective irradiance relative to a 270 nm monochromatic source for 8 h of exposure per day. (Details of the calculation and interpretation of "effective irradiance" are given in section 6.

This exposure limit is applicable for acute effects only. The extent to which it must be changed when long-term effects are taken into account is unknown, because of lack of information concerning the dose-effect relationships in human skin carcinogenesis.

It must be recognized that significant nonoccupational exposure to UVR occurs from exposure to sunlight, particularly during the summer months, and throughout the year in the tropics. Thus, exposure limits for the general population are difficult to recommend.

The use of artificial UVR of appropriate wavelengths in suberythemal doses is also proposed for prophylactic purposes in populations living in UVR-deficient areas of the world, and for workers employed in workplaces without natural illumination.

Finally, the document describes existing protection and control measures such as the containment of UVR sources, and methods for personal protection including the use of sunscreen preparations, clothing, transparent material for eye and skin protection, and behavioural modifications.

1.2 Recommendations for Further Studies

The following recommendations pertain to information needed for the adequate evaluation of health risks and the establishment of appropriate protective measures and guidelines.

1.2.1 Measurement of ultraviolet radiation from natural and artificial sources

1.2.1.1 *Measurement devices*

Instruments are needed that can integrate incident UVR from 200 to 320 nm according to the "effectiveness action spectrum" for skin and eye proposed in section 6, in order to enforce the proposed standard for occupational exposure to UVR. Such instruments do not exist at present.

The design and accuracy of instruments for measuring UV-A (320—400 nm) should be improved.

Models for the evaluation of the effective absorbed dose in the critical cells of the skin must be developed taking spectral efficiency, pigmentation, skin thickness, and other relevant factors into consideration.

1.2.1.2 *Monitoring of natural sources*

Accurate and continuous measurement of the UVR reaching the earth from the sun and sky (direct and global) is necessary to:

(*a*) establish baseline levels;

(*b*) establish the range of natural existing variation;

(*c*) monitor persistent changes resulting from various causes (e.g., pollution); and

(*d*) establish, more reliably, the relationship between the status of the stratospheric ozone layer and effective UVR for various biological systems.

Measurements of the spectral distribution of solar UVR should be continued. A network of integrating UV-B meters should be established. Regular observations carried out in many areas of the world with identical instruments for long periods (a minimum of one complete sunspot cycle) are needed to obtain information on UVR climatology. Of particular importance are measurements north of latitude 55° and in the region of the tropics.

An instrument capable of measuring UVR of wavelengths shorter than 290 nm should be developed, since such wavelengths can reach the earth, if the stratospheric ozone layer is compromised.

1.2.1.3 *Monitoring of artificial sources*

Environmental monitoring of UVR sources is necessary to recognize and control direct and stray radiation. Wherever chemical substances are handled, the monitoring should cover the whole of the UVR spectrum.

1.2.1.4 *Development of personal monitoring devices*

Population studies using personal monitoring devices for UV-B radiation are needed to determine the fraction of the daily natural UV dose received by persons at risk either from UVR deficiency or excess, or from occupational exposure. The daily amount of UVR received by human skin must vary greatly with occupation, behaviour, and local climatic and environmental conditions. Little is known about these factors and this seriously interferes with the interpretation of existing data on the relationship between UVR and the development of skin cancer and of chronic skin and eye damage. Thus, the development of personal UVR monitoring devices is of the utmost priority.

1.2.1.5 *Improvement of high intensity sources*

One major problem in applying data from field measurements of UVR to the projection of changes in the incidence of skin cancer is

the uncertainty of the shape of the action spectrum for skin carcinogenesis. Although the general direction and approximate limits of this action spectrum seem to parallel those for skin erythema, the fine structure of the carcinogenesis action spectrum is not known. The main reason for this is the lack of high intensity, narrow band, UV sources capable of irradiating relatively large areas (e.g., even the surface of one mouse). Improved high intensity, large-area solar simulators for chronic (1—2 year) animal studies are also urgently required.

1.2.2 Effects of UV-B, UV-A, and visible light on cells and their constituents

Most of the information on the chemical and biological effects of UVR comes from experiments using UV-C (particularly 254 nm) radiation not normally found in sunlight reaching the earth's surface. There are recent studies showing direct and indirect effects on cells and cellular constituents of UV-B, UV-A, and visible light that differ considerably from those of UV-C. Thus, the chemical and biological effects of the wavelengths of UVR found in sunlight should be studied. There is much evidence that visible light can, under different conditions, either help cells to repair UVR-induced damage or can potentiate the detrimental effects of UVR. Thus, to better understand the effects of sunlight on man and his environment, experiments should be performed using natural sunlight or artificial lamps with well-known continuous spectra.

1.2.3 The relationship between ultraviolet radiation and skin cancer

(*a*) A study is required of the effects of the interaction between UV-B and the rest of the solar spectrum in relation to DNA repair, malignant transformation, and skin tumour development.

(*b*) Cellular genetics should be studied in relation to differences in UVR sensitivity, and defects in DNA repair.

(*c*) Investigation is needed of the influence of change in the dose-rate of UV-B on skin carcinogenesis. Preliminary experiments show that protracting the delivery of a dose of UVR significantly increases skin carcinogenesis.

(*d*) It is recommended that the effect of varying intervals between UVR exposures during carcinogenesis experiments should be studied in detail.

(*e*) Studies are required to develop additional animal models, particularly for the study of the experimental induction of malignant melanoma.

1.2.4 Epidemiological studies of skin cancer melanoma and UVR deficiency in man

1.2.4.1 *Non-melanoma skin cancer*

Since incidence data are extremely difficult to obtain accurately, prevalence data over a wide span of latitudes should be obtained first. Areas of study should be separated by at least 500 km north-south over a latitude span reaching beyond the most populated areas. The effect of altitude needs to be investigated. Data should include age at which the first tumour appears, sex, occupation, skin phenotype, and estimate of solar UV-B dose, obtained by personal dosimeters. It is of the utmost importance that all these studies be performed with a unified protocol, so that valid comparisons can be made. Promising areas for such studies are Australia (particularly Queensland), Finland, Scandinavia, South Africa, Yugoslavia, southern USSR, and the USA.

1.2.4.2 *Malignant melanoma*

While much less common than non-melanoma skin cancer, malignant melanoma is a serious cancer with a survival rate similar to that of cancer of the breast. The relationship of malignant melanoma to UVR may be less obvious than that of non-melanoma skin cancer, and more detailed studies of the epidemiology, anatomical distribution, and associated factors of this severe skin cancer are urgently needed.

1.2.4.3 *Identification of populations with an increased risk of skin cancer*

Existing population studies on the prevalence or incidence of skin cancer suggest, very strongly, that persons with certain phenotypes such as fair skin, light eyes, and freckles, who burn easily and tan poorly, are at higher risk of developing skin cancer than others, and that this is a genetic trait (Celts).

Efforts should be made to develop simple screening methods for the identification of the most susceptible members of the population.

1.2.4.4 *UVR deficiency*

A study of the extent and distribution of the health effects of UVR deficiency is needed. The existing epidemiological studies in the USSR should be extended to other populations.

1.2.5 Studies of the interaction of ultraviolet radiation and environmental chemicals

Too little is known about the mechanisms of interaction of UVR and environmental chemical agents on biological systems. Many widely distributed natural or artificial chemicals (pesticides, halocarbons, etc.) can be altered by UVR, resulting in photoproducts that may be less or more biologically effective than the parent compound. Furthermore, many chemicals can be activated by UVR *in situ* in biological systems and this activation may elicit a biological effect which neither the chemical nor the radiation alone exhibits (Psoralens).

Studies of the chemical, physical, and biological interaction of light and chemicals on biological systems at the subcellular, cellular, organ, and whole organism levels are much needed. Methods should also be developed to predict the extent and type of the photoinjury caused by such agents.

An international registry and notification of photobiologically-effective agents would speed identification of such agents. This is particularly important for manufacturers and users of solaria for human use, now widely produced in various parts of the world.

1.2.6 Studies of beneficial effects

In the early photobiological literature, claims were made, supported by few data, of beneficial effects of UVR (other than Vitamin D production and subsequent effects on mineral metabolism). In recent years, scientists in the USSR have placed particular emphasis on studies of the primary mechanisms of beneficial UVR effects. More detailed comparable studies, particularly in man, under carefully controlled conditions, need to be carried out to determine the importance of such effects on man.

1.2.7 Control measures and protection

1.2.7.1 *Control measures*

Known UVR-emitting artificial sources should be clearly identified by appropriate hazard labels. Where possible, such sources should be housed in protective enclosures and equipped with appropriate safety devices including those necessary for eye and skin protection.

Appropriate information concerning the spectral composition, intensity, and handling of such sources should be provided. Licensing of high intensity sources is recommended.

1.2.7.2 *Sunscreen preparations*

Existing sunscreen preparations differ widely in their effectiveness, cosmetic acceptability, and usefulness. Studies are needed to find new UVR absorbers, particularly in the UV-A region. Vehicles for application need to be improved to make such preparations resistant to wash-off and to ensure simple methods for the application of a sufficiently thick and even film to the skin.

Methods for the uniform testing of sunscreens for effectiveness need to be developed and should be standardized and accepted on an international basis. Search for a systemically effective sunscreen is needed.

1.2.7.3 *Behavioural modifications*

It is essential to educate the general population and workers concerning the profound importance of sunlight and the possibilities of either UVR deprivation or of acute and chronic UVR injury. It is also important to overcome the lack of respect for the biological effects of sunlight, simply because sunlight is ubiquitous, and the concept that, if something is natural, it must be totally beneficial and safe.

2. PROPERTIES AND MEASUREMENT OF ULTRAVIOLET RADIATION

2.1 Sources

The UVR spectrum may be divided into three major components which induce significantly different biological effects: UV-A — wavelengths from 400 nm to 320 nm (synonyms: long wave UVR, near UVR, black light); UV-B — 320 to 280 nm (synonyms: middle UVR, "sunburn" radiation); UV-C — 280 nm to 200 nm (synonyms: short wave UVR, far UVR, germicidal radiation). Wavelengths below 200 nm are of little biological significance, since radiation in this region ("vacuum UVR") is absorbed in very short pathlengths in air (Fig. 1).

2.1.1 Solar radiation — the biologically active UVR spectrum

The sun, being essentially a very hot black body radiator, emits radiation within a wide range of wavelengths. The relative inten-

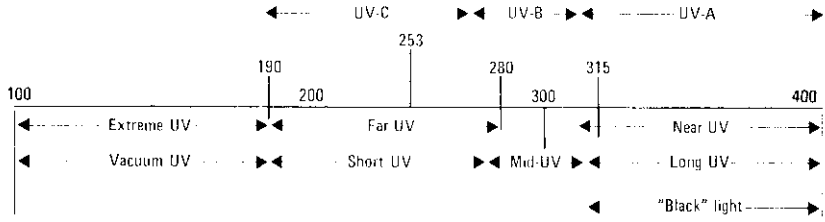

Fig. 1. The major components of the UVR spectrum.

sities of UV and visible radiation that reach the earth's surface depend, to a considerable extent, on attenuation by the atmosphere because of absorption and scattering. Below 320 nm, the intensity of UVR falls very rapidly because of absorption by stratospheric ozone. Virtually no radiation below 288 nm reaches the earth's surface. Thus, most known biological effects of solar radiation are confined to the extreme short end of the terrestrial solar spectrum and involve not more than about 1.5% of the total solar energy reaching the earth.

UVR is not only present in the direct solar beam, but also reaches the earth's surface as diffuse radiation, the solar UVR being scattered within the atmosphere. Under hazy and cloudy conditions this component can be very important.

2.1.1.1 *Influence of stratospheric constituents*

The solar UVR flux that reaches the surface of the earth is a function of the solar spectral irradiance at the upper surface of the atmosphere and the absorption and scattering of UVR by the atmosphere. In the stratosphere, the spectral irradiance of the sun is mainly absorbed by ozone. Molecular ozone has a strong absorption band in the UVR centred at 250 nm and extending beyond 350 nm. The absorption coefficient falls off rapidly with wavelength and the attenuation of the incident solar flux is, therefore, a strong function of wavelength. In order to determine the impact on man of a change in the amount of ozone, these solar irradiances must be weighted with a suitable response function for human skin.

The percentage increase in erythema-producing UVR is approximately 2 times the percentage decrease in ozone (Schulze, 1970).

2.1.1.2 *Influence of clouds, haze, and smog*

In addition to the absorption of the incident solar irradiance by ozone there is also molecular scattering by air and aerosols; reflection, scattering, and attenuation by clouds, haze, and smog near the ground; and reflection from the ground. The computation of the direct and diffuse radiation that impinges on a surface near the

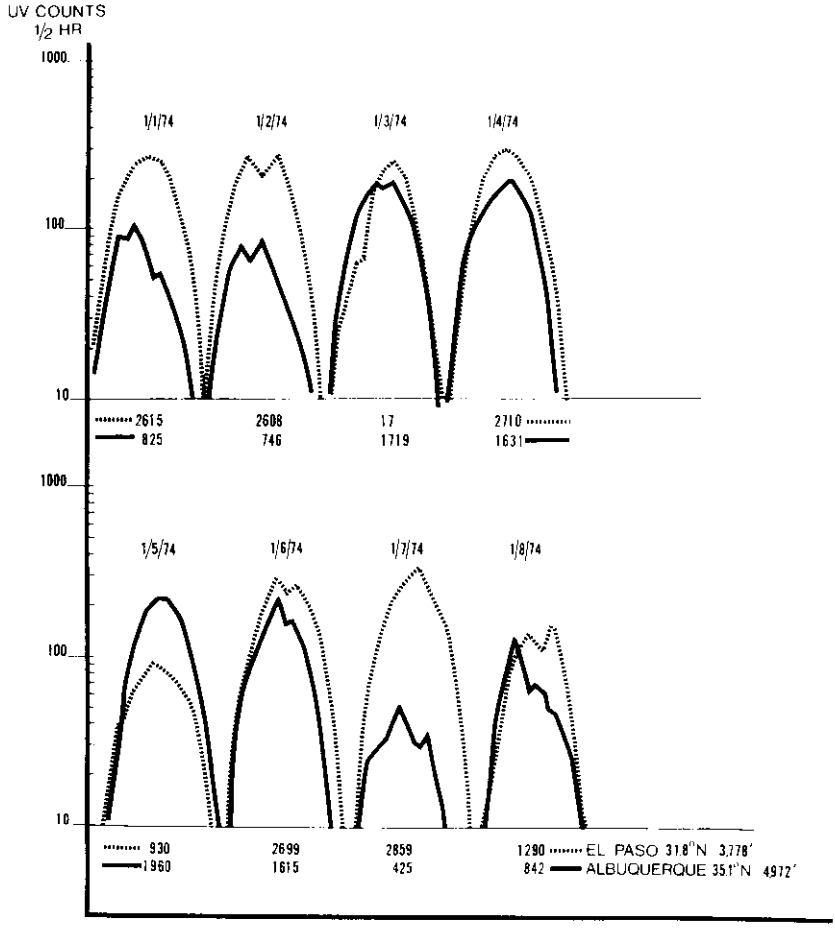

Fig. 2. Comparison of half-hourly readings of UVR at El Paso, TX and Albuquerque, NM. Note: Much more cloud cover in Albuquerque (From: Berger et al.,1977).

ground is well understood in theory, but difficult to carry out in practice, particularly if clouds, haze, and pollution are present (Belinsky & Andrienko, 1974; Green et al., 1975).

The major factors affecting the amount of UVR in the 290—320 nm range that will reach the earth's surface are solar elevation (thus, season and latitude), and the type and amount of cloud cover and aerosols. The importance of atmospheric conditions and their variability from hour to hour and from day to day have been measured by Bener (1972) and Berger et al. (1975) (Fig. 2). Data on the

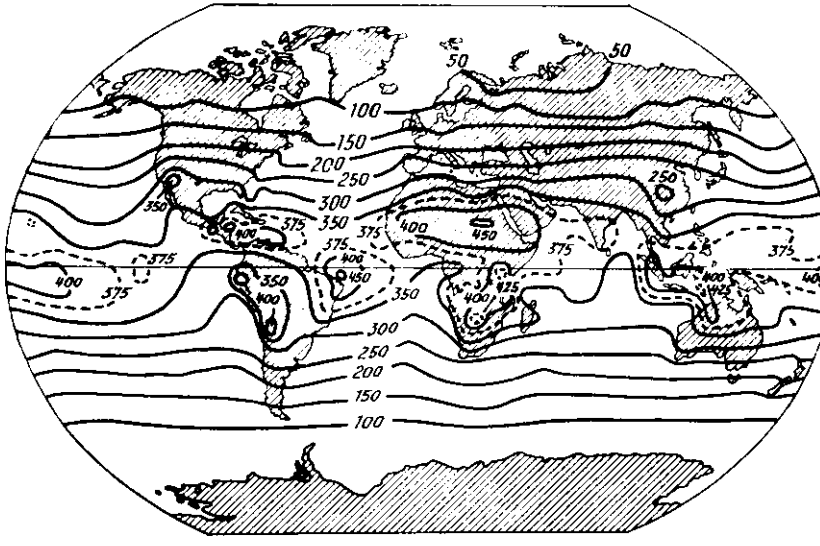

Fig. 3. The global distribution of UVR (From: Schulze,1970).

effect of clouds, haze, and albedo have also been published by the Moscow State University group (Garadza, 1974).

2.1.1.3 *Amount of sea level solar ultraviolet radiation in the biologically active UVR spectrum*

The spectroradiometric measurements of global and sky UVR performed by Belinskij & Garadza (1962), Belinskij et al. (1968), Garadza (1965, 1967), Garadza & Nezval, (1971), Bener (1972), and Belinsky & Adrienko (1974) have served as the standards for all modern calculations, model systems, and comparisons with other measuring devices (Green et al., 1976). The global distribution of UVR has been illustrated by Schulze (1970) (Fig. 3).

Long-term results of actual measurements with an analogue integrating UVR dosimeter, having an action spectrum similar to that of skin erythema, are also available (Scotto et al., 1976). From these measurements, it is apparent that there are daily fluctuations, throughout the year, at each location. Weekly patterns are less erratic, and seasonal variations depend on the latitude. The solar UVR that causes skin erythema reaches a maximum intensity between 10h00 and 14h00. About 60% of the daily dose reaches the ground between 10h00 and 14h00, and 80% between 9h00 and 15h00 (Fig. 2). Similar observations over a shorter period of time, using an instrument based on a filtered selenium photocell, have given virtually the same results (Garadza, 1965).

2.1.2 Artificial sources

Any material heated to temperatures exceeding 2500 K begins to emit UVR. For practical purposes, sources emitting significant amounts of biologically effective UVR can be classified into confined gas discharge arcs, fluorescent lamps, and incandescent sources. It should be noted that any UVR source emitting intense radiation below 260 nm will produce ozone, which has to be removed to prevent any health hazard.

2.1.2.1 *Gas discharge arcs*

The optical spectra produced by arcs depend on the nature of the gas molecules through which the current discharge takes place, its pressure, and the electrical conditions in the discharge.

Direct gas discharge arcs are widely used for the generation of UVR. Generally, they differ from each other in such respects as the type of gas, pressure, starting mechanisms, lamp shape, reflector systems, electrodes, etc. (Andreev et al., 1975). As there is such a wide variety of these arcs, it is not possible to describe them all. However, the most important types are listed below.

Low pressure mercury arcs. These vapour lamps emit several narrow UV bands. Most of the emitted power is of a wavelength of 253.7 nm, which is near the maximum for germicidal effectiveness, hence its usefulness in the control of microorganisms.

High pressure mercury arcs. These vapour arcs (operating at 20—100 atmospheres, i.e., 200—1000 kPa, and usually encased in quartz envelopes) emit much broader and more intense bands of UVR than low pressure mercury arcs at wavelengths of 254, 297, 303, 313 and 365 nm. They are extensively used in industry in photochemical reactors and in printing. Other uses include phototherapy of skin diseases (Meyer & Seitz, 1949; Nilender & Gavanin, 1971).

High pressure xenon arcs. These arc lamps may operate at very high internal pressures, and have the advantage that the spectral distribution of their radiant output shows a continuum similar to that of the sun above the stratosphere. Their output is quite constant over long periods of time, and they are available in a variety of configurations. The major problem with xenon arcs is their very high emission in the near infrared region (Gavrilova et al., 1975). Their uses are similar to those of mercury arcs.

Flash tubes. Another form of gas discharge arc that produces UVR is usually referred to as the flash tube. The gas within a flash tube is excited and/or ionized, when a capacitor is discharged, to pass an avalanche of fast electrons through the gas between the electrodes. Depending on the gas used, i.e., xenon, krypton, argon, neon, etc., different optical spectra are produced.

2.1.2.2 *Fluorescent lamps*

A fluorescent lamp contains an electric arc discharge source. UVR, generated at high efficiency by mercury vapour in an inert gas at low pressure, activates a coating of fluorescent material (phosphor) on the inner surface of a glass tube. The phosphor simply acts as a "transformer", converting shorter wavelength UVR into longer wavelength radiation, i.e., UV and/or visible light. The spectral characteristics, which depend on the phosphor used, vary with the gas pressure in the lamp, and the temperature at the coldest point in the lamp.

"Fluorescent Sun" (FS) type UVR emitters. "Fluorescent Sun" type emitters contain a phosphor that emits more than half of its radiant output at wavelengths shorter than 340 nm. In general, the range of UVR emitted is from 275 to 380 nm, but the maximum is located at 313 nm. Thus, this light source is extremely effective in producing suntan, sunburn, and, at least in animals, cutaneous cancer. The linear configuration of fluorescent lamps has a distinct advantage for any application where a uniform irradiation field of considerable size is required. The disadvantage of these lamps is that there is very much less energy output per unit area compared with compact mercury or xenon high pressure arc sources (Sozin, 1975).

"Black Light" (BL) type UVR emitters. The "Black Light" type UVR emitters are very similar in construction to the FS lamps, except that the phosphor used emits radiation ranging from 300 to 410 nm, with a maximum in the 350—365 nm region. Usually, BL lamps emit less than 0.1% of their total UVR in the less than 320 nm (i.e., biologically most effective) region. Their primary use is for producing fluorescence in a variety of paints and inks. In recent years, such BL lamps have been used together with photoactive drugs such as 8-methoxypsoralen in phototherapy of skin diseases (Parrish et al., 1974).

2.1.2.3 *Carbon arcs*

The arc is due to an electric discharge between two carbon electrodes in air at atmospheric pressure. The output of radiation from a carbon arc increases with increase in arc current and its more or less continuous shape depends, in part, on the type of metal added to the electrodes. The use of these arcs has been limited, because of gaseous waste products that require adequate venting, and the maintenance problems that result from consumable electrodes.

2.1.2.4 *Quartz halogen lamps*

These are tungsten filament lamps, enclosed in a quartz envelope, filled with a small amount of a halogen gas, usually iodine or

bromine. This allows operation at much higher temperatures without deposition of the metal on the envelope. Such lamps, which may operate at temperatures up to 3500 K or more, are stable and very intense. Their UVR output is mainly in the region above 330 nm, and their primary use is in illumination and as reference standard lamps.

2.1.2.5 *Oxyacetylene, oxyhydrogen, and plasma torches*

Oil, coal, and gas flames normally operate below 2000 K and, thus, emit virtually no UVR. Oxyacetylene and oxyhydrogen flames burn at a much higher temperature and solids heated by these two flames may radiate UVR.

Welding produces UVR in broad bands, which often appear as a continuous spectrum. The intensities of the various bands depend on many factors including the materials from which the electrodes are made, the discharge current, and the gases surrounding the arc. Arc welding is a common cause of UVR eye and skin damage.

The plasma torch can produce temperatures of over 6000 K (the temperature at the surface of the sun) and intense UVR can result. Exposure to radiation from plasma torches can result in keratoconjunctivitis and sunburn, if eyes and skin are not protected.

2.2 Detection and Measurement of Ultraviolet Radiation

The measurement of UVR differs from that of visible radiation in that the eye cannot be used directly as a detecting instrument. Thus, other means for detection must be used, which can either be based on a physical principle, or on a chemical or biological reaction. The physical detectors are mainly used to measure instantaneous irradiance, whereas the chemical and biological detectors are normally used to determine radiant exposure (dose).[a]

2.2.1 Units and conversion factors

Table 1 describes terms frequently used in radiometric techniques, and Table 2 gives a simple scheme for conversion between commonly used irradiance units.

In addition to these energy units, units of biological effect, based on interactions between UVR and living organisms, have been proposed. The oldest of these is the Finsen. More recently, a system of bactericidal units for evaluating UVR on the basis of its disinfectant effect and a system of erythema units for evaluating UVR on the basis of its beneficial effects on man have been described

[a] Throughout the document, the term dose refers to the action spectrum weighted radiant exposure.

Table 1. Some basic radiometric terminology

Term	SI units	International symbol	Definition	Comments and Synonyms
Wavelength	nm, μm	λ		Nanometer = 10^{-9} metre (also called "millimicron", mμ; μm, micrometer, micron = 10^{-6} metre
Radiant energy	J	Q_e		1 joule = 1 watt per 1 second
Radiant flux	W	Φ, P_e	$\frac{dQ}{dt}$	Rate of radiant energy delivery ("radiant power"). mW = 10^{-3}W μW = 10^{-6} W
Radiant intensity	W/sr	I_e	$\frac{dP_e}{d\Omega}$	Describes the radiant flux emitted by the source into a given solid angle (solid angle expressed in steradians).
Irradiance	W/m^2	E_e	$\frac{dP_e}{dA}$	In photobiology, has been expressed in W/cm^2, mW/cm^2 or μW/cm^2. Radiant flux arriving over a given area. Note implied dependence of irradiance on the angle of the area being irradiated, relative to a beam. In a collimated, uniform beam, the irradiance E_e on a planar surface varies directly with cos Θ, where Θ = angle of incidence from normal to the surface ("dose-rate", "intensity", see section 2.2.1-1).
Radiant exposure	J/m^2	H_e	$E_e \times t$	Has been expressed as J/cm^2 or mJ/cm^2. ("exposure dose", "dose", see section 2.2.1).

Note: The subscript "e" serves to distinguish radiometric quantities from photometric quantities, which have a "v" subscript. The "e" subscript is often dropped when only radiometric terms are used.
t = exposure in seconds

Table 2. Conversion between irradiance units

		W/m^2	mW/cm^2	μW/cm^2
1 W/m^2	=	1	0.1	100
1 mW/cm^2	=	10	1	10^3
1 μW/cm^2	=	0.01	10^{-3}	1
1 erg/cm^2 · s	=	10^{-3}	10^{-4}	0.1
1 erg/m^2 · s		10^{-7}	10^{-8}	10^{-5}

Similar conversions hold for radiant exposure units, if watts (W) are replaced by joules (J) in the table.

(Lazarev & Sokolov, 1971, 1974). In order to allow for intercomparison with other measurement units, the bactericidal and erythema quantities are now expressed in SI units (Sokolov, 1975, 1976).

2.2.2 Chemical and biological detectors

2.2.2.1 *Photographic plates*

The photographic plate is the usual detector in UV spectroscopy. The degree of blackening of the plate is a measure of radiation

intensity. The measurement is made photometrically by means of some form of densitometer. Under carefully controlled conditions of exposure and development, this method is capable of a high degree of accuracy.

Ordinary photographic emulsions are sensitive in the region of 280 to 500 nm.

2.2.2.2 *Chemical methods*

Chemicals which undergo some measurable change on exposure to UVR can be used for the measurement of radiant exposure. These methods are relatively simple, but are slow and require laborious analysis. They are sensitive to temperature and to small amounts of impurities. The most widely used detector has been the acetone-methylene blue reaction. A more accurate actinometer is based on the rate of photochemical decomposition of oxalic acid in the presence of uranyl acetate. A system based on the photolysis of iron (III) oxalate is more sensitive (Meyer & Seitz, 1949; Koller, 1965). Recently, chemical dosimeters with action spectra similar to that of human skin erythema have been reported by Zweig & Henderson (1976). Challoner et al., (1976) have used change in the coloration of a plastic film for this purpose.

2.2.2.3 *Biological detectors*

The human skin has been used as a UVR dosimeter in an indirect fashion (Robertson, 1975) and some work using microorganisms as a UVR dosimeter has been reported (Latarjet, 1977; Billen & Green, 1975).

2.2.3 Physical detectors

Physical detectors have been reviewed by Koller (1965) and Kiefer (1971).

2.2.3.1 *Radiometric devices*

These radiation detectors depend for their response on the heating effect of radiation. The change of temperature due to heating can, for example, be detected with a thermopile or a resistance thermometer, that is a bolometer. Their spectral response is normally quite constant over a wide range of wavelengths. Because these sensors detect energy, they are not very sensitive to UVR and are mainly used for standardization.

2.2.3.2 *Photoelectric devices*

These are detectors based on a quantum effect such as the production of electrons by absorbed photons. Their sensitivity varies inherently with the energy of the photon (the wavelength of the radiation). The place and width of the spectral response band depends on the detector material. In general, these detectors are much more sensitive than radiometric sensors.

Photomultiplyers, photovoltaic cells, and some semiconductors can be used for detecting UVR.

2.2.4 Measuring devices

In order to perform specific UVR measurements, the detector will normally be placed behind some wavelength selective device such as a bandpass filter or a monochromator.

It is very important that particular attention is paid to the form of the spectral response, as this determines how the result can be used.

For instance, the results from an instrument with a response according to the skin erythema will not be valuable for atmospheric research, or other biological effects, e.g., vision. This is because most of the detail of the spectral information is lost by integration over a specific action spectrum curve. On the other hand, high resolution data from a spectroradiometric device can be integrated afterwards for various uses. However, such measurements are much more complicated and expensive. Thus, there will always be a conflict between the information really needed and the amount of effort needed to acquire the data.

Analogue integrating dosimeters are designed to simulate the action curve of a particular process, such as skin erythema (Robertson, 1969; Berger et al., 1975; Lazarev et al., 1975; Sivilova et al., 1975). Measurements with such a sensor are applicable only to biological responses with the same, or very similar, action spectra.

3. BIOLOGICAL EFFECTS OF ULTRAVIOLET RADIATION ON UNICELLULAR ORGANISMS, MAMMALIAN CELLS AND TISSUE, AND INVERTEBRATES

3.1 Introduction

All photobiological responses to UVR and visible radiation are dependent on the energy of the incident photons, with a maximum

response at a fairly well-defined photon energy within a limited range, and a "threshold" beyond which the lower photon energies are very much less effective. This is mainly because of the ability of biologically important molecules to absorb appropriate photons, since without such absorption no effect is possible.

The biological effectiveness of a beam of radiation depends on the photon flux and on the relative efficiency of the photon energy to produce a particular biological effect. When the beam contains photons with a range of energies, it is assumed that the overall effect is equal to the sum of all the individual contributions determined by the product of the intensity at each photon energy and its relative biological efficiency. The most spectacular photobiological effects, other than vision, involve photons of energy greater than about 3.9 eV (wavelength less than 320 nm). There are, however, some processes that operate on photons with energy between 4 and 3 eV and even less. When the effectiveness of a beam is to be evaluated, it is essential that the relative efficiency of all photon energies (or wavelengths) be known and allowed for, by comparing the appropriate action or response spectrum with the intensity spectrum of the beam.

3.1.1 Absorption spectra

Absorption of photons of UVR by a molecule results in the conversion of radiant energy into rotation-vibrational energy, and a change in the electronic configuration inside the molecule. In the ground state, most of the molecules are in a singlet state and absorption of light causes a transition into an excited singlet state from which they may pass into the excited triplet state of lower energy. For many molecules this metastable state is chemically reactive. However, the opposite is true for oxygen.

The light-absorbing capacity of a molecule depends not only on the electronic configuration of the molecule but also on the possibility of higher energy states (Smith & Hanawalt, 1969). The absorption spectrum of a given substance is the quantitative description of its capacity for the absorption of photons in a particular range of electromagnetic frequencies.

Among the components of living matter, only the unsaturated organic compounds should be taken into consideration, since others show negligible absorption (at least above 200 nm). The effects on water need not be dealt with, since it has practically no absorption above 185 nm (Jagger, 1969).

Chromophores are the chemical groupings of a molecule that can absorb photons. Molecular constituents that contain conjugated double bonds freely absorb energy in the UV region. Benzene rings with one or two atoms of nitrogen show high absorption in the

UV-B. Porphyrins, some steroids, and long-chain compounds such as carotene show good absorption in the UV-A.

In the nucleic acids, the absorption takes place in the purines and pyrimidines which absorb at 260 nm.

As far as proteins are concerned, tyrosine, tryptophane, and peptide bonds are the major chromophores. Absorption of UV photons by a protein is roughly equivalent to the sum of the absorption by its constituent amino acids. The absorption peak is usually located at 280 nm.

3.1.2 Evaluation of administered and absorbed doses

While it is easy to measure the dose administered, the dose absorbed depends on: the composition of the medium, the constituents of which absorb differently in the UVR; the thickness of the medium; and on the heterogeneity of the cell material itself including the thickness of the cell layer, the distribution of the intracellular organelles and pigments, and the structure and configuration of the molecules at the time of irradiation (Jagger, 1967). As with microorganisms, most of the work on this subject has been done using the low pressure mercury arc, but more reports are now appearing in relation to UV-A and UV-B.

In the UV-C, cells absorb in the nucleic-acid band with a peak at 260 nm. Absorption between 270 and 290 nm with a peak at 280 nm corresponds to absorption by proteins (amino acids). In the UV-A and the UV-B, absorption varies considerably, depending on the quantity of absorbing intracellular molecules (porphyrins, haemoglobin, cytochrome, carotene, etc.) found in the natural state in certain cells.

3.1.3 Action spectra

An action spectrum indicates the wavelengths that are most capable of producing a given effect. Comparison of an action spectrum with an absorption spectrum of certain constituents of an irradiated substance or cell often makes it possible to identify the component responsible for the effect obtained.

In more complex systems, where secondary reactions enter into the effect measured, the identities of the absorption and action spectra become less definite, and the conclusions to be drawn, much less certain.

In bacteria for example, the curve of effectiveness of the UV wavelengths will peak at 265 nm and is similar to the absorption spectrum of nucleic acids. It may be deduced that the main target is DNA (Smith & Hanawalt, 1969).

3.2 The Molecular Basis of the Effects of Ultraviolet Radiation on Living Matter

3.2.1 Molecular lesions in DNA

Deoxyribonucleic acid (DNA) is one of the most important target molecules for photobiological effects. DNA can be represented as a double-stranded helix built up of purine and pyrimidine bases, held together by sugar and phosphate groups. If the features of the DNA macromolecule and the universality of the cell structure of living organisms in which DNA represents the genetic heritage are considered, it can be anticipated that any lesion inflicted on DNA, however slight, may have serious repercussions. A lesion in a cell genome is always serious, because, in general, the genome exists only in one copy in the cell concerned, whereas a lesion in a protein, even of the same magnitude, may remain undetected because there are many copies of the proteins. The latter is also true of ribonucleic acids (RNA).

Most studies have been performed with low pressure mercury arcs emitting primarily UVR of 254 nm. Excellent reviews of this subject include those by Setlow (1968), Latarjet (1972), and Smith (1974).

The effect of UVR is above all destructive. The most common changes produced in DNA are damage to the bases and to the polynucleotide chains. Damage to the bases may be unimolecular or bimolecular. Since pyrimidine bases are ten times more sensitive to UVR than purine bases, the only unimolecular reaction discussed will be the formation of pyrimidine hydrates.

Bimolecular reactions are very numerous. They may occur between two bases, or between a base and another molecule. The most important effect is the formation of dimer compounds, particularly thymine dimers. Thymine dimers were demonstrated by Beukers & Berends (1960) in frozen solutions of irradiated pyrimidine (a special orientation of the bases being necessary before the dimers could be formed). The dimer brings about a twisting of the secondary helical structure of DNA and causes local denaturation. New biochemical methods have made it possible to detect dimers *in vivo* in all types of irradiated cells studied. The number of dimers has been shown to be proportional to the dose of UVR and to vary with wavelength with a peak at 280 nm. While the production of dimers has been shown to be directly linked to the harmful effects of UVR on biological material, it is not the only serious lesion produced in DNA by UVR.

Dimers are normally produced by UV-B but can also be formed after exposure to UV-A (Pollard, 1974) and after photosensitization reactions (Lamola & Yamane, 1967). Product additions to DNA bases are very numerous (Smith, 1974). Cross-links between DNA

bases and proteins are generally formed after exposure to very high doses of UV-A (Varghese, 1973). They also occur following exposure to UV-A in the presence of photosensitizers such as acridine.

Following exposure to UV-A, numerous addition products are formed with photosensitizing agents including the aromatic ketones, acetophenone, and benzophenone (Helene & Charlier, 1971), or the furocoumarins (Chandra, 1972). Polynucleotide chain breaks represent another type of lesion that may occur in DNA. RNA, the structure of which is similar to that of DNA, can be directly affected by UVR, but since the biosynthesis is a continuous process and RNA exists in multiple copies, very high doses of UVR are needed before such lesions have any serious repercussions. UVR also produces dimers in RNA (Huang & Gordon, 1973).

The proteins that make up the bulk of the cell may sustain damage to the secondary or tertiary structures. Breaks may occur in peptide chains or bonds or cross-links (Smith, 1974).

3.2.2 Consequences of photolesions

The distortion produced in the DNA-molecule prevents it from carrying out its functions, i.e., transcription and replication may be blocked. These lesions can be recognized by repair enzymes or may act as a signal for other biological processes to intervene. They may result in cell death, genetic recombination, mutagenesis, or even carcinogenesis.

Inhibition of DNA synthesis by UVR has long been known to occur (Kelner, 1953) and has been shown to be a sensitive parameter for evaluating the effects of UVR (Smith & Hanawalt, 1969). The restarting of DNA synthesis after a more or less long delay shows that photolesions can be repaired and these mechanisms are of greatest importance. Synthesis and transcription of RNA may also be blocked (Sauerbier, 1976).

3.2.3 Repair of UVR-induced lesions

The existence of several distinct repair mechanisms that operate in almost all cells but vary considerably in their respective effectiveness has been demonstrated in *in vivo* studies of UVR-induced DNA lesions. The importance and complexity of the repair processes has been described in numerous reviews and in a book by Hanawalt & Setlow (1975).

3.2.3.1 *Prereplication repair*

Photoreactivation. Photoreactivitation was the first discovered and most primitive mode of repair. As long ago as 1949, both Kelner and Dulbecco noted that certain bacteria contained a so-called

"photoreactivating" enzyme. The enzyme has been shown to recognize the dimer and to bind to DNA in the dark. In a wet medium and with exposure to visible light or long-wave UVR (330 to 550 nm), which provides the energy needed for the reaction, the enzyme monomerizes the dimer by breaking the cyclobutane linkages, thus restoring the molecule to its original state. It is the only repair mechanism in which a primary UVR lesion can be chemically reversed and where repair is completed in a single enzymatic stage (Rupert, 1975). This mode of repair has been demonstrated in all living organisms including mammals.

Excision repair. Unlike photoreactivation, this repair process does not require light. It takes place through recognition of the lesion by complex enzyme mechanisms. This repair process is not specific for UVR-induced dimers. Similar lesions caused by nitrogen mustard, 4-nitroquinoline, mitomycin C, nitrous acid, ionizing radiation etc., can be repaired by the same process.

Following the formation of a dimer, DNA is incised at the bases near the dimer by a specific endonuclease. The DNA segment bearing the dimer is then eliminated by an exonuclease and the gap thus created is filled by local synthesis of DNA, the intact homologous strand serving as a template. The continuity of the strand is re-established by a ligase that welds the ends of the resynthesized portion to the undamaged continuous segment (Boyce & Howard-Flanders, 1964; Pettijohn & Hanawalt, 1964; Setlow & Carrier, 1964). This type of repair has been demonstrated in all living organisms including mammals.

3.2.3.2 *Repair during or after replication*

This type of repair is not initiated by enzymatic recognition of the lesion. In this case, replication does occur but the lesion is ignored or bypassed. There remains a gap in the DNA on the side opposite to the damaged region which can be filled by a process of "recombination". Homologous DNA molecules with photolesions can use a process for the exchange of intact genetic material to weld together the undamaged segments and restore a normal DNA molecule (Rupp & Howard-Flanders, 1968).

This mode of repair has also been observed in various types of cells. However the operational capacity of such repair processes is different from that of photoreactivation. These processes may become more easily saturated and, above certain UVR doses, the proportion of unrepaired lesions increases considerably.

3.2.3.3 *SOS repair*

Since repair yields are never complete, the residual lesions may then cause errors such as mutations, the frequency of which seems

to depend on the effectiveness of the repair systems. Witkin (1969) has analyzed the processes of error-prone repair in bacteria, which Radman (1975) named SOS repair.

It occurs in phage and bacterial DNA which still contains lesions such as dimers. These can block the normal operation of other repair processes. The presence of these lesions represents an SOS signal for the triggering of certain repair mechanisms that are normally repressed. Replication is then effected by fraudulent incorporation of bases that cause mutations.

3.3 Bacteria and Yeasts

Most of the principles of molecular photobiology have been established as a result of work on *Escherichia coli* and its numerous mutants, and on the specific phages that infect it. However, it must be remembered that these results may not, in all cases, be valid for mammalian cells.

3.3.1 Effects on bacterial cell constituents and macromolecular synthesis

Apart from chromosomes, structures containing membrane-bound DNA and structures containing RNA are the main targets for UVR-induced lesions, which are reflected in alterations in the templates needed for macromolecular syntheses. DNA synthesis is first blocked, at least for a time. The blockage is photoreversible. Changes in other biochemical constituents of varying importance may occur (Jacobson & Yatvi, 1976).

3.3.2 Sublethal effects

Functional alteration is shown by a slowing-down of the growth rate of bacteria, which may also grow abnormally without dividing into filaments.

Survival is evaluated on the basis of counting the colonies that can be formed by surviving cells. This method is one of the most sensitive and most commonly used for evaluation of the biological effects of UVR at the cellular level.

3.3.3 Effects of ultraviolet radiation of wavelengths longer than 280 nm

Effects produced by UVR longer than 280 nm can be divided into those specific to these wavelengths and those that are similar to the

effects of UV-C. The increase in complexity of the mechanisms that come into play at these wavelengths has been demonstrated by Mills et al., (1975) and Jagger (1976).

A cell irradiated at 254 nm is said to tolerate 5 1/2 times as many dimers as one irradiated at 365 nm. To kill *E.coli*, a dose of UV-A one thousand times greater than that of UV-C or UV-B is required (Tyrell, 1973).

A review by Jagger (1976), which emphasizes the complexity of the processes induced by UV wavelengths other than 254 nm, affords a glimpse of the difficulties that will be encountered in interpreting results relating to eukaryotic cells.

3.3.4 Genetic factors in photosensitivity

The UVR resistance or UVR sensitivity of the various bacterial mutants depends on the genetic make-up of the species concerned. The UVR doses that have to be used to produce the same effect, and the number of dimers, the induction and excision rate of which are responsible for this sensitivity, vary considerably (Hill, 1958; Setlow & Duggan, 1964; Lewis & Kumta, 1972). The enzymes responsible for the repairs of the lesions are also genetically coded as are the enzymes responsible for regulating the expression of the repair enzymes (Hanawalt & Setlow, 1975).

3.3.5 Repair of photolesions in bacteria

All the modes of repair described in section 3.2 are applicable to, and were mainly discovered in, bacteria. As long ago as 1963, Setlow & Setlow determined, *inter alia*, the photoreactivation mechanisms demonstrating that monomerization was related to the decrease in the number of photolesions.

3.3.6 Yeasts

Yeasts are microorganisms but are nevertheless eukaryotic cells. Resnick (1969), Fabre (1971), Cox & Game (1974), and Haynes (1975), among others, have obtained a great variety of mutants with different photosensitivities. These mutants differ from the wild type with regard to UV lethality, mutagenesis, and recombination. Genetic analysis has shown that several recessive genes are involved in the control of these responses in a way that is already much more complex than that found in bacteria. Moustacchi et al. (1975) have reviewed the specific aspects of repair mechanisms in yeasts as a model for eukaryotic cell systems.

3.4 Protozoa

Protozoa, including the ciliata paramecium, tetrahymena, and blepharisma, and amoebae have proved very useful as tools for studies on the biological effects of UVR (Škreb et al., 1972; Whitson, 1972).

3.5 Effects on Mammalian Cells in Culture

An attempt has been made to apply the knowledge of the mechanisms of photolesion formation and repair discovered in microorganisms to a model more similar to the human body; namely established strains of mammalian cell cultures. The strains most commonly used are HeLa (human cells of cancerous origin), mouse L fibroblasts and Chinese hamster cells.

The ability of a surviving cell to form a colony (Lee & Puck, 1960) and the numerous parameters used in radiobiology (Elkind & Whitmore, 1967) have been widely used to study the effects of UVR on this material. Among the numerous works on this subject, reference has often been made to the review paper by Rauth (1970).

3.5.1 Sublethal effects

The most marked effects of UVR on cells are death, mutagenesis, and malignant transformation. Sublethal effects include various degrees of inhibition of growth and colony-forming ability. At low doses, the growth of L fibroblasts is merely slowed down. Higher doses, however, bring about lysis of the cells (Djordjević & Tolmach, 1967), although the value of lysis as a parameter is doubtful. All cell strains give a similar response.

In a study of the colony-forming ability of synchronized and then irradiated cells, Djordjević & Tolmach (1967) and Han & Sinclair (1969, 1971) found that cells were quite resistant at the beginning of G_1 but that sensitivity began to increase at the end of G_1 reaching a peak in the middle of the S phase of DNA synthesis. Thereafter, sensitivity gradually decreased. In G_2, the situation varied according to the type of cell. However, all authors agree that peak sensitivity occurs from the beginning to the middle of the S phase of the cell cycle.

3.5.2 Effects of UV-A

Studies of the effects of UV-A on bacteria have made it possible to elucidate, at least in part, the complex phenomena that occur in mammalian cells. Wang et al. (1974) showed that cells can be

damaged by UV-A or visible light (300—420 nm with a peak at 365 nm). The shoulder of the inactivation curve changes according to cell density, but the curves remain similar according to the origin of the strain.

Evaluation of viability with trypan blue stain showed that, after exposure to 2×10^4 J/m^2, 99 % of human cells, 90 % of mouse cells, and 50 % of hamster cells were destroyed.

The fact that survival depends on the density of the cell population suggests that perhaps some of the effects of UV-A are indirect. This is supported by the observation of Wang (1975) that the medium in which cells have been irradiated is toxic. Wang et al. (1974) have also shown that riboflavin may cause considerable photosensitization of cells exposed to UV-A.

3.5.3 Lesions produced in DNA

The lesions produced by UVR in mammalian cellular DNA may be divided into two categories that are not mutually exclusive, i.e., those that prevent replication processes and those that permit replication processes, but with considerable error.

3.5.3.1 *Pyrimidine dimers*

It is thought that, as in other types of cells already mentioned, the formation of pyrimidine dimers results in the essential lesion that causes most of the effects observed. However, not all the observed effects can be attributed to dimers and other photoproducts should not be neglected.

3.5.3.2 *DNA-protein cross-links*

As demonstrated some time ago (Smith & Hanawalt, 1969), DNA-protein cross-links are to be expected in view of the configuration of the DNA molecule, with its backbone folded back on itself and its association with chromosomal proteins.

DNA-protein cross-links may also help to kill cells by preventing the switching-on of repair processes (Todd & Han, 1976).

3.5.4 The consequences of photolesions in mammalian cells

3.5.4.1 *Inhibition of DNA synthesis*

As in microorganisms, the major effect in mammalian cells is a more or less marked and long-lasting inhibition of DNA synthesis. The rate of synthesis can be estimated directly by incorporating tritiated thymidine into the DNA.

3.5.4.2 *Chromosome aberrations and mutagenic effects*

As regards the effects of UVR on the chromosomes of mammalian cells, several types of lesions were described long ago including breaks and rearrangement. A review has been published by Rauth (1970). These lesions have been studied (among others) in Chinese hamster cells and human lymphocytes. Chromosome lesions are generally produced by low doses of UVR. Their production is enzyme-dependent and is related to repair mechanisms (Bender et al., 1973). They do not necessarily appear after the first division (Parrington, 1972). They can be photoreactivated and, therefore, are probably produced by pyrimidine dimers (Griggs & Bender, 1973). Rommelaere et al., (1973) discovered another widespread type of lesion in the form of sister-chromatid exchanges, the frequency of which increased greatly after UV irradiation. This parameter has been shown to be extremely sensitive (Ikushima & Wolff, 1974) and, thus, valuable in detecting very low doses of UVR, although it is not specific to that agent.

UV and X-ray irradiation exert a synergistic effect on the frequency of chromosome breaks in human lymphocytes (Holmberg & Jonasson, 1974).

3.5.5 The repair of photolesions

Animal cells in culture also possess the ability to repair photolesions in DNA. While the lesions are comparable to those observed in bacteria, and have already been described, there are some differences in the repair mechanisms (Hanawalt & Setlow, 1975).

3.5.5.1 *Photoreactivation*

It was believed that photoreactivation was absent from the cells of placental mammals. However, Sutherland (1974), using appropriate biochemical techniques, isolated an enzyme in human leukocytes with properties similar to those of the photoreactivating enzyme. In mammals, this enzyme is probably not expressed or is masked by other more effective repair mechanisms. Its presence in other tissues — nervous, hepatic, and renal — which are never exposed to light, suggests that it may have other functions.

3.5.5.2 *Excision repair*

The number of dimers formed in human cells increases linearly with the dose of UVR, if the cells are fixed immediately after irradiation (Cleaver & Trosko, 1969). After a variable lapse of time, cells begin to excise their dimers in the way already described (Cleaver et al., 1972). Edenberg & Hanawalt (1973) showed that,

four hours after irradiation with 0.2 J/m², about 50% of the dimers had been excised. The proportion varied between 30 and 90% depending on the type of cell.

Repair replication had already been detected by autoradiography and shown to be unscheduled DNA synthesis which differed from the synthesis of normal replication (Rasmussen & Painter, 1964).

Excision repair has been detected in rodents even though the efficiency is very low.

3.5.5.3 *Repair during or after replication*

Numerous authors have shown by various biochemical methods that synthesis of DNA of low relative molecular mass takes place immediately after irradiation and that, a short time afterwards, this newly-formed DNA is of normal mass (Painter, 1975).

The dimers prevent replication from being carried out continuously. Replication probably occurs between the dimers that have not yet been excised, leaving gaps in the new strands opposite each dimer of the parental strand (Lehmann, 1972). The mechanism by which replication fills the gaps has not yet been properly elucidated, nor has the degree to which the replication is error-free. It is probable that part, at least, of the repair is inaccurate as a result of errors of replication opposite a lesion. Depending on the degree of accuracy, either repair is total or a lesion persists that may lead to death, mutation, or carcinogenesis.

3.5.5.4 *SOS repair*

As will be seen later, in mammalian cells, the repair systems of the host cell may play a part in repairing an irradiated virus developing in the cell.

3.5.6. Effects on cell-virus relationships

3.5.6.1 *Sensitivity to viral infection*

Infection with herpes virus is enhanced in mammalian cells exposed to UV-A (Mills et al., 1975). Relatively low exposures increase infectivity by 20—30% and it remains high for several days.

3.5.6.2 *Viral transformation*

UV-C increases the rate of transformation of mouse and hamster cells by various viruses (Lytle et al., 1970). However, it does not induce direct transformation in all cell species. Certain photosensitizing agents enhance this viral transformation (Casto, 1973).

3.5.6.3 Activation of viruses

Since some mammalian cells harbour viruses that normally remain latent, their activation or induction might transform them and endow them with the characteristics of cancer cells. UV-C exposure of rat or hamster cells, transformed by certain oncogenic viruses, can activate the production of virus particles (Hellman et al., 1974), whereas irradiation of normal cells can activate tumour viruses of the leukemia-leukosis type (Lytle, 1971).

However, there is nothing to show that malignant transformation necessarily involves the development of an oncogenic virus.

3.6 Effects on Invertebrates

Since the invertebrates are extremely heterogeneous, it is very difficult to draw general conclusions, and the data on the response of certain invertebrates will be given without such conclusions.

3.6.1 Effects on eggs and embryos of invertebrates

Hamilton (1973) emphasized the value of invertebrate eggs for radiation studies. Since UVR has low penetration, only very transparent small eggs can be totally irradiated. The others must be stripped or dechorionated by physical or chemical means. The whole egg or part of an egg has been irradiated with UVR mainly to destroy certain cells, in order to watch how development proceeds in their absence and thus deduce the role they play. Some doses, while not preventing segmentation, arrest the onset of differentiation at the sensitive stage represented by the end of blastulation and the beginning of gastrulation.

Wavelengths of 225—313 nm have caused appreciable delays in development. Undivided eggs have been shown to be highly sensitive to UVR (Hsiao, 1975). There has been very little work using UV-A.

In conclusion, it may be said that, in general, eggs are well protected against the harmful effects of UVR. If they are directly exposed, they respond to UV irradiation by means of the mechanisms already described. From the time when the cells begin to differentiate, the quality and intensity of the photolesions and their repair depend on the stage of differentiation of the embryo. If it is not an advanced stage, regulatory mechanisms sometimes enable photolesions produced at an early stage, when the cells are still totipotential, to be eliminated naturally.

3.6.2 Effects on insects

Insects comprise a major part of ecosystems. UVR may act on the vital processes of the insects in different ways and these have been summarized by Hsiao (1975).

From the large numbers of papers that have been written, a first conclusion is that UV-B is perceived by numerous insects. Several diurnal and nocturnal species show positive phototropism towards UVR. Most of the UV-A lamps used to trap insects have an emission spectrum with a peak at 360 nm corresponding to the peak sensitivity of the UV receptors in the insects. However, the peak differs slightly for each species.

Solar UVR has been found to modify the biological clock in insects and other arthropods.

Photoreactivation and other types of repair have been demonstrated in insects.

3.7 Modification of the Effects of Ultraviolet Radiation by Chemical Agents

Numerous chemical agents increase the photochemical reactivity of nucleic acids. They act in various ways, by becoming incorporated in the nucleic acids, or by forming various complexes with them that increase their absorption or reactivity. They can also absorb UVR directly and transfer the energy to nucleic acids.

Various physical factors may change the intensity of irradiation and the efficiency of the repair systems.

The way in which irradiation is carried out, i.e., whether it is continuous or fractionated, total or partial is also important in the evaluation of the final results.

3.7.1 Halogenated analogues

Incorporation of 5-bromouracil (5-BrU) and 5-bromodeoxyuridine (5-BUdR) sensitizes both viruses and cells to UVR. A very detailed review has been made by Hutchinson (1973).

3.7.2 Caffeine

Caffeine is a trimethylxanthine that acts by inhibiting the repair systems. At doses not themselves toxic, caffeine considerably increases the effects of UVR.

The absence of any effect of caffeine on excision repair suggests that it acts by interfering with a post-replication system (Cleaver & Thomas, 1969).

3.7.3 Furocoumarins

Photosensitizers are becoming increasingly important among agents that modify the effects of UVR on biological systems.

Furocoumarins are natural products isolated from plants. Important applications in therapy have led to thorough studies of their mode of action at the molecular level (Chandra, 1972; Pathak et al., 1974).

Musajo et al., (1974) have shown, *in vitro*, that furocoumarins exert photosensitizing effects following irradiation at wavelengths of 320—400 nm. These effects result from the formation of certain addition products with DNA and particularly from the linking of the furocoumarin molecule with the pyrimide bases. These products may cause breaks in the molecule and thus prevent if from carrying out its functions. Oxidation of amino acids may also occur in proteins.

The so-called 'linear' furocoumarins such as psoralen react with native DNA in the presence of UVR to make monofunctional and bifunctional addition products. The latter cause cross-linking between the DNA strands. Certain so-called 'angular' furocoumarins (angelicin) can only give rise to monofunctional addition products.

These addition products cause lesions that can be repaired by the excision repair mechanism. Monofunctional addition products seem to be easier to repair than bifunctional products (Chandra et al., 1976).

Depending on their molecular structure, not all the furocoumarins show the same degree of photosensitization. Ben Hur & Elkind (1973) demonstrated that, following exposure of hamster cells to UV-A, 11% of the addition products were formed between the complementary strands. During incubation in the dark, 90% of the cross-links gradually disappeared from the DNA.

These reactions have found applications in the treatment of certain skin diseases, particularly psoriasis.

3.7.4 Other photosensitizing agents

Charlier & Helene (1972) carried out an *in vitro* analysis of the photochemical reactions of benzophenone and acetophenone with purine and pyrimide derivatives in aqueous solution during irradiation with light between 400 and 600 nm. Dimers and chain breaks were the essential lesions.

The effects of light on bacteria in the presence of photosensitizing chemicals such as toluidine blue and acridine yellow were compared by Harrison (1967). The four sorts of lesions observed — lack of colony-forming capacity, DNA lesions and mutations, changes in cell permeability, and enzyme inactivation — were similar in both cases.

Rauth & Domon (1973) studied the mechanisms of photosensitization in animal cells in cultures with 1-cyclohexyl-3(2-morpholinyl-4-ethyl) carbodiimide metho-p-toluene sulfonate (CMEC), which binds preferentially to partially denatured regions of DNA after irradiation at 254 nm, thus inhibiting replication and increasing lethality.

3.7.5 Protection by carotene

Since the work of Cohen-Bazire & Stanier (1958), some investigations have established the protective role of carotene against the photodynamic effects of light, in very special cases. Since the energy level of carotenes is very low, they can accept, by transfer, the energy of sensitizers transformed into the triplet state and even the energy of oxygen transformed into the singlet state by exposure to light.

Mutant strains of bacteria and fungi lacking carotenoids have proved much more sensitive to photodynamic effects than normal strains, but this effect is only valid for wavelengths shorter than those that carotenes absorb (Mathews & Krinsky, 1965).

3.8 Conclusions

Knowledge of the molecular basis for the biological effects of UVR has emphasized the importance of the photolesions produced in DNA and the effectiveness of the enzymatic stages of repair, both of which depend on the genetic make-up of the organism concerned.

Studies of the sensitivity of mutants, on one hand, and of factors able to modify the effects of irradiation, on the other, will, perhaps, make it possible to strengthen repair systems and to increase the resistance of organisms to UVR.

The great differences observed make it difficult to lay down protection standards.

4. THE BIOLOGICAL ACTION OF ULTRAVIOLET RADIATION ON VERTEBRATE ANIMALS

4.1 General Aspects

The anatomical structure of the skin of vertebrate animals resembles that of man in many respects. The surface stratum

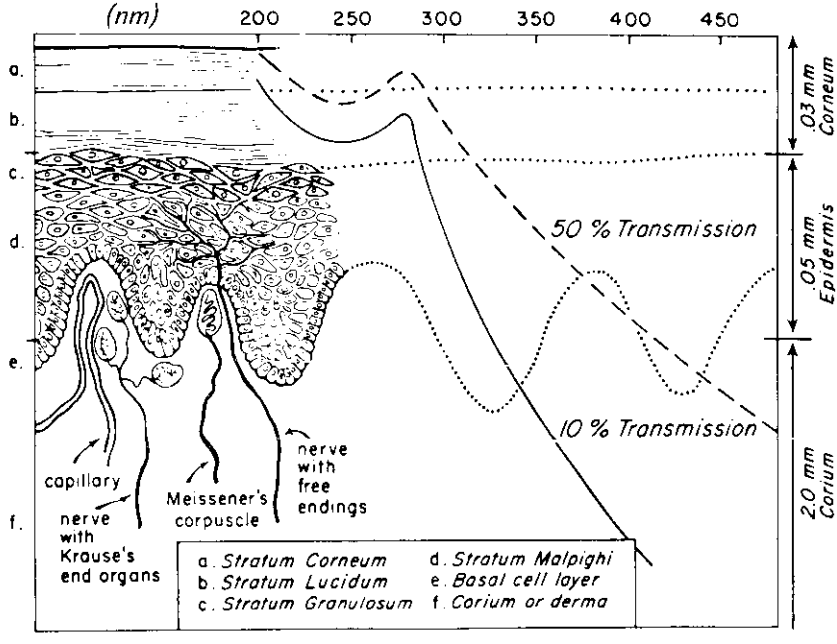

Fig. 4. Penetration of human skin by UVR.

corneum is important in affecting the penetration of UVR (Fig. 4), the thicknesses of the stratum spinosum and stratum granulosum also affect the relative amounts of UVR reaching the dermis. Other constituents of the skin, e.g., the melanocyte population, the Langerhans cells, vascular structures, as well as cutaneous innervation vary in amount and distribution from species to species, but remain basically the same.

4.2 Acute Reactions in the Skin

4.2.1 Epidermal changes

Histological investigations of the early effects of UV irradiation on animal skin show the changes that occur in the epidermal cells particularly well.

Twenty-four hours after a single irradiation of skin with an unfiltered mercury vapour lamp at doses between four and eight times the minimal erythema dose, distinct signs of cell injury can be seen including vacuolation of the cell cytoplasm and increased or decreased density of the nucleus (Stenbäck, 1975a).

One distinctive feature, observed in both man (Daniels et al., 1961) and experimental animals (Woodcock & Magnus, 1976) 24 hours after exposure, is the presence of "sunburn cells" (SBC), scattered diffusely throughout the superficial epidermis. These cells are characterized by a densely-staining, glassy, homogeneous cytoplasm and pyknotic nuclei. The appearance is similar to that of an individual cell undergoing keratinization and thus, the process is regarded as a form of individual cell shrinkage necrosis or dyskeratosis.

Following these early effects, hyperplasia, induced by radiation, is observed (Blum et al., 1959; Stenbäck, 1975a). An increase in mitosis indicates the onset of hyperplasia, which begins after about two days.

Quantitative measurements have been made of the following aspects of the effects of single doses of UVR on mouse skin (Blum et al., 1959): *(a)* incidence of mitotic figures; *(b)* number of epidermal cells per unit area; *(c)* epidermal thickness; *(d)* dermal thickness; *(e)* mean nuclear diameter; and *(f)* number of groups of mitotic figures. All the aspects measured changed in a similar fashion quantitatively following irradiation; they increased rapidly at first, reaching a maximum and then fell gradually towards normal. Soffen & Blum (1961) found a gradual increase in epidermal thickness reaching a maximum between 8 and 14 days. These changes represent repair of the cell injury caused by UVR; at the same time, the hyperplasia protects against further UV irradiation.

For a long time, it was believed that thickening of the horny layer was the essential adaptive change to UV irradiation in the environment. The idea now prevails that melanin granules in the horny layer and the Malpighian layer accumulate to form a protective screen which is not only significant, but possibly even more important for light protection than the thickness of the horny layer alone.

4.2.2 Erythema and inflammation

Sunburn (UVR erythema) and suntanning are the visible signs of UV injury to the skin and the repair of such injury. UV erythema is evidence of an inflammatory reaction to radiation, and appears after a latent period of a few hours.

Erythema caused by UVR is confined to the exposed areas and reflects blood vessel dilation and increased blood flow in the dermis. It is often assumed that the initial photochemical reaction is in the epidermis, where photon absorption by keratinocytes may lead to liberation of intracellular substances that diffuse into the

papillary dermis to cause vasodilation. This diffusion theory is supported by the existence of a latent period between exposure and erythema, and by the fact that much of the radiant energy of the erythemogenic wavelength region is absorbed by the epidermis. However, there may also be direct injury to the vascular endothelium or to other sites in the dermis.

Most studies of the mechanism of "sunburn" have used artificial sources of UV-B or sources in which the spectral distribution is such that UV-B is assumed to provide the major erythemogenic influence. In experimental animals, the vascular response to UVR is biphasic. A transient immediate vasopermeability is followed, after a latent period of 2—8 hours, by a delayed, prolonged, increased, vasopermeability and vasodilation. In some animal models, the initial vasopermeability is accompanied by a faint erythema, which may begin during exposure. This immediate effect has been attributed to histamine release, possibly due to a direct effect of photons on dermal mast cells. There is evidence that serotonin may also play some role. In rats and guineapigs, serotonin and histamine antagonists suppress the immediate phase of UVR vascular responses. *In vivo* studies of human skin have shown the transient appearance of kinins within minutes of UV irradiation. Kinin was not found after the onset of delayed erythema.

The mediators of the delayed phase of UVR-induced vascular response have been difficult to define. Antihistamines do not suppress the delayed erythema phase of the vascular response to UVR in guineapigs, rats, or man. Kinins have been stated to be either absent or not elevated. Delayed erythema was not suppressed by various inhibitors of proteases, plasminogen activitors, or kallikrein. Serotonin has been found in urine following exposure to UVR, but the significance of this finding is not clear.

More recently, prostaglandins, a group of long-chain fatty acids with vasoactive properties, have been implicated as possible mediators of the delayed phase of erythema. Prostaglandins are produced in human and animal skin (prostaglandin groups E and F), intradermal injection of prostaglandins produces erythema (PGE mainly, PGF group are much less active), and furthermore the production of prostaglandins increases following UVR exposure. Indomethacin is a potent inhibitor of the conversion of arachnidonic acid to active prostaglandin, a reaction catalyzed by the enzyme prostaglandin synthase. Topical indemethacin produces a profound and prolonged blanching of UV-B-induced, delayed erythema in both human subjects and guineapigs. In man, intradermal indomethacin has been shown to consistently decrease erythema due to UV-B but not all areas of erythema caused by irradiation with UV-C; these effects appear to be due to the inhibition of prostaglandin synthase.

It has been suggested that the complex reaction known as "sunburn" may result from the release of hydrolytic enzymes and possibly other substances by lysosomes within keratinocytes.

Histochemical studies of human skin exposed to UVR were consistent with the theory that specific damage to lysosomal membranes caused partial to complete rupture and release of enzymes.

The release of lysosomal enzymes may not only lead to damage of the keratinocytes but may also release enzymes, vasodilator substances, or subsequently formed cell-breakdown products into the dermis, where they may directly or indirectly lead to erythema. It has been suggested that the immediate erythema caused by UV irradiation results from disruption of lysosomes of endothelial cells with release of chemical mediators. The delayed erythema could then result from secondary diffusion of proteinases from the epidermis, following lysosomal rupture. It is also possible that direct photon damage to the lysosomes of mast cells of the dermis or endothelial cells of dermal blood vessels may play a role in the delayed erythema of sunburn.

Multiple chromophores may exist in skin, and irradiation probably leads to activation of a complicated cascade of mediators, the final endpoint of which is erythema. Multiple pathways may exist. It is also possible that photons have direct effects on blood vessels or nerves. UVR causes dilation of isolated exposed dermal blood vessels. Dermal proteins may be directly changed by radiation (Magnus, 1977).

4.2.3 Tanning

In addition to erythema, another consequence of exposure to UVR is the pigmentation of the skin generally known as "tanning". This becomes noticeable about 48 h after exposure and increases gradually for several days. Tanning is, in part, due to migration of the pigment melanin already present in the basal cells to the more superficial layers of the skin where it has a greater effect on the appearance of the reflected light. It is also partly due to the formation of new pigment.

It is generally accepted that repeated irradiation with UVR induces increases in the population of melanocytes in the epidermis of man and experimental animals. With regard to the mechanism of this phenomenon, the following processes or possibilities have been considered: *(a)* increased division of melanocytes; *(b)* activation of pigment formation in amelanogenic melanocytes: *(c)* migration of dermal melanocytes into the epidermis; *(d)* various combinations of these processes (Quevedo et al., 1965). That division of melanocytes occurs has been shown in murine skin by Quevedo et al. (1963).

Further, published reports have provided evidence in support of the occurrence of activation of amelogenic melanocytes in man (Mishima & Widlan, 1967) and experimental animals (Reynolds, 1954; Quevedo & Smith, 1963; Miyazaki et al., 1968; Sato, 1971). However, the relative contribution of each process remains to be established. In a study using tritiated thymidine, it was demonstrated that approximately 1.1% of dopa-positive epidermal melanocytes were labelled in hairless mice receiving 9 daily exposures to UVR (Sato & Kawada, 1972). However, an attempt to trace the labelled melanocytes using split epidermal sheets was unsuccessful.

4.3 Acute Changes in the Eye

4.3.1 Photokeratitis and photoconjunctivitis

Although more energetic than the visible portion of the electromagnetic spectrum, UVR cannot be detected by the visual receptors in mammals, including man, because of absorption by the ocular media. Thus, exposure to UVR may result in ocular damage before the recipient is aware of the potential danger. Many cases of keratitis of the cornea and cataracts of the lens have been reported due to exposure to UVR produced by welding arcs, high-pressure pulsed lamps, and the reflection of solar radiation from snow and sand.

Extensive reviews of the literature on the biological effects of UVR have been compiled by Verhoeff et al. (1916) and Buchanan et al. (1960). Verhoeff and his colleagues included all the, then available, research data in their report and formulated some of the basic hypotheses regarding ocular damage caused by UVR. Research on threshold values and destructive and repair processes was summarized by Duke-Elder (1926). Buschke et al. (1945) stressed the destructive effects of UVR on the corneal epithelial cell nuclei, the loss of epithelial adhesion to Bowman's membrane, and the inhibiting effects of UVR on the healing process.

In studies by Cogan & Kinsey (1946), a monochromator was used to evaluate the sensitivity of the cornea to individual spectral lines. Their work, which was, for the most part, carried out with one to four rabbits, provides the most reliable quantitative data on damaging threshold values of UV energy of individual wavelengths. They established a long wavelength limit of between 306 and 326 nm and a threshold of 152 J/m^2 at 288 nm for the rabbit.

Ordinary clinical photokeratitis is characterized by a period of latency that tends to vary inversely with the severity of exposure. The latent period may be as short as 30 min or as long as 24 h, but is usually 6—12 h. Conjunctivitis follows, often accompanied

by erythema of facial skin and eyelids. There is a sensation of a foreign body or "sand" in the eyes and various degrees of photophobia, lacrimation, and blepharospasm. The importance of these acute symptoms lies in the fact that the individual is visually incapacitated for 6—24 h and that the ocular system, unlike the skin, does not develop tolerance to repeated exposure to UVR. Almost all discomfort disappears within 48 h, and exposure rarely results in permanent damage.

Pitts & Kay (1969) and Pitts (1970) sought to establish the experimental threshold for photokeratitis in rabbits and primates, including man. Rabbits and monkeys showed a maximum sensitivity to UVR at 270 nm. The radiant exposure threshold for man at 270 nm was 50 J/m^2 compared with 110 J/m^2 for the rabbit and 60 J/m^2 for the monkey.

The UVR incident on the eye is absorbed in turn by the cornea, the aqueous humor, the lens, and the vitreous humor before reaching the retina. Absorption is greater in the lens than in the cornea, and is least in the aqueous humor. Below 300 nm, most of the UVR is absorbed in the cornea and aqueous humor and very little penetrates as far as the lens.

As a result of observations at above-threshold intensities, it was felt that the reaction of the cornea to exposure to UVR wavebands of 220 to 250 nm was different from that to wavebands of 250 to 310 nm. For exposures below 250 nm, signs and symptoms occurred soon after exposure, and symptoms always returned to normal approximately 14 h later. For exposure above 250 nm, symptoms did not generally occur until 9 to 11 h after exposure, and visual acuity remained below normal for 24 h after exposure. The differences observed were attributed to the differences in the absorption of the different wavebands. The shorter wavebands are absorbed in the outer corneal epithelial layers, which undergo rapid change, whereas the longer wavebands are absorbed in the deeper epithelial layers which show delayed changes because these cells are more viable. Thus, the lesions produced by shorter wavelengths are rapidly repaired while, at the longer wavelengths, there is a delayed and more serious response (Pitts & Cullen, 1977).

4.3.2 Cataracts

A cataract is a partial or complete loss of transparency of the crystalline lens or its capsule. The wavelengths that affect the lens appear to be in the same area as those that are most effective in producing erythema on human skin.

Bachem (1956), using a filtered UVR system, concluded that exposure to repeated high doses of longer UVR wavelengths could

cause cataracts through cumulative effects. He reported that the action spectrum for cataracts began abruptly between 293 and 297 nm, reached a peak near 297 nm, and fell abruptly near 313 nm. Minimal effects existed through the remainder of the near UVR. In both the rabbit and guineapig, reversible lenticular "blurring" occurred 5 to 10 days after exposure. With repeated excessive exposures to the 297—365 nm wavebands, irreversible lenticular opacities occurred after a latent period of between 2.5 and 15 months.

Bachem (1956) concluded that since daylight does not contain any UV-C or far infrared, and since both the visible and near infrared are freely transmitted by the ocular media, it would appear that UV-B and A are responsible for cataracts.

The chemical effects of UV-A exposure on tryptophan were studied by Zigman et al. (1973) using human crystalline lenses. They found that exposure of tryptophan to UV-A led to the formation of chromatic photoproducts which bound to the lens proteins, altered their colour and changed the solubility. Human lens material without added tryptophan did not show chromatic changes on exposure to UV-A, until 48 h after exposure. Tryptophan showed an excitation wavelength at 278 nm and a fluorescent emission at 330 nm. However, following exposure to UV-A, tryptophan showed an additional 360 nm excitation and 440 nm fluorescence similar to that found in the brunescent human cataract lenses. The UV irradiance for these studies was 30—50 W/m^2 at 365 nm and exposures were made for at least several hours. These exposure levels exceed those expected from sunlight for the same period of time.

Thus, exposure of the eye to UV-A, for sufficient periods of time, with an irradiance comparable to the irradiance level of sunlight may interfere with the synthesis of lens proteins, catalyse insoluble lens protein, and may result in chromatic changes in the lens. While the basic mechanisms remain to be found, the evidence clearly demonstrates that both *in vitro* and *in vivo* exposure to UV-A can enhance cataractous changes in the crystalline lens.

Recently, Pitts & Cullen (1977) have studied the effects of the 300 nm—400 nm wavelength range on the rabbit eye *in vivo*. The criteria used to determine corneal damage were epithelial debris, epithelial stippling, epithelial granules, epithelial haze, epithelial exfoliation, stromal haze, stromal opacities, and endothelial disturbances. Anterior chamber signs included flare and cells. The crystalline lens criteria were subcapsular opacities, capsular and stromal haze, stromal opacities, and increased prominence of the anterior suture. Criteria for the iris were the presence of the anterior chamber signs, changes in clarity of the iris stroma, and sluggish pupillary response.

Tables 3 and 4 show data for corneal and lenticular damage in the 290 nm—400 nm wavelength range for the rabbit. Limited data above 300 nm for the human eye do not allow a detailed comparison; however, the human corneal threshold was considerably below that for either the rabbit or the nonhuman primate.

Table 3. UV threshold data for the rabbit cornea and lens[a]

Wavelength (nm)	Threshold radiant exposure (J/m^2)			Threshold radiant exposure permanent damage (J/m^2)	
	corneal threshold	lens threshold	time to disappear	lens threshold	time for permanent damage to appear
295	200	7500	24 h	10 000	2 h
300	500	1500	3 days	5000	24 h
305	700	3000	7 days	5000	24 h
310	550	7500	2 weeks	15 000	24 h
315	22 500	45 000	1 week	60 000	24 h
320	75 000	> 80 000	—	—	—
335	109 000	> 150 000	—	—	—
365	> 250 000	> 250 000	—	—	—

[a] From: Pitts & Cullen (1977).

Table 4. Permanent lenticular opacities[a]

Wavelength (nm)	Radiant exposure (J/m^2)	Appearance of lens opacities	Permanence[b] of lens opacities
300	5000	24 h	permanent
305	5000	24 h	permanent
310	15 000	24 h	permanent
315	60 000	24 h	permanent

[a] From: Pitts & Cullen (1977).

[b] Lenticular opacities present one month after exposure.

Phototoxic psoralen derivatives have been used recently in the treatment of certain dermatological conditions. Such compounds caused UV-A-induced corneal opacities and cataracts in mice (Griffin, 1959; Koch, 1967).

Research on the effects of psoralens on the production of cataracts in man needs to be pursued. As more and more people are subjected to dermatological treatment using UV photosensitizing compounds, the role of these compounds and their effects on the ocular system should be defined.

4.4 Effects of Long-Term Exposure of Skin to UVR

UV irradiation induces an inflammatory response and ulceration in both the epidermis and the dermis, the latter being infiltrated with leukocytes in the region of the lesions, and to a much lesser extent between them. These lesions ulcerate and the epidermis may disappear for a time in the centre. However, peripherally there is particularly active hyperplasia. The basal membrane (between the epidermis and dermis) may disappear for a time in the regions of these "open" lesions. Between the lesions, the infiltration of leukocytes is relatively slight.

Injury to the epidermis and dermis, brought about by long-term exposure to UVR leads to dermal alteration, fibrosis, and elastosis, as well as to epidermal atrophy. However, experimental production of cutaneous elastotic changes in animals by artificial UV irradiation has only been reported rarely. Using histochemical methods, Sams et al. (1964) demonstrated focal dermal elastosis in mice after prolonged exposure to artificial UVR. UVR-induced changes in connective tissue were also seen in rat skin by Nakamura & Johnson (1968).

4.4.1 UVR-induced mutagenesis and carcinogenesis

4.4.1.1 *Mutagenesis*

The nature of the effects of UVR on DNA, described earlier, shows the importance and the specificity of the lesions in genetic material and focuses interest on the mutations that might result in the various cell types studied. The production of such mutations has best been demonstrated in bacteria.

Among many others, Grossman (1968), Eisenstark (1971), and Witkin (1976) have proposed, analysed, and verified some complex mechanisms that control UVR-induced mutagenesis. It will be recalled also that, according to the results obtained by Radman (1975), most of the UVR-induced mutations would appear to be errors introduced in the DNA during error-prone SOS repair.

Mammalian cells in culture have proved to be very suitable material for the study of UVR mutagenesis (Kao & Puck, 1969). There is quite good agreement between the dose of UVR and the proportion of mutants (Bridges & Huckle, 1970).

Fox (1974) has shown that caffeine can reduce the rate of mutations induced by UVR in cultures of rodent cells by inhibiting a process of error-prone repair.

Isolation and study of UVR sensitive mutants in animal cells have found remarkable applications in the study of various human

xeroderma pigmentosum mutants (Cleaver, 1973). However, such mutations in mammalian germinal cells are not possible, because the cells are located below the depths of penetration of UVR.

4.4.1.2 *Mechanism of UVR carcinogenesis*

In order to understand the possible mechanisms of UVR carcinogenesis, it has been necessary to study the formation and excision of pyrimidine dimers, unscheduled DNA synthesis, and all the data valid for the range from bacteria to mammalian cells.

It is now generally believed that UVR carcinogenesis results from a succession of events originating in a photolesion of the genetic material.

From the numerous studies that have led to en elucidation of some of these mechanisms, it emerges that faulty DNA repair can increase the frequency of carcinogenesis in the following ways: by causing alterations in DNA, which also find expression in an increased frequency of chromosome aberrations and a rise in mutation rate; by increasing the rate of transformation of normal cells into cancer cells; and by facilitating the expression of latent oncogenic viruses able to trigger cancerous growth (Setlow, 1973; Trosko & Chu, 1973).

Errors induced by DNA repair during the initiation phase of carcinogenesis seem to be the most likely mechanism leading to UVR cancers.

4.4.1.3 *Tumour types*

Epidermal tumours. The first visible step in UVR-induced epidermal tumour formation in animal skin consists of cell proliferation, i.e., an increase in the number of squamous cells and cell layers, which gradually become papillomatous in character (Stenbäck, 1978). This is accompanied by an increase in cellular atypia, nuclear enlargement, hyperchromatism, indentation, and prominence of nucleoli. This basically proliferative response is frequently replaced by a dysplastic progression showing a solar keratosis-like pattern with cellular pleomorphism, occasionally with pseudoepitheliomatous hyperplasia-like features, which ultimately invade the dermis. The tumours first seen are acanthomatous papillomas (trichoepitheliomas), with a predominantly epithelial component or fibropapillomas in which the tumour is composed of a fibrous stroma covered by squamous epithelium.

The malignant tumours that ultimately develop are squamous cell carcinomas of different types including: solid keratin containing tumours; moderately differentiated, individually keratinizing tumours with distinct intercellular bridges; and less-differentiated,

non-keratinizing spindle cell tumours, in which ultrastructural analysis reveals squamous cell patterns.

Keratoacanthomas, i.e., proliferating epithelium on a cup-shaped base, are relatively more frequent in animals of different species receiving large doses of UVR than in animals treated with chemical carcinogens.

Epidermal tumours are easily induced by different agents in mouse skin (Stenbäck, 1969). Winkelman et al. (1960) reported the production of squamous cell carcinomas on the backs of hairless mice exposed to UVR. Further studies established that carcinomas could be induced in this animal almost to the exclusion of sarcoma formation (Epstein & Epstein, 1963). In early studies, epithelial tumours were reported in both rats and mice (Findlay, 1930; Herlitz et al., 1930; Putschar & Holz, 1930), but in later studies the deeper lying dermal tumour response to UVR predominated. No mention of skin sarcomas was made, however, in the studies of Beard et al. (1936) on albino rats in which 12 animals exhibited 9 carcinomas of the external ear, 6 sarcomas of the eye, and 1 carcinoma of the skin of the nose.

The difference in the distribution of tumour types, with sarcomatous growth predominating in haired mice and carcinomas in man (Urbach, 1969) may, in part, be explained by the difference in penetration of UVR, a greater amount reaching the dermis in mice (Kirby-Smith et al., 1942; Everett et al., 1966).

Dermal tumours. Another type of neoplastic progression seen in mice, particularly after intensive treatment with large doses of UVR over a short time period, consists of ulceration, scarring, and the subsequent formation of dermal tumours. These tumours begin as aggregates of regularly built, elongated cells with small monomorphic nuclei. Epithelial proliferation is occasionally observed as a secondary phenomenon. The tumours rarely extend grossly through the surface. In the early stages, they appear to be papillomas, although they consist entirely of fibroblastic cells. Some tumours are remarkably acellular, with a prominent fibrillary pattern. The tumours are composed of large, polymorphic cells with prominent nuclei. Ultrastructural analysis shows the predominant cellular components — a dark cell type, with hyperchromatic nuclei and scanty cytoplasm, and a light cell type, with large nuclei and abundant cytoplasmic ribosomes (Stenbäck, 1975a). The same cell types are also seen in malignant tumours, in which the cellular polymorphism frequently is considerable, with nuclear atypism and enlargement, numerous nucleoli and a generally disorganized arrangement. Sarcoma induction is partly species-specific, as these tumours were not seen in UV-irradiated Syrian golden hamsters (Stenbäck, 1975b) nor were they seen in hairless mice

(Epstein & Epstein, 1963) or guineapigs, susceptible to chemical sarcoma induction (Stenbäck, 1969, 1975b).

An infrequent neoplastic alteration in several animal species is the vascular tumour (Stenbäck, 1975b). This begins as a proliferation of dilated vascular spaces with regular endothelial lining. Rarely, the endothelium proliferates to the point of forming angiosarcomas, or invasive tumours composed of large, atypical cells arranged in a nodular pattern.

The role of the dermis in epidermal tumour formation has been emphasized by numerous investigators (Orr, 1938; Mackie & McGovern, 1958). A proliferation of elastic tissue was induced experimentally in mice, by Sams et al. (1964), through repeated exposure to UVR. Similarly, Magnus & Johnson (1965) stimulated formation of elastotic tissue, following early destruction of elastic fibres, with radiation of 300 nm from a monochromatic source. Nakamura & Johnson (1968) reported that dermal elastic tissue proliferation occurred in albino rats after chronic irradiation with UVR, only after discontinuation of the exposure. It was postulated by Johnson et al. (1968) that this change was the result of photochemically-induced alterations in fibroblast function, rather than the degradation of normal elastic fibres. In support of this concept, Epstein et al. (1969) noted that unscheduled DNA synthesis occurred in connective tissue cells of the upper dermis within minutes of exposure to UVR shorter than 320 nm, demonstrating a direct effect of UVR on dermal fibroblasts.

Because of its frequent association with skin cancer formation, actinic elastosis has been considered to play an important role in tumour development. However, Sams and his co-workers (1964) and Graham & Helwig (1965) demonstrated that actinic elastosis was not essential fo the development of epidermal malignancies. Furthermore, the experimental production of elastosis in animals has not been associated with cancer formation, nor has UVR-induced experimental cancer depended on the presence of this change (Epstein & Epstein, 1963).

Adnexal tumour formation is not as common in UVR-treated animals (Stenbäck, 1975) as in, for example, carcinogen-treated rats (Zackheim, 1964; Stenbäck, 1969). Hyperplasia and cystic disorganization of hair follicle walls is very common, but rarely progresses to grossly visible neoplasia. Trichoepitheliomas with barely visible follicular arrangements are rarely seen. Even more uncommon are hamartomatous tumours, hair follicle-derived trichofolliculomas, and sebaceous gland tumours. Sebaceous gland epitheliomas and carcinomas are even rarer. In a study in 1930, Putschar & Holtz reported only a very small number of basal cell carcinomas in rats.

Pigmented tumours. Studies on the induction of pigmented tumours with UVR have been less successful. Benign, dermal melanocytic lesions, or blue nevi, have been observed in hairless mice exposed to UVR (Epstein et al., 1967). They were grossly seen as papules, 2—20 mm in diameter, histologically composed of tightly arranged, heavily pigment-laden polyhedral cells. Subcutaneous accumulation of pigmented cells has also been seen in pigmented animal strains, as well as in the skin of the Syrian golden hamster (Stenbäck, 1978). Such tumours were possibly spontaneous, as the incidence was very low — only around 4% — and unrelated to treatment. They were composed of polyhedral or spindle-like cells arranged in a whorl-like pattern beginning as hyperplasia of perifollicular melanocytes, before spreading both laterally and deeply in the dermis. These tumours do not show junctional activity; they do not metastasize and rarely kill the host.

Melanomas, the type of greatest interest from an epidemiological standpoint, are rarely seen in animals. Benign melanocytomas are easily induced by treatment with chemical carcinogens as shown by Shubik et al. (1960) and Rappaport et al. (1961). Fortner et al. (1961) reported spontaneous melanomas in hamsters, similar to those in man. However, the sensitivity of these animals to UVR is not known. The effect of pigment, in general, in animal models has received little attention. Freeman & Knox (1964a) induced melanocytoma in 67% of a pigmented strain of rats. The tumours had an average latency period of 193 days. In albino rats there was an 8% tumour incidence with a 283-day latency period.

4.4.2 Species-specificity

Three specific factors — pigment, hair, and thickness of the stratum corneum — have been found to alter susceptibility to tumour induction. It was found that pigmented mice required significantly more radiation to induce tumours than albino animals. Hair offered even greater protection (Blum et al., 1959), and thus the hairless rat appeared to be a likely subject for tumour induction studies. However, the results of Hueper's (1941) extensive studies indicated that this animal was, in fact, quite resistant to UV penetration because of its thick stratum corneum. Since pigment, hair, and the stratum corneum were limiting factors, the ears of albino mice and rats became the traditional test sites for experimental production of cancer by UV irradiation. A remarkable amount of quantitative data has been accumulated using this system. The usual tumour produced in this tissue was a sarcoma (Roffo, 1934; Grady et al., 1943b). Thus, the albino ear model could not be used for evaluating qualitative changes associated with epidermal carcino-

genesis, which is the primary process induced by UVR in human skin.

Winkelman and his co-workers (1960) reported the production of squamous cell carcinomas on the backs of hairless mice exposed to UVR. Further studies established that carcinomas could be induced in this animal almost to the exclusion of sarcomas (Epstein & Epstein, 1963; Epstein, 1965). In addition, UVR-induced pigmented tumours were reported in pigmented hairless mice (Epstein et al., 1967). Thus, the hairless mouse has provided a model for both the qualitative and quantitative examination of the carcinogenicity of UVR.

Though penetration of UVR appears to be of obvious importance, other factors also influence the type of growth induced by UVR. Grady et al. (1943 a) found that the size of individual doses did not have any effect on the carcinoma/sarcoma ratio in the albino, hairy mouse but that reduced intervals between exposures increased the number of epidermal carcinomas. These findings suggest that various tissues respond differently to the carcinogenic effects of UVR (Stenbäck, 1975a). In part, this may be associated with differences in penetration of various wavelengths of UVR. Furthermore, there are great species differences in the repair capability of cells.

4.4.3 Ultraviolet radiation as an initiating agent

The two-stage concept for skin tumour formation proposed by Berenblum & Shubik (1949), supposed formation of dormant tumour cells by a single application of a carcinogen. These latent tumour cells were provoked by the subsequent application of a promoter to form visible tumours. In his studies on the induction of skin cancer by exposure to UVR, Blum (1969) indicated that the process was continuous beginning with the first exposure and progressing to ultimate tumour formation. Blum's conclusions were based on experiments in which he (Blum et al., 1943) and Rusch et al. (1941) could not produce tumours, unless exposures were carried out over a minimum of 2 1/2 months, regardless of the amount of energy used. Blum's experiments suggested that, with shorter exposure periods, tumour formation was not accelerated enough to become visible within the lifetime of the experimental animal. Epstein & Roth (1968), using a single exposure to UVR as an initiatior and treatment with croton oil as a promotor, concluded that croton oil stimulated tumour formation, the characteristics of which were established by initial exposure to UVR. The results of these studies were significantly different from those encountered when a chemical carcinogen was used as the initiator (Stenbäck, 1969).

4.5 Interactions between Ultraviolet Radiation and Chemicals

4.5.1 Chemically-enhanced photocarcinogenesis

An equally significant problem concerns photo-induced carcinogenesis following the application to the skin of agents which are phototoxic, but not in themselves carcinogenic.

A portion of the sunlight spectrum is carcinogenic, even in the absence of an exogenous photosensitizer. At the current rate of introduction of new compounds into the environment, it has become increasingly important to determine whether a readily demonstrable property, such as phototoxicity, can be used to predict compounds or treatment regimes that could enhance photocarcinogenesis.

Concepts of chemical interaction with UVR-photocarcinogenesis are of recent origin. Blum (1969) and Emmett (1973) reviewed a number of reports dealing with the influence of phototoxic substances on photocarcinogenesis. The results frequently appeared to be in disagreement, a situation possibly reflecting differences in technique, including solvent, routes of administration, light sources, criteria for tumour recognition, and in statistical evaluation (Blum, 1969). In addition, characteristics of some compounds (toxicity, carcinogencity, instability) rendered their interactions with light complex, and their analysis difficult.

The relative enhancing effects on photocarcinogenesis of two widely recognized photoactive compounds 8-methylpsoralen, (8-MOP) and anthracene were studied by Forbes et al. (1976). Both compounds were phototoxic, but only the 8-MOP solutions markedly enhanced photocarcinogenesis. Thus, the ability of a chemical to induce phototoxicity is not always sufficient to augment photocarcinogenesis.

4.5.2 Interaction between light and chemical carcinogens

The fact that UVR can alter several phenanthrene carcinogens photochemically has been known for some time. The studies of Davies et al. (1972 a, b) showed that the carcinogenicity of 7,12 dimethylbenz(a)anthracene (DMBA) was reduced by light according to the demonstrable photochemical lability of the compound. There was also evidence that an additional time-dependent factor could influence this effect. Thus, it appears that, at least in the case of DMBA-treated animals, light may contribute in two opposing ways: *(a)* by degradation of the carcinogen to non-carcinogenic products and *(b)* by stimulating a phototoxic response that appears to coincide with a relatively increased tumour yield.

Depending on the wavelengths of the UVR used, carcinogens can be photodegraded to a less carcinogenic compound, or can induce

phototoxicity which may augment carcinogenesis or cause such a severe local phototoxic reaction that the epithelial skin cells are nearly all destroyed. Thus, either enhancement or inhibition of skin carcinogenesis may occur, depending upon the carcinogen and the wavelength of the light source used.

4.5.3 UVR-induced carcinogen formation

The photochemical conversion of sterols to carcinogenic substances has been proposed as a potential explanation for the cancer-causing effects of light upon skin (Black & Douglas, 1973). It has recently been demonstrated, *in vitro*, that one such compound, cholesterol-5a-oxide, which possesses carcinogenic properties (Bishoff, 1969), is formed in human skin exposed to UVR (Black & Lo, 1971).

4.6 Physical and Quantitative Aspects of Ultraviolet Irradiation in Animal Studies

4.6.1 Carcinogenic action spectrum

Determination of the effective wavelengths or "action spectrum" is one of the primary objectives in the study of photobiological responses. However, data are not available for the action spectrum of UVR-induced cancer formation. The paucity of this information for one of the most extensively studied photobiological reactions is due to a number of factors, including the large number of potential wavelengths, the considerable number of animals necessary and the length of time (a matter of many months or years) required for exposure to each wavelength, the difficulties in immobilizing experimental animals, and the need for an especially good monochromator with practically no stray light contamination. Though the complete curve of the carcinogenic spectrum is not known, certain aspects have been determined by less sophisticated methods. Roffo (1934) reported that windowglass filtration eliminated the carcinogenic effects of sunlight on white rats. Thus the offending rays of the sun would be found approximately between 290—320 nm. A number of investigators using mercury arc and fluorescent sun lamps with filters have confirmed that, under their experimental conditions, 320 nm represented the longer wavelength limit for cancer formation (Griffin et al., 1955; Blum, 1969). Furthermore, carcinogenic responses have been produced by radiation as short at 230.2 nm (Roffo, 1934) and skin cancer has long been known to be induced by UV-C and UV-B. Thus the action spectrum appears to include wavelengths between 230 and 320 nm but wavelengths between 290 and 320 nm have been shown to have significantly

greater carcinogenic effects than UVR shorter than 260 nm (Rusch et al., 1941; Blum, 1943; Blum & Lippincott, 1943; Kelner & Taft, 1956; Tung et al., 1971).

Freeman (1975) performed a series of experiments to provide more specific comparative data by testing the hypothesis that the action spectrum for carcinogenesis parallelled that for erythema. In these studies, squamous cell carcinomas developed at approximately the same rate and frequency, when UVR exposure was proportional to that for erythema, with a decreasing potency from 300 to 320 nm. No tumours occurred in mice exposed to 290 nm. These cancer-producing wavelengths are also responsible for the normal phototoxic sunburn reaction. Longer UV and visible light are neither erythema-producing nor carcinogenic under ordinary conditions.

It cannot be assumed that the action spectra for human skin erythema and mouse skin photocarcinogenesis are similar, unless a common chromophore or action mechanism is involved. Setlow (1974) proposed that the common denominator was the action spectrum for affecting DNA. Making some allowance for the skin transmission of UVR, he showed that the shapes of action spectra for DNA, erythema, and possibly skin cancer production were similar and could be made to coincide.

4.6.2 Dose-response relationships

The second law of photochemistry (the law of reciprocity of Bunsen & Roscoe) states that photochemical action depends only on the product of the light intensity and the duration of exposure. This law, however, holds only for primary photochemical action, and cannot be applied to secondary reactions. Since the biological endpoints that can be observed, such as erythema, pigmentation, skin cancer production, etc., are certainly indirect effects, and since we still know little about the primary photochemical reactions that underlie them, it is not surprising that "reciprocity" holds only for some of the effects studied.

In the first quantitative photocarcinogenesis experiments ever performed, Blum (1969) found that, within relatively narrow limits (approximate factor of 5), differences in dose, intensity, or interval between doses did not alter the shape or slope of tumour incidence curves, but only their positions on the log-time axis. Blum, however, was careful to point out that this was only true as long as the experimental conditions remained the same until the time the tumours appeared.

With the accumulated data, he surmised that UVR-induced cancer formation was a continuous process that began with the initial exposure and that the appearance of tumours within the lifetime

of the animal depended on sufficient acceleration of the growth process.

In the majority of studies on photocarcinogenesis, fixed doses of UVR have been given at a fixed dose rate, and the interval between doses altered, but in increments of at least 24 hours. Such experiments, while very valuable, are far removed from the conditions found in nature under which human skin is exposed. Man is exposed to a relatively low UVR flux that varies with time of day, season, and environmental conditions, such as cloud cover, and also during the exposure period.

Two recent animal experiments have shown that both varying the UVR dose increment and varying the dose-rate while the daily dose remains constant, affects UVR-induced skin carcinogenesis.

In the first experiment, groups of hairless mice were exposed to doses of UVR from a bank of "Fluorescent Sun" (FS) lamps known to produce skin cancer in these animals. Equal doses of UVR were delivered in periods of 5 minutes, 50 minutes, or 500 minutes. Thus, while the doses (given 5 times weekly) were the same, the flux varied by a factor of 10 or 100. Striking differences in both tumour development time and tumour yield were noted. The animals given the total UVR dose in 5 minutes developed tumours later and in smaller numbers than those given the same total dose in 50 or 500 minutes (Forbes, personal communication). Thus, protracting the UVR dose over longer time periods resulted in a striking increase in the carcinogenic effects of the radiation.

In another experiment, mice were exposed to UVR doses per day differing by a factor of two. As Blum had found previously, the lower daily dose resulted in the delayed onset of first tumours without significantly changing the shape of the response curve (Forbes, 1978).

4.6.3 Physical factors influencing UVR carcinogenesis

Although the tumour-promoting properties of such physical factors as freezing, scalding, and wounding have been described for chemical carcinogenesis systems, little information is available about the effects of these factors on UVR-induced cancer formation. Bain & Rusch (1943) reported that increasing the temperature to 35—38°C accelerated the tumour growth rate. The stimulating effects of heat on UVR carcinogenesis were confirmed by Freeman & Knox (1964b). Heat also enhanced the acute injury response to UVR.

Temperature does not affect the photochemical reactions that follow UV irradiation, but it does affect many of the biochemical reactions that follow the initial photochemical change (Blum, 1941,

1969). Although it is known that heat adversely affects photosensitivity (Lipson & Baldes, 1960), and other phenomena of light injury (Bovie & Klein, 1919; Hill & Eidenow, 1923), and that heat alters the effects of X-ray (Carlson & Jackson, 1959), the influence of heat on burns produced by sunlight or UVR has rarely been considered (Freeman & Knox, 1964b).

Other studies have shown that high winds and high humidity significantly increase tumour incidence (Zilov, 1971; Owens et al., 1977).

4.7 The Immune Response to Tumour Induction

A number of studies have shown that the immune status of the host and tumour induction are potentially interactive processes. Chemical carcinogens cause alterations of the host immune-response, the type and extent of which depend on the tumour-inducing agent (Curtis, 1975). UVR also profoundly affects immunological reactivity, particularly the immune response to skin tumours induced by UVR. Studies leading to this conclusion were prompted by an observation by Kripke (1974) that tumours induced by UVR in C3Hf mice were highly antigenic and are usually immunologically rejected when transplanted to normal, nonirradiated syngeneic recipients. This raised the question as to why these tumours were able to grow progressively in their primary host without succumbing to immunological rejection. In an extensive series of experiments, Kripke & Fisher (1976) found that pretreatment of mice with UVR for periods of time too short to induce skin tumours made them unable to reject transplants of UVR-induced tumours, even though such transplants were immunologically rejected by unexposed animals. This indicates that UVR-exposed mice are systemically altered in a way that prevents immunological rejection of highly antigenic UVR-induced tumours.

Similarly, inability of unexposed secondary hosts to reject UVR-induced tumours after transfer of lymphoid cells from UVR-treated mice has been established, and demonstrates the immunological nature of the systemic alteration in the UVR-treated mice (Fisher & Kripke, 1977). Furthermore, the failure of lymphoid cells from UVR-exposed mice to react against UVR-induced tumours is due to the presence of suppressor T lymphocytes in the lymphoid organs of UVR-treated animals. In spite of their inability to reject highly antigenic UVR-induced tumours, UVR-exposed mice respond normally to most other antigens (Kripke, et al., 1977; Norbury et al., 1977). The one exception is that UVR-treated mice have a transient defect in antigen processing in the skin, which is reflected in their inability to develop contact hypersensitivity reactions (Jessup et al., 1978).

The finding that a selective immunological defect precedes the appearance of UVR-induced primary tumours suggests that the immune system might control early UVR-induced skin cancers and that tumours ultimately appear because of this interference by UVR with host defence mechanisms.

The carcinogenic action of polycyclic hydrocarbons has been associated with their immunosuppressive action (Stenbäck, 1969). Immunodeficiency states and immunosuppression therapy are both associated with an increased tumour incidence. Immunosuppressive agents, such as antilymphocyte serum, enhance both chemically- and UVR-induced tumour formation (Nathanson et al., 1973, 1976).

5. EFFECTS OF ULTRAVIOLET RADIATION ON MAN

5.1 Beneficial Effects

In addition to the direct effects on the skin, UVR produces a number of systemic effects. It has the capacity to increase the tonus of the sympathico-adrenal system, enhances mitochondrial and microsomal enzyme activity and the non-specific immunity level, and increases the secretion of a number of hormones (Tung, 1976).

Systolic and diastolic blood pressures are reduced before sunburn appears and may even be reduced with exposures so mild that no visible erythema is produced (Aitken, 1937). Blood pressure gradually falls for 24 hours, and lowered pressure may persist for several days. Studies have demonstrated that the exercise tolerance of children receiving UVR through the winter is greater than that of control groups not receiving radiation (Ronge, 1948; Zilov, 1971).

Other changes that have been attributed to UVR exposure include reduction in serum cholesterol, increase in the glucose tolerance curve, and decrease in serum tyrosine (Kameneckaja & Mitrofanova, 1975).

Seasonal changes in various diseases are often considered to be evidence of UVR effects, but there are many other climatic variables that change with the season, including temperature and daylength. Blood volume, blood content of the skin, blood flow in the skin, and hydration of the skin due to sweating vary with seasonal adaptation. Thus few changes in disease patterns can be attributed to the effects of UVR alone.

Data have been obtained indicating that the body's tolerance towards exposure to chemical substances such as nitrites, benz-

pyrene, carcinogens etc, which produce general toxic, carcinogenic, and allergenic effects depends, to some extent, on the degree of exposure to UVR (Gabovic et al., 1975; Prokopenko & Zabulueva, 1975; Prokopenko, 1976). Prophylactic treatment with UVR preceding specific immunization reduces the risk of vaccination allergy and helps to increase the effectiveness of the immunization (Talanova et al., 1975).

Where sizeable populations live in far northern areas, it is now generally acknowledged that a long period of UVR deficit may have a harmful effect on the human body. Numerous investigations indicate that lack of exposure to solar UVR can lead to the development of a pathological condition known as "UVR deficiency" or "light starvation". The most frequent manifestation of this disease condition is a disturbance in mineral metabolism and the development of Vitamin D deficiency and rickets in children, accompanied by a sharp reduction in the defensive powers of the body, making it particularly vulnerable to unfavourable environmental factors. The development of UVR deficiency is confirmed by data from a survey conducted, mainly among children, in different photoclimatic zones of the USSR (Belikova et al., 1975; Dancig, 1975), and from a survey of ships' crews working in the north and in the tropics.

Vitamin D. Sunbathing is popular, and there is a widespread feeling that "sunlight is good for you", but the physiological benefits that presumably underlie the feeling of well-being have not been adequately explained or studied.

The only thoroughly established beneficial effect of UVR on the skin is the conversion of 7-dehydrocholesterol to Vitamin D_3. Several investigators have helped to promote the understanding of the mechanisms of Vitamin D production and its metabolism and functioning.

It has long been noted that prolonged limitation or complete absence of exposure of the human skin to solar UVR makes natural activation of Vitamin D impossible and is an important factor in the spread among the population of "chronic latent D avitaminosis" reflected in widespread rickets and dental caries. Data from the previously mentioned survey by Belikova et al. (1975) indicate that, despite an overall reduction in the incidence of rickets and in its severity, it is still frequent among young children in the north of the USSR. Morbidity indices for rickets at latitude 65°N are 2.5—3 times as high as at latitude 45°N.

Comparative investigations among healthy children aged 3—6 years in the central zone of the USSR and beyond the Polar Circle have also confirmed that disturbances in mineral metabolism in children in the far north occur earlier and are more marked (Talanova & Zabalueva, 1972).

In this connection, it is of some interest that Vitamin D deficiency may have a direct effect on the pathogenesis of dental caries (Dancig, 1974).

The problems associated with UVR deficiency are frequently enhanced by social factors and by degree of pigmentation (Loomis, 1970).

Phototherapy. Some information on the beneficial effects of UVR comes from the past and present use of sunlight and UVR in medical treatment.

In the pre-antibiotic era, several forms of skin tuberculosis and skin infections were treated with UVR. At present, UVR treatment in medicine is largely confined to treating skin diseases, such as psoriasis, acne, atopic dermatitis, and recurrent boils. There have been reports that UVR, administered in gradually increasing doses, has been helpful in the treatment of both chronic pneumonia (Boguckij et al., 1975), and rheumatic diseases in childhood (Karacevceva, 1971).

5.2 Induction of Erythema in Human Skin

Erythema solare, or more commonly "sunburn", consists, in its mildest form, of a reddening of the skin that appears 1—6 hours after exposure to erythemogenic UVR and gradually fades in 1—3 days. In its more severe forms, sunburn results in inflammation, blistering, and peeling of the skin; it is followed by tanning of the skin, which becomes noticeable within 2 or 3 days of irradiation.

The amount of radiation required to produce solar erythema provides a convenient measure of UVR dosage. The actual amount of energy required varies with the wavelength of the radiation, since some regions of the spectrum are more effective than others. Because of large variations from one individual to another, as well as variations between different parts of the body, an "erythema unit" cannot be determined with the same accuracy as physical units or even units of visual luminosity. There are also appreciable variations in a given individual from time to time, depending upon such factors as physical condition and previous exposure. The methods for evaluating erythema introduce additional variables. There is a latent period after exposure before reddening of the skin is observable. Thus, the length of time after exposure that the observation is made will affect the results. In spite of these limitations, a "sunburn unit" (SU), based on the effect of solar UVR on the average untanned human white skin, provides a useful method of rating and comparing various sources of UVR.

The use of the SU (Lazarev & Sokolov, 1971) is based upon the applicability of the Bunsen-Roscoe law of reciprocity (see section

4.6.2). Over a reasonable range of exposure times, skin erythema depends on the total UVR dose, but is independent of exposure rate and duration (Seidl, 1969).

Monochromatic sources of radiation are not generally considered, but the erythemal effectiveness depends upon the sum of the effects of those wavelengths that are present. In the case of a line spectrum, the total effect is calculated by adding the weighted intensities of the various lines of the source, the weighting depending on the action spectrum in use.

By adopting this method, the erythemal equivalent of any particular distribution of radiant energy may be calculated and expressed as the equivalent amount of energy at a particular wavelength (e.g., 296.7 nm) that would produce the same erythemal effect as the given heterogenous radiation (section 6).

Numerous factors contribute to the complexity of the erythema response (skin temperature, sweating, dose-rate, etc., section 6). In applying the reciprocity law to polychromatic radiation, the fact that the observed differences in biological effects of different wavelengths may introduce inaccuracies must be considered.

5.2.1 Action spectra of human skin erythema

Hausser & Vahle (1927) reported the first precise determination of the action spectrum for the erythema of human skin; a double peak was shown with maxima at about 250 and 297 nm and a minimum at about 280 nm. In these and related studies, the skin of several individuals was exposed to UVR from a mercury arc passed through a double-quartz-prism monochromator, and the influence of wavelength, exposure time and rate of exposure upon the nature, degree, and course of erythema was examined. Similar action spectra were published by Coblentz et al. (1932), Lukiesh et al. (1939), and Magnus (1977) (Fig. 5).

5.3 Natural Protection against Erythema-inducing Ultraviolet Radiation

5.3.1 Melanin (see also section 4.2.3)

Skin tanning during and following sun exposure is one of the major protective devices of the skin against further damage by UVR. The UVR range from 290 to 320 nm produces sunburn and subsequent new pigment formation. UVR in the range of 320 to 400 nm produces little erythema, except at very high doses, but may produce immediate pigment darkening and other increases in melanin pigment in those who have this capacity.

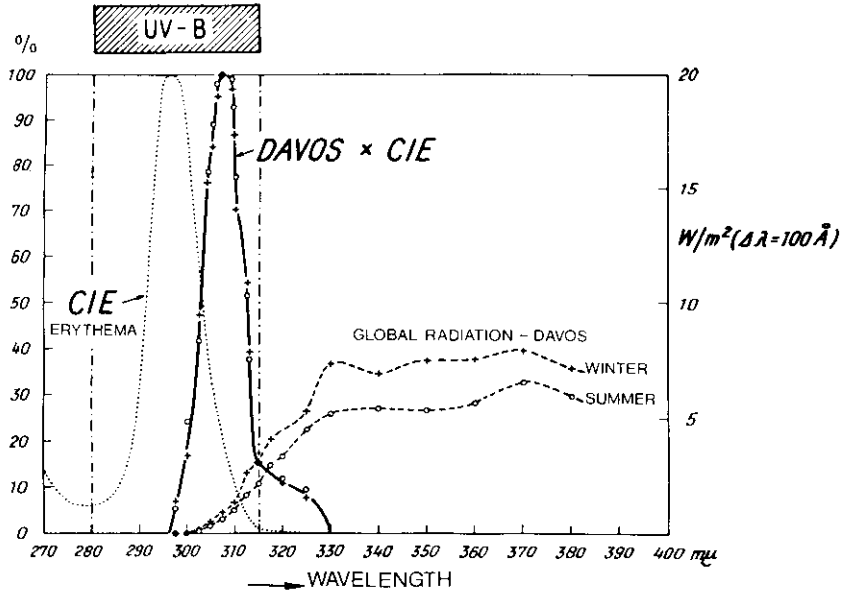

Fig. 5. Erythema action spectrum (From: Magnus,1977).

Constitutional skin colour in man is the "baseline" colour that develops in the absence of exposure to solar radiation or other environmental influences and results from genetically determined levels of melanin pigmentation. Facultative skin colour or "tan" is the increase in melanin pigmentation above the constitutional level which is induced by UVR or by pituitary hormones such as the melanocyte-stimulating or the adrenocorticotropic hormones. The facultative tanning (darkening) response induced by solar irradiation can be divided into immediate tanning (IT), which occurs within minutes of exposure to sunlight, and delayed tanning (DT), which becomes evident several days after exposure (for review see Fitzpatrick et al., 1974).

Immediate tanning (IT). IT, also called immediate pigment darkening (IPD), is best seen in pigmented individuals. In general, the darker the unexposed, baseline, inherited colouration, the greater the ability to exhibit IT.

Within 5—10 min of exposure to the noonday sun, a gradual darkening is noticed, which is confined to exposed skin. If exposure continues, darkening increases until it reaches a maximum after about 1 h of irradiation. The colour ranges from light brown to dark brown or, in the more deeply pigmented races, from grey-brown to black. Brief exposures to sunlight may lead to slight to moderate IT, which begins to fade within 30 min of the end of

exposure and is scarcely visible after 3—8 h. Prolonged exposure to sunlight or high-intensity artificial long wave UVR sources can lead to striking IT that lasts longer than 36 hours. IT is optimally produced by both long wave UVR and visible light.

Delayed tanning (DT). DT, also referred to as "true melanogenesis", becomes visible 72 hours after exposure to UVR, although electron microscope studies have shown ultrastructural evidence of the formation of new melanosomes and melanin much earlier. The major action spectrum of DT is the same as that for sunburn but DT can also follow exposure to UV-C and UV-A and shorter wavelength visible light.

Exposure to UVR can also modify the pattern of distribution of melanosomes in keratinocytes. In Mongoloid peoples, repeated UVR exposure results in a predominance of non-aggregated single melanosomes. Interpretation of variations in melanosome packaging within the epidermis must take into account the history of the previous exposure of individuals to solar radiation and other factors.

Once present, melanin acts as a neutral density filter and decreases the amounts of UVR that can reach the lower layer of the skin containing viable keratinocytes or penetrate into the dermis to strike blood vessels. As constitutional or facultative pigmentation increases, the dose of UVR required to produce erythema increases.

5.3.2 Thickening of the stratum corneum

Thickening and brownish discoloration of the stratum corneum of light-exposed areas of human skin are noted after exposure to UVR. While a protective effect unquestionably exists, it is of relatively less practical importance than the protection afforded by melanin pigmentation.

5.4 Solar Elastosis and Other Dermal Effects of Ultraviolet Radiation (See also section 4.2)

Sunlight may have many effects on the skin, and one of the most important both clinically and cosmetically is aging. Gross changes in actinically damaged skin are a dry, coarse, leathery appearance, laxity with wrinkling, and various pigmentary changes. Frequently, in elderly and even in some relatively young fair-skinned adults, there is a striking difference between light-exposed regions and those protected by clothing. A weather-beaten farmer often appears considerably older than a clerk of comparable age. Black skin has natural protection because of its high melanin content and elderly Negroes often appear deceptively young (Silverstone & Searle, 1970).

It now seems clear that collagen degeneration in the dermis is independent of age and is determined simply by the cumulative amount of injury from UVR. This depends on the degree and frequency of exposure and the extent of natural (and artificial) protection afforded to the patient's skin by the thickening of the stratum corneum, melanin pigment, clothing, or chemical sunscreens.

The visible cutaneous changes usually interpreted as "aging" are apparently due, to a large extent, to chronic exposure to sunlight.

5.5 Ultraviolet Radiation and Skin Cancer in Man (See also Section 4.2)

Classical evidence supporting the role of sunlight, particularly of UVR, as a causal factor in human skin cancer can mainly be summarized in the form of six associations of skin cancer (Urbach et al., 1972):

(a) Association with exposed areas of the skin. Among white-skinned people, skin cancers occur most frequently on the parts of the body most exposed to sunlight — the head, neck, arms, and hands, and the legs of women.

(b) Association with protection against UVR. Among races with dark skin, in which pigment filters UVR, there is very little skin cancer and the disease does not occur predominantly in areas of the skin exposed to the sun. Sunburn and skin cancer arise in the same tissue, and UVR is known to cause sunburn. It appears that those who are more susceptible to skin cancer sunburn more easily. White-skinned people of Celtic origin are more susceptible to both skin cancer and sunburn while those of Latin origin are less susceptible.

(c) Association with the amount of exposure to the sun. Among fair-skinned people, there appears to be a greater prevalence of skin cancer in those who spend more time outdoors.

(d) Association with the intensity of solar exposure. The incidence of skin cancer among white-skinned people increases with increasing proximity to the equator and thus with increasing solar radiation and intensity of UVR.

(e) Association with UVR in laboratory studies. Skin cancer can be produced in mice with repeated doses of UVR in the same spectral range that produces sunburn in the human skin.

(f) Association with insufficient ability to repair DNA damaged by UVR. Those with the recessive disease xeroderma pigmentosum, who have a defect in DNA repair, develop skin cancer prematurely. Such persons are photosensitive, and develop tumours, induced by exposure to solar UVR. They frequently die of skin cancer before reaching adult life.

5.5.1 Anatomical distribution of skin cancer

Numerous studies have shown that, in fair-skinned people, skin cancers arise primarily on sites exposed to sunlight. It has been demonstrated that about 90% of all basal cell carcinomas and more than half of all squamous cell carcinomas occur on the head and neck. The majority of those squamous cell cancers not occurring on the head and neck are found on the hands and forearms; the ears of females are markedly protected by hair (Silverstone & Searle, 1970; Swanbeck & Hillstrom, 1971).

Comparing the sites of non-melanoma cancers with studies made of the geometry of insolation of the head and neck areas, it becomes clear that two thirds of all basal cell carcinomas occur on the skin sites receiving the highest doses of UVR, and that virtually all squamous cell carcinomas occur at these sites (Urbach et al., 1972).

The anatomical distribution of malignant melanoma, a less common but more deadly form of skin cancer, suggests a less striking association with UVR exposure. However, there has been a considerable increase in the prevalence of this type of cancer on the legs of women during the past 25 years and a special form of melanoma, lentigo maligna, almost always arises on the face.

5.5.2 Occupation and skin cancer

As has been pointed out previously, surveys of the incidence of skin cancer other than malignant melanoma are, generally, not very reliable. Consequently, data concerning the relationship between occupation and skin cancer incidence are also scarce. From the studies carried out in Queensland, Australia, and in Galway, Ireland, the most reliable sources, it appears that those in outdoor occupations are the most highly exposed and, therefore, at the highest risk. Thus farmers, fishermen, sailors, and others such as road workers, roofers, policemen, and postmen, have a higher incidence of skin cancer than office and factory workers (Swanbeck & Hillström, 1971; Gordon & Silverstone, 1976).

5.5.3 Genetics and skin cancer

In several carefully controlled studies comparing patients with non-melanoma and melanoma skin cancer to age-sex matched controls from the same populations, a distinct association was found between skin cancer and light coloured eyes, fair complexion, light hair colour, poor ability to tan, ease of sunburning, and a history of repeated severe sunburn. Furthermore, whenever looked for, there was a higher prevalence of Celtic stock among skin cancer patients (Silverstone & Searle, 1970; Urbach et al., 1972). Xeroderma

pigmentosum (XP) is a hereditary skin disease in man. Studies on cells from the patients have supplied the most decisive arguments regarding the relationships between photolesion repair and carcinogenesis. Persons suffering from this disease show abnormal pigmentation and a high incidence of skin cancers triggered off by exposure to the solar UVR. Cleaver (1973), who was the first to draw attention to the possible causes of the disease, has written a critical review of the main biochemical and genetic studies which reveal the extreme complexity, but also the ingenuity and logic of the molecular processes that play a part in the development of the disease.

In general, it has proved possible to establish a correlation between the level of DNA repair and the seriousness of the symptoms in XP patients.

Numerous and more complex studies have shown that the various degrees of UVR sensitivity observed in XP patients correspond to different sensitivity mutants. Using techniques such as cell fusion and complementation, several groups have been distinguished that are characterized by various defects in the repair mechanisms (Kraemer et al., 1975). Some mutants show normal excision but no repair synthesis (Lehmann et al., 1975). In others, repair replication would seem to be normal, but chain breaks appear more slowly than in normal cells. Caffeine emphasizes these differences still further (Fornace et al., 1976).

Although the mechanisms are far from completely elucidated, they show the considerable value of this kind of genetic disorder, in which the problems of the photolesions and their repair and of carcinogenesis are intimately linked.

5.5.4 Geographical distribution of non-melanoma skin cancer

Incidence data for skin cancer, other than melanoma, must be treated with considerable reserve. Many cancer registries do not register non-melanoma skin cancer at all, and those that do are uniformly incomplete, since most of these tumours are treated in physicians' offices and either not reported at all or reported without histological verification.

A survey of the recorded geographical distribution of non-melanoma skin cancer has been made by Cutchis (1978) (Fig. 6 and 7). From the data of Scotto et al. (1974), it appears that in Iowa, USA, for instance, the incidence of skin cancer in males rose from 61.4/100 000 in 1950 to 174/100 000 in 1972. This approximately 3-fold increase is also noticeable in all areas in Texas, with the exception of El Paso, where the incidence rate actually decreased, and Houston, where the increase was apparently only 2-fold. The Texas data (MacDonald, 1976) showed that incidence rates increased with descending latitude, but not in a stepwise fashion. In the most

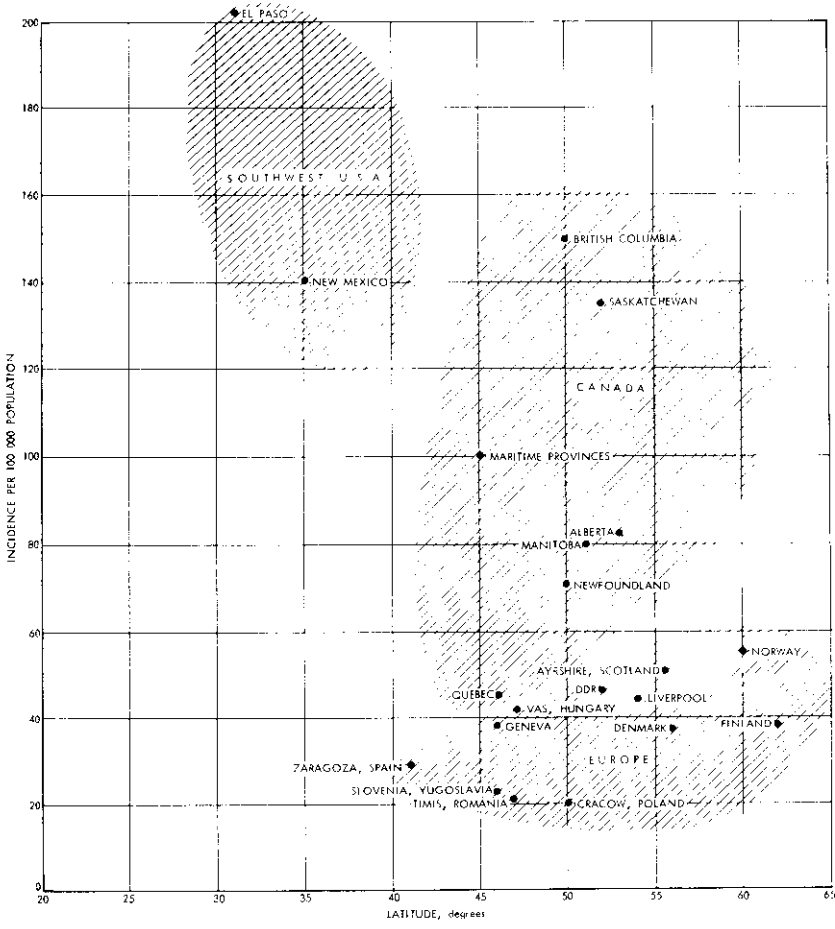

Fig. 6. Non-melanoma skin cancer, age-standardized incidence for white males, based on data from Waterhouse et al.(1976). Reservation must be made for a too low recording of these cancers in some areas (From: Cutchis,1978).

recent 5-year period (1962—1966), the rate for El Paso was 183/100 000 and that for San Antonio (1°further south) was 147.35/100 000. In San Antonio, a large part of the permanent population consisted of retired military personnel and their families. Most of these people had spent much less time in the sunny south than the permanent population in El Paso. The highest incidence rate was found at Corpus Christi at latitude 28°N (371/100 000). This was significantly greater than the incidence at Harlingen (284.5/100 000), at latitude 26°N. At Corpus Christi, there was another factor in-

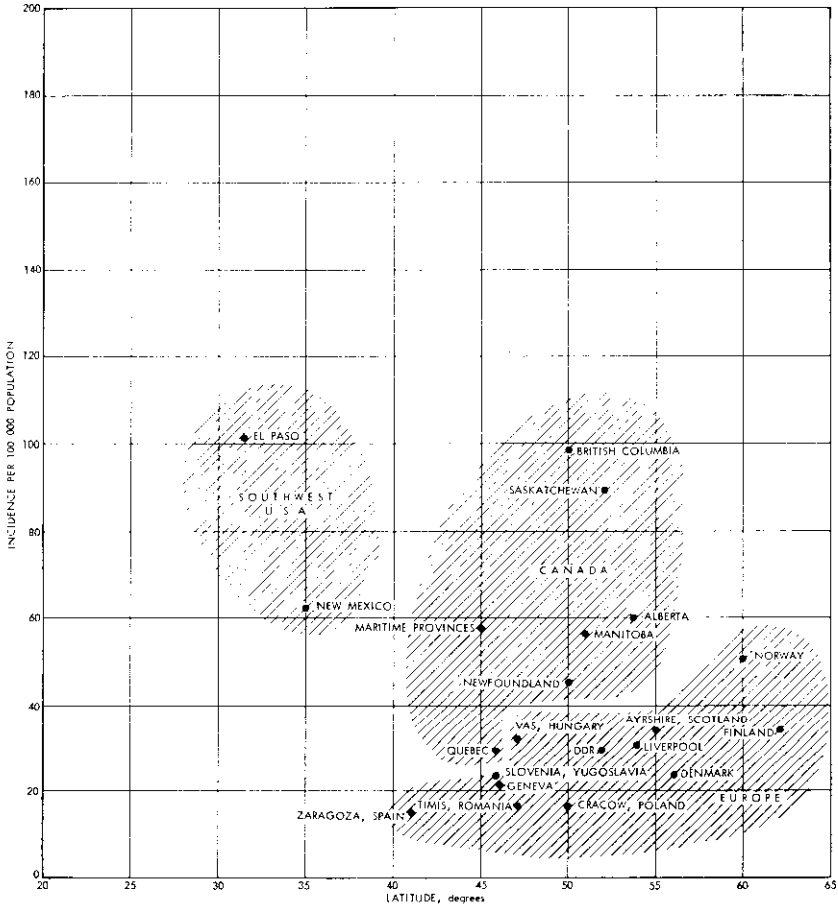

Fig. 7. Non-melanoma skin cancer, age-standardized incidence for white females, based on data from Waterhouse et al.(1976). Reservation must be made for a too low recording of these cancer in some areas (From: Cutchis,1978).

volved besides exposure, i.e., a great preponderance of Celtic inhabitants whose forebears migrated to that area about a century ago. Thus the disproportionately high incidence of skin cancer in Corpus Christi could be due to a combination of intense insolation and a very susceptible population, a situation similar to that existing in Queensland, Australia.

These findings demonstrate how important the confounding social factors can be in evaluating skin cancer statistics in relation to UVR exposure.

Europe. In Europe, just as in the USA and Australia, a marked north-south gradient of non-melanoma skin cancer exists.

In 1976, Waterhouse et al. reported skin cancer incidence rates for males and females as follows: Sweden — 10.6 and 6.5/100 000; Denmark — 33.4 and 24.5; Federal Republic of Germany — 7.3 and 4.6; UK — 40.3 and 21.4; and Yogoslavia — 23.2 and 22.8. Other reports suggest incidences in the German Democratic Republic of 43.9 and 40.3/100 000 (Herold & Berndt, 1968), and in Bulgaria, of 42.2 for rural and 25.0 for urban people (Anchev et al., 1968).

In the USSR, skin cancer morbidity increases from north to south. According to these data, skin cancer represents 15—26% of the total cancer morbidity in the south, and 9—14% in the north (Čaklin, 1974).

Africa. Information concerning skin cancer in Africa, gathered from various sources, but mainly from the reports of Oettle (1962) and Davies et al. (1965), show that the native Africans have extremely low rates of both non-melanoma and melanoma skin cancer.

The incidence rates in the Johannesburg Bantus and in Uganda are of the order of 1—2/100 000 for non-melanoma skin cancer (almost all squamous cell carcinomas of the lower extremities) and 0.4—0.6/100 000 for malignant melanoma (almost all located on the foot) (Oettle, 1962). A more recent study in the Sudan shows a somewhat higher incidence rate, particularly for squamous cell carcinomas (Malik et al., 1974).

The exceptions are albino Negroes, who are extremely prone to the development of skin cancer. In South Africa, albinism is quite common among the Bantus. Oettle (1962) estimated a crude annual incidence rate of 579/100 000 for male and 408/100 000 for female albino Bantus for squamous cell carcinomas of the skin. Interestingly, the rates for basal cell carcinoma were recorded as only 36/100 000 for both sexes combined, as only 1 case was found.

India. Incidence data for skin cancer in India are not available. However, it is clear that the majority of skin cancers seen in hospitals occur in fair-skinned people. Among native indians, special types of squamous cell carcinomas of the skin are found such as the Kangri, Dhoti, and Chutta cancers, which are presumably due to extreme heat, smoke, and chronic friction (Mulay, 1962).

China and Japan. While incidence figures are again not available, it is clear that skin cancer is uncommon in the Province of Taiwan, China, and Japan. This is also borne out by a reversal of the usual basal cell to squamous cell carcinoma ratio. Squamous cell carcinomas are 2—3 times more common than basal cell cancers, and may arise at the site of premalignant skin changes such as burns, chronic trauma, or secondary to arsenic ingestion (Miyaji, 1962; Yeh, 1962).

Australia and New Zealand. Probably the best skin cancer

surveys of recent years have been carried out in Australia, particularly in Queensland, by Gordon & Silverstone (1976). Their values for the incidence of skin cancer in various parts of Australia are reported in Table 5.

Table 5. Skin cancer in Australia[a]

State	Annual incidence per 100 000 population			
	Male		Female	
	Crude	Age standardized	Crude	Age standardized
Victoria (40°S)	68.5	66.6	50.5	38.5
Queensland	265.1	265.1	174	155.8
Brisbane (28°S)	242		172	
Townsville (19°S)	466		300	

[a] From: Gordon & Silverstone (1976).

Comparable demographic data in those areas of the world that are warm and sunny and to which people from northern Europe including the United Kingdom have migrated are given in Table 6.

Table 6. Examples of high incidence of skin cancer. Annual incidence per 100 000 population by sex[a]

Region	Male	Female	Latitude
S.W. England	28	15	53°N
South Africa — Cape Whites	133	72	35°—25°S
Texas (non-Latin)	168	106	28°—32°N
Queensland (Whites)	265	156	28°—10°S

[a] From: Gordon & Silverstone (1976).

Skin cancer tends to appear at a much earlier age in the Queensland population than in populations living further away from the equator.

If the distribution of annual solar UVR (Green et al., 1975) is plotted against the incidence of skin cancer on a global basis, it can be shown that skin cancer incidence doubles for every 10°decrease in latitude. The Australian data would fit this concept, particularly in Queensland, where the difference in incidence between Brisbane and Townsville is about two to one and the difference in latitude about 9°.

Not as much work on skin cancers has been done in New Zealand as in Australia; however good estimates of skin cancer incidence have been reported by Eastcott (1962). These are: 113/100 000 for basal cell carcinoma, 38/100 000 for squamous cell carcinoma; and 5.5/100 000 for malignant melanoma. These rates are considerable

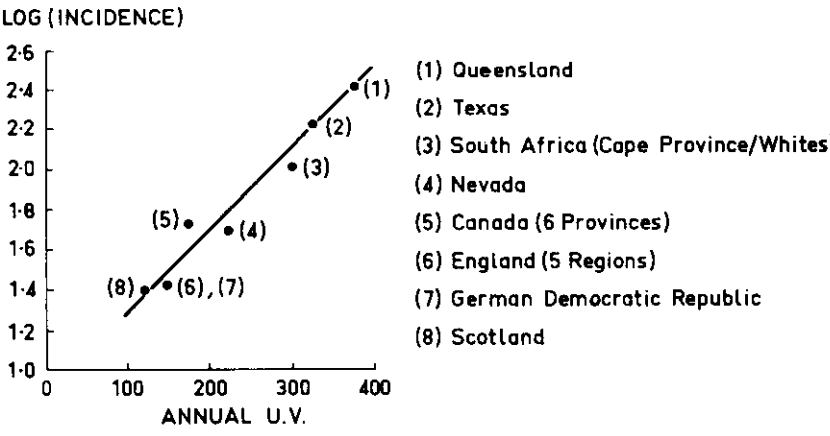

Fig. 8. Logarithm of incidence rates for skin cancer, excluding melanoma, per 100 000 male population for eight regions against annual UV solar radiation in watt seconds per cm^2 (10 mμ). Equation of fitted line is log (rate) = 0.00119 (UV) + 0.8508 (From: Gordon & Silverstone, 1976).

lower than those for Australia, but New Zealand is much further from the equator and thus receives less UVR.

5.5.5 Dose-response relationship for skin cancer (see also section 4.5.2)

Although a correlation between the incidence of skin malignancy and solar UVR levels has not yet been established with great accuracy, it has been possible to demonstrate a correlation between latitude and skin cancer incidence (Gordon & Silverstone (1976), Fig. 8). Some confounding factors have been obtained from animal experiments.

There are data that indicate that physical and chemical factors may attenuate or intensify the carcinogenic effect of UVR (Sviderskaja, 1971). Chronic exposure of animals to small doses of ionizing radiation reduces resistance to the carcinogenic effects of UVR, increasing the incidence and reducing the length of the latent period. UV-B radiation has variable effects on the growth of transplanted and chemically induced tumours. UV-B radiation can affect the resistance of the body to tumour formation, increasing it with use of sub-erythemal doses and considerably reducing it with large doses (Dancig et al., 1975). These data, although obtained in animal systems only, may be of great significance for human health, since the resistance of the body to exposure to various harmful factors in the environment operates against a certain background of natural UVR.

5.5.6 Mortality from skin cancer

In contrast to malignant melanoma, where mortality in most series still exceeds 40%, the fatality rate in non-melanoma skin cancer is as low as 1%. However, it would be incorrect to try to draw conclusions from disease specific mortality rates.

5.5.7 Malignant melanoma

Both the incidence and the mortality rates of malignant melanoma are rising rapidly in all countries in which they have been studied, with mortality rates doubling in a 10—15 year period (Elwood & Lee, 1975).

The incidence varies from less than 1/100 000 in Japan, Nigeria, and India to as high as 24/100 000 in Queensland, Australia. The rise in incidence and mortality has been much greater in younger people than in those over 65 years of age, implying that a causal mechanism operates from an early age. The increase has been greater at certain body sites and thus the site distribution has changed. The most striking increase in incidence has been on the lower limbs in females and the trunk in men (MacGovern, 1977).

In countries where such data are available, there is a distinct association between latitude of residence and development of malignant melanoma (Lancaster, 1956; Magnus, 1973; Movshovitz & Modan, 1973; Elwood et al., 1974). The closer to the equator and the longer the residence in countries with high insolation, the higher, in general, is the incidence of malignant melanoma.

However, while there is usually a demonstrable latitude gradient within a country, the latitude association in much less marked than that for non-melanoma skin cancer. For instance, incidence rates for malignant melanoma in Norway and Sweden are much higher than in England and France both of which are much further south (Cutchis, 1978, Fig. 6 and 7).

Basal cell and squamous cell carcinoma, which are considered to be due primarily to chronic UV-B exposure, are commonest on the areas of skin exposed to sunlight, occur at a later age than malignant melanoma, and are strikingly associated with severe solar damage to the skin. In contrast, malignant melanoma occur more often on the trunk of men and legs of women than non-melanoma skin cancer, and only one type, the lentigo maligna melanoma (comprising not more than 15% of all melanoma), is associated with histological UVR-induced skin damage (McGovern & Mackie, 1959).

Thus, it appears that non-melanoma and melanoma skin cancers are related to UVR exposure in different ways. Table 7 lists the similarities and differences between these two types of tumours. Parallel increases in melanoma and non-melanoma skin cancer cannot be expected, as the latent period for malignant melanoma

is apparently much shorter than that for non-melanoma skin cancer. Reasons suggested for the differences between the two types include: the greater sensitivity of melanocytes to UVR (McGovern, 1977); the presence of some secondarily produced circulating factor (Lee & Merrill, 1970); and intermittent overdoses of UVR (Fears et al., 1977).

In the absence of an experimental animal model, and with the present state of knowledge, it must be assumed that there is some association between UVR and the development of malignant melanoma. Thus any additional UVR exposure of susceptible individuals may increase the risk of development of this very serious malignant skin tumour.

Table 7. Comparison of epidemiological factors in the etiology of malignant melanoma and non-melanoma skin cancer

Factor	Malignant melanoma	Non-melanoma skin cancer
Latitude of residence	Increases linearly within countries, incidence not strictly related to latitude globally.	Increases geometrically with latitude.
Age of onset	3rd and 4th decade most common.	6th to 8th decade most common.
Sex	Moderate preponderance for females.	Great preponderance for males.
Anatomical distribution: Male, white	Back, anterior torso, upper extremity, head, and neck.	Head and neck (particularly ears and lip), upper back, hand, upper extremity.
Anatomical distribution: female white	Back, lower leg, upper extremity, head, and neck.	Head and neck (ears and lower lip, spared), hands, upper extremity, anterior chest.
Anatomical distribution: Black and oriental	Soles, mucous membranes palms, nail bed. (all sites rare).	Anterior lower extremities, other (all sites rare).
Racial (genetic) factors	Celtic background, Scandinavians. Rare in pigmented races.	Celtic background, Scandinavians. Rare in pigmented races.
Possible etiological factors	Genetic (xeroderma pigmentosum XP, B-K mole) Physical (UVR, trauma) Chemical (PCBs[a], α-DOPA) Developmental (nevi)	Genetic (XP) Physical (UVR, X-ray) Chemical (arsenic, coal tar).

[a] PCBs = polychlorinated biphenyls.

5.6 Phototoxic and Photoallergic Diseases

5.6.1 Phototoxicity

Light-induced damage to the skin that does not depend on an allergic mechanism may be considered phototoxic. Theoretically, these reactions will occur in everyone, if the skin is exposed to enough light energy of the proper wavelengths and if enough molecules that

will absorb these wavelengths are present. The radiation must penetrate to the absorbing molecules for the reaction to occur. Clinically, phototoxic reactions are usually characterized by erythema (and at times oedema) occurring from a few minutes to several hours after exposure, followed by hyperpigmentation and desquamation. The sunburn reaction is the classical example of response to a phototoxic effect (Ippen, 1969).

From the clinical point of view, the erythema produced by various phototoxic agents differs greatly in type of onset and type of reaction; the ability of the agents to elicit pigmentation also varies.

In contrast to the usual acute solar erythema, which begins after a latent period of a few hours, peaks at 24 h, and subsides in a few days to be replaced by moderate melanin pigmentation, the erythema due to photodynamic compounds appears immediately after or during radiation, may be associated with striking wheal formation, and disappears in 3—6 h. Pigmentation is usually minimal.

The erythema due to furocoumarins (8-MOP) begins later than that caused by solar radiation, peaks at 48—72 h, may persist for days, and is followed by very intense pigmentation.

Despite a considerable amount of investigation, the mechanisms by which phototoxic responses occur are not well understood. In the case of the exogenous photosensitizer, either the molecule alone or a complex of the chemical and cellular organelles becomes excited by the absorption of light; triplet states and free radicals, or both, may be formed.

Certain dyes and chemicals such as methylene blue, acriflavine, rose bengal, and porphyrins produce photochemical effects on living and non-living substrates only in the presence of oxygen. The photodynamically active substance becomes excited and forms a triplet state or a free radical. The excited chemical may also form peroxides and then oxidize the substrate. Other possibilities include passing the energy from the excited chemical to the biological substrate, which then becomes oxidized, or the activated chemical may be able to accept electrons, resulting in the oxidation of the substrate. After excitation, the photosensitizing molecules return to the ground state and are structurally unchanged.

Photosensitizing compounds may be endogenous, i.e., formed in the body, usually by abnormal metabolism (e.g., porphyrins), or exogenous, i.e., contacted externally or given as medication.

Exogenous photosensitizers may reach the skin by topical or systemic routes and the reactions may be phototoxic or photoallergic in nature. The action spectra for most of the phototoxic agents that may cause skin disorders in man lie in the long-wavelength UVR range (320— 400 nm).

Contact photosensitizers include: cosmetics such as perfumes,

colognes, after-shave lotions (essential oils and psoralens), lipsticks (fluorescein derivatives), creams, and hair preparations (coal tar derivatives); and plants that cause phytophotodermatitis such as Persian limes, pink rot-infested celery, many members of the Umbelliferae and Rutaceae orders. These problems are primarily due to psoralen compounds and therapeutic agents including phenothiazines and sulfonamides (usually used therapeutically), halogenated salicylanilides, sunscreens, and blankophores (usually photoallergic).

Systemic photosensitizers include: thiazide diuretics; antibacterial sulfonamides; sulfonylurea antidiabetic drugs; phenothiazines (especially chlorpromazine); and antibiotics (especially dimethylchlortetracycline).

A large number of other drugs may occasionally induce photosensitivity.

5.6.2 Photoallergy

Photoallergy can be defined as an acquired altered capacity of the skin to react to light energy alone or in the presence of a photosensitizer (Harber & Baer, 1969).

In photoallergic reactions, the photosensitizer leads to the formation of the photohapten, which binds (covalently) with a suitable carrier molecule to form the complete photoantigen. The carrier may be a protein, polypeptide, mucopolypeptide, mucopolysaccharide, or other macromolecule present in the skin. Once developed, photoallergy can apparently occur with light energy alone, but presumably small quantitites of the photoantigen are still present in the skin and involve a circulating antibody or a cell-mediated response. In contrast to phototoxicity, photoallergy is uncommon and is characterized clinically by such reactions as immediate urticaria or delayed papular or eczematous responses similar to contact dermatitis.

The hallmark of a sunlight-induced reaction, whether toxic or allergic, is the distribution of the eruption. The exposed areas of the face, neck, upper extremities, and, in women, the anterior surface of the legs and the proximal, dorsal areas of the feet are mainly involved. Exposure while driving may accentuate the eruption on the side of the face and arm adjacent to the window. The upper eyelids, subnasal and submental areas, flexural aspects of the wrists, and the antecubital fossae tend to be spared. Clothing generally provides protection, but reactions can be produced by penetration of UVR especially through the light fabrics worn in summer.

The most common photoallergens are: 3,5-dibromosalicylanilide (3,5 DBS); 4,5 dibromosalicylanilide (4,5 DBS); tribromosalicylanilide (TBS); hexachlorophene; bithionol; and trichlorcarbanilide.

5.7 Pterygium and Cancer of the Eye

While detailed epidemiological evidence does not seem to exist, there is a clinical impression among competent ophthalmologists that a latitude gradient exists for the development of pterygium of the eye, a benign hyperplasia of the bulbar conjunctiva which may eventually interfere with vision by growing over the pupil (Dolezova, 1976).

Epidermoid carcinoma of the bulbar conjunctiva is a rare neoplasm which appears with increased frequency in people living in the tropics or subtropics (Afghanistan, Colombia, Ethiopia, Haiti, Malawi, Middle East, Nigeria, Pakistan, Senegal, South Africa, and Uganda). It has also been reported in cattle in the same region. Such tumours of the eye can be induced in experimental animals with artificial UVR. Early lesions, which are exophytic and tend to be papillary, are often accompanied by basophilic degeneration of subepithelial collagen and chronic inflammation.

The tumours are moderately to poorly differentiated keratinizing epidermoid carcinomas.

In contrast to carcinoma of the skin, carcinoma of the eye is more common in dark-skinned people, probably because of much greater UVR exposure, and lack of pigment in the conjunctiva.

6. EVALUATION OF HEALTH RISKS TO MAN

6.1 The Significance and Extent of Different Environmental Sources of Ultraviolet Radiation and Pathways of Exposure

The major health risks from natural UVR arise from chronic, excessive, and unwise exposure to solar radiation. Section 2.1.1 of this document describes in detail the wavelengths and quantities of solar UVR that reach the earth and factors affecting it.

Briefly, depending on latitude and stratospheric ozone concentration, the shortest wavelength measured (at noon, near the equator) in solar radiation is about 290 nm. In most regions of earth, the lower cut-off limit is at about 295 nm. The spectral composition and radiation intensity of solar UVR is greatly influenced by latitude, season, time of day (i.e., angle of the sun), cloud cover, and the albedo of the surface. About two thirds of the skin-erythema-producing solar UVR reaches the earth between 10h00 and 14h00.

In man, the extent of human exposure to solar UVR varies with posture. In the upright position, esentially only portions of the head, back of the neck, shoulders, forearms, and hands are exposed. In addition, the skin of the thighs and upper arms may be heavily

exposed in some occupations such as driving a tractor. Exposure also varies with time of day and local weather conditions; clothing (wearing of hats, short- or long-sleeved shirts, shorts, etc.); work and social habits; and ground albedo (snow, ice, and sand being the only effective reflectors).

The maximum amount of solar UVR to which an individual could be exposed in one day, represents about 25 minimal erythema skin doses, i.e., about 7500 J/m^2 of radiation equivalent to the skin erythema effect of 297 nm monochromatic UVR.

Occupational exposure from artificial sources is either inadvertent, when the sources produce UVR as a by-product, or deliberate, when sources are designed to generate UVR to use its properties. Depending on the characteristics of the source (section 2.1), the spectral composition of the emitted UVR can contain wavelengths in the UV-A, UV-B, and UV-C regions.

Some industrial processes in which UV energy is a by-product are welding, plasma torch operations, photoelectric scanning, and hot metal operations. Because of the germicidal properties of certain portions of the UV spectrum, artificial sources are used in hospitals, biological laboratories, schools, and industry. Other common applications are illumination, advertising, crime detection, chemical synthesis and analysis, photoengraving, food, water, and air sterilization, vitamin production, and medical diagnosis. Many other occupations are listed in Table 8. New sources, such as UV lasers and fluorescent panels, are being developed.

Table 8. Occupations potentially associated with UVR exposure

aircraft workers	furnace workers	oil field workers
barbers	gardeners	pipeline workers
bath attendants	gas mantle workers	plasma torch operators
brick layers	glass blowers	printers railroad track workers
burners, metal	glass furnace workers	ranchers
cattlemen	hairdressers	road workers
construction workers	herders	seamen
cutters, metal	iron workers	skimmers, glass
drug makers	lifeguards	steel mill workers
electricians	lithographers	stockmen
farmers	metal casting inspectors	stokers
fishermen	miners, open pit	tobacco irradiators
food irradiators	nurses	vitamin D preparation makers
foundry workers		welders

The amount of UVR exposure from artificial sources depends on the spectral composition, radiant intensity, distance from source, shielding, etc., and must de determined for individual conditions.

6.2 Types of Biological Effects and Their Significance for Human Health

Since UVR penetrates essentially only into the skin and eyes of man, the deleterious effects on these organs are of the greatest

importance. The acute and chronic effects of UVR are described in detail in sections 4 and 5. Also of concern, however, are the deleterious effects of "UVR deficiency" which can occur at latitudes of about 60° (section 7.2).

Acute effects of UVR in the 250—320 nm wavelength range consist of reddening, swelling, and blistering of the skin, occurring 3—24 h after exposure, followed in 3—6 days by the production of melanin ("suntan"), in those capable of producing this pigment.

Acute effects on the eye consist of painful keratoconjunctivitis, which recedes in 36—48 h.

After many years of repeated UVR exposure, the skin of susceptible individuals becomes leathery, wrinkled, and discoloured ("aging changes") and skin cancer may develop (sections 5.4 and 5.5). The degree to which these changes develop depends not only on the UVR dose, but also, to a large extent, on the genetic background, and particularly on the ability of the skin to pigment. For this reason, "aging" changes and skin cancer are very much less common in genetically heavily pigmented individuals.

The development of "aging" changes is irreversible, and presents a major cosmetic (and thus psychological) problem, particularly for women.

While skin cancer, with the exception of malignant melanoma, is rarely fatal, it constitutes a social burden in terms of loss of work, and medical expenses.

6.3 The Risk Associated with Combined Exposure with Other Agents

The interaction of UVR of various wavelengths, particularly UV-A (320—400 nm), with natural and artificial chemical agents may result in a variety of deleterious effect not elicited by UVR or the chemical agents alone.

Among the most common of these effects are the phenomena of phototoxicity, photoallergy, and chemically enhanced photocarcinogenesis (sections 4.5 and 5.6). Fortunately, the actual risk from such photobiological responses is small, as yet.

Of the phototoxic agents, the psoralens (furocoumarins) occur in the rind of most citrus fruit, and in many green leafy plants. Contact occurs most often in fruit pickers, others involved in the citrus industry, and through the use of bergamot-containing perfumes. The phototoxic reactions simulate sunburn. Acute skin and eye phototoxicity are frequent, and sometimes serious, problems in workers handling tars, such as roofers and road workers. Similar findings have been made in creosote workers (Emmett, 1977a). Chronic phototoxicity, and perhaps enhancement of carcinogenicity

can also be induced by coal tar products and phenanthrene carcinogen-containing materials. At risk are roofers, road workers, and those in the tar and pitch-using industries. The extent of augmentation of photocarcinogenesis in man by this route is not known.

The introduction of man-made photoactive chemicals into the environment is increasing. Serious, although small, outbreaks of photoallergic reactions have been reported caused by soap additives (halogenated salicylanilides), antibiotics (bithionol, griseofulvin), drugs (chlortetracycline, thiazides, chlorpromazine), and, most recently, compounds deliberately used in photochemical processes, such as printing inks (Emmett, 1977b).

As yet, the risk of such reactions occurring is very small, but with the continued introduction of new chemicals into the environment, it is bound to increase.

6.4 The Population at Risk — Geographical Distribution, Genetic Influences and Occupation

As far as exposure to solar UVR is concerned, virtually the whole of the world's population is at some risk. However, the degree of risk varies greatly.

Of primary importance is the geographical distribution of the population. Between latitudes 30° and 50°, the intensity and amount (dose) of erythema-effective (and presumably carcinogenic) solar UVR increases linearly with latitude towards the equator. This increase, however, is modified by such conditions as cloud cover, the presence of aerosols and "smog", the altitude above sea level (approximately a 15% increase in UVR for each 1000 metres elevation), and the degree of obstruction of the sky by mountains, buildings, trees, etc.

Another factor of importance is genetic. Constitutional skin pigmentation acts as a highly protective factor against the deleterious effects of UVR on skin. Consequently, at least as far as advanced "aging" changes and skin cancer are concerned, only subjects with minimal or slight constitutional pigmentation are at risk. More than two thirds of the world's population is more or less dark skinned and has little chance of developing such UVR-induced changes. However, pale skinned human beings living in tropical climates run a very high risk of developing skin cancer. The highest incidence of solar skin neoplasms exists in Queensland, Australia, where the combination of a primarily Northern European and Celtic population and a latitude near the equator results in a greater risk from occupational and social outdoor exposure. In

contrast, little skin cancer is found in the native populations of tropical Africa, although latitude and exposure are similar.

Table 9 shows the best available estimate of the number of workers at risk from industrial exposure to various sources of UVR in the USA. Data from other countries were not available to the Task Group.

Table 9. Number of workers exposed to UVR (estimate from Chicago Metropolitan Survey extrapolated to the population of the USA)

Manufacturing		
standard industrial classifications 19—39		211 000
Transportation and communication		
standard industrial classifications 40—49		49 000
Wholesale, miscellaneous retail, service stations		
standard industrial classifications 50, 55, 59		17 000
Services		
standard industrial classifications 70—89		41 000
	Total	320 000

As already pointed out, workers in many occupations are exposed to various levels of artificial UVR.

6.5 The Reliability and Range of Known Dose-Effect and Dose-Response Curves

6.5.1 Dose-effect curves for acute skin erythema

Erythema due to 254 nm radiation appears within 3—4 h of exposure, reaches a peak between 8 and 12 h, and begins to subside markedly by 24 h. Even at its peak intensity, the colour is a pale pink-red, and it is very difficult to be certain of the minimal erythema dose. At very low doses (of the order of less than 50 J/m^2), a weak effect can be recognized, which is clearly (because of the shape and reasonably sharp borders) produced by the radiation. However, it is not clear that this represents true erythema; the colour is yellowish brown and seems to be extremely superficial, almost on the surface of the skin. As reported by Hausser, even five times the minimal erythema dose does not produce any severe erythema at a wavelength of 254 nm. In contrast, with the minimal erythema dose (MED) for wavelengths from 280—313 nm, the erythema is quite sharply defined. The erythema produced by wavelengths 297, 303, and 313 nm is deep red-purple and peaks in 24—28 h. It persists for 3—5 days and imperceptibly changes into pigmentation.

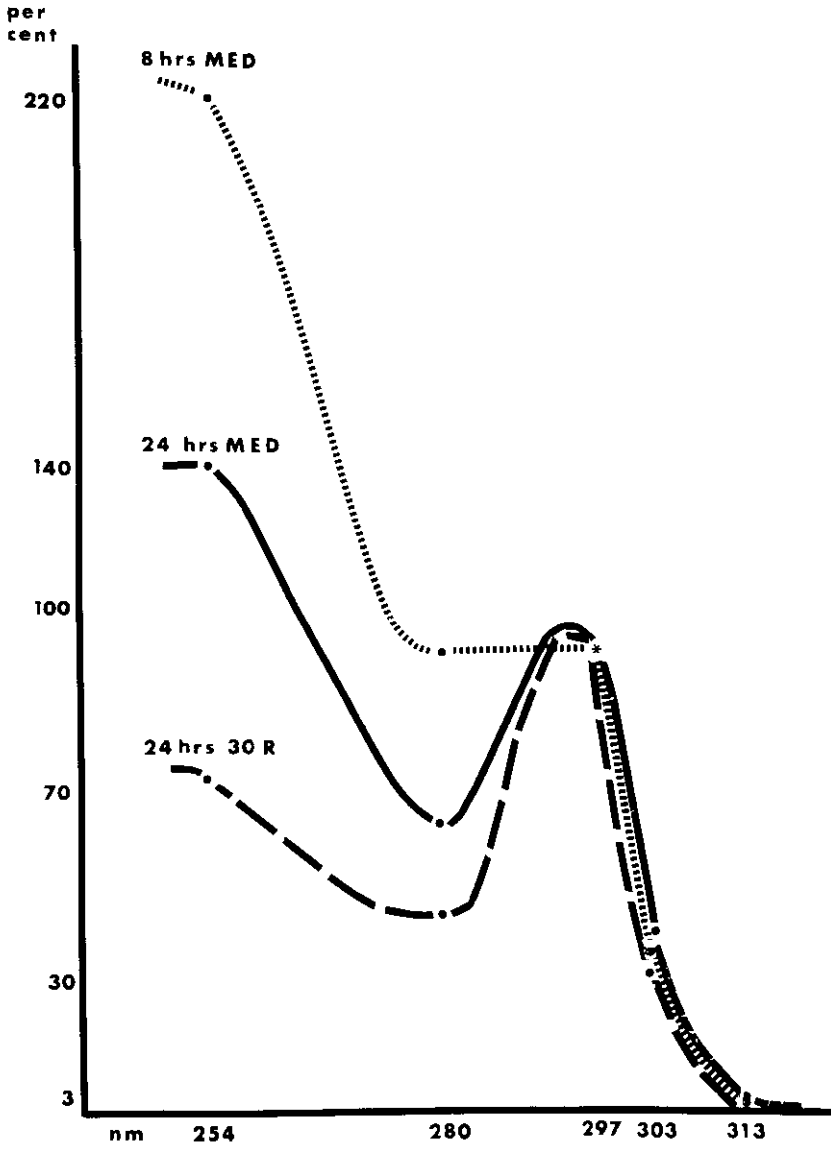

Fig. 9. "Action spectrum" of human skin. Averages of relative values for 5 subjects, abdominal skin. Note great similarity for wavelength from 297—313 nm, and marked differences for 8-h (after irradiation) MED, 24-h (after irradiation) MED, and a curve constructed by using values for moderate erythema (30 R).

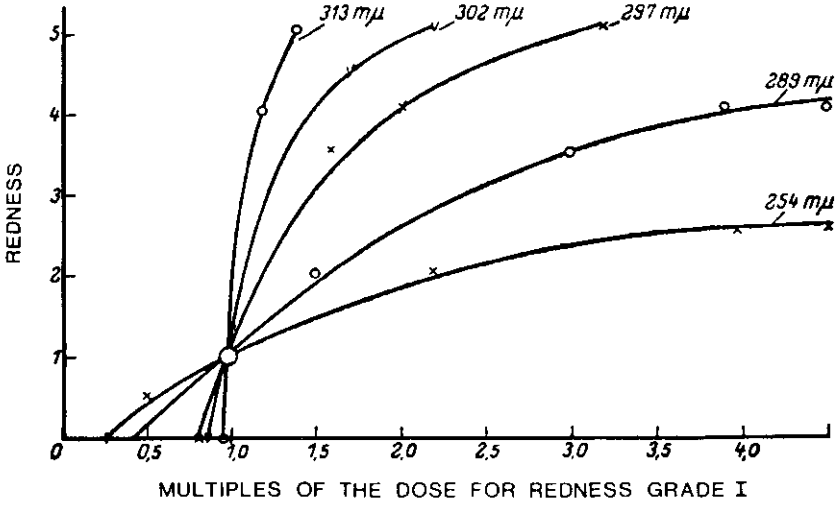

Fig. 10. The "erythema range" effect (From: Hausser & Vahle,1922).

6.5.2 Averages and limits, minimal, and slightly more than minimal erythema doses

The great effect of time after irradiation and of choice of degree of redness on the "action spectrum" of human skin is shown in Fig. 9 and Table 10. Preliminary experiments suggest that the true sensitivity peak lies between 290 and 294 nm. From 297 nm on, there appears to be remarkably good agreement between most published figures. The disagreement at shorter wavelengths is clearly because of differences in time of evaluation, the difficulties inherent in the delineation of "minimal erythema", and possible differences in skin thickness.

Furthermore, if an erythema grade slightly above minimal is used as a reference point, the resultant action spectrum closely approaches that originally described by Hausser & Vahle (Fig. 10).

Table 10. Averages and limits (J/m²) for minimal erythema doses (MED) read at 8 and 24 h and for a "moderate" erythema dose read at 24 h (30 R). All radiation given at the second exit slit, bandwidth 2.16 nm.[a]

nm	MED 8 h (J/m²)	MED 24 h (J/m²)	30 R 24 h (J/m²)
254	63 (35—84)	100 (60—170)	194 (100—400)
280	140 (50—240)	220 (120—336)	320 (230—480)
297	140 (60—240)	140 (60—240)	140 (70—200)
303	390 (280—480)	410 (340—480)	450 (400—480)
313	6320 (4500—7700)	6800 (5400—7700)	7240 (5400—7700)

[a] From: Berger et al. (1967).

6.5.3 The "erythema range" effect

One of the important observations of Hausser & Vahle (1922) was that there appeared to be a significant difference between the doses needed to produce slight and maximal erythema at different wavelengths. This concept is of great potential significance for the prevention of sunburn and the understanding of diseases due to light. In Fig. 10, data are plotted from an experiment designed by Hausser to test this effect, which show that 5 times the minimal erythema dose produces much less than the maximal erythema at 254 nm, while 2.5 times the minimal erythema dose produces maximal erythema at 303 nm. While it takes much more energy to produce any erythema at 303 nm than at 254 nm, not much more than the threshold dose produces a significant burn.

These observations are of great importance because they show that the acute biological effects of several wavelengths in the UV-B proceed at different time scales, and have very different dose-response relationships. Thus, the usual assumptions that it is realistic to weight the effectiveness of different wavelengths in a continuous UVR source (such as the sun) by an action spectrum obtained for a threshold effect with a monochromator is not correct, nor is it appropriate to consider the effect of these wavelengths to be biologically equivalent.

Unfortunately, in the absence of knowledge of chromophores or biological mechanisms, there is no better way of comparing the effectiveness of sources of different UVR composition than the present method of calculating the skin erythema effectiveness of UV-B.

As in all photobiological cutaneous effects, pigmentation plays a major role in the sensitivity of the skin to UVR. Heavily pigmented people are 10—20 times less sensitive than untanned fair-skinned people. As far as is known, the action spectra for erythema are similar for all races, differing only in the amount of energy necessary to produce threshold effects.

6.5.4 Dose-response curves for keratoconjunctivitis

These are essentially similar to those for erythema, except that the peak of the action spectrum is located at 270 nm. This is most likely because of the absence of a filtering stratum corneum and because the conjunctiva is not pigmented. The peak of 270 nm is therefore used for the normalization of the dose limits of broad band sources.

6.5.5 Dose-response relationship for photocarcinogenesis

Most of the existing evidence is consistent with the concepts that UV-induced photodamage to skin is the main causal factor in the development of skin cancer, that the development of skin

cancer is a stochastic effect, and that there is no threshold (sections 4.3 and 5.5).

Thus, a relationship should exist between skin cancer incidence and accumulated dose, using a sensitivity function. In mice, the quantitative relationship between UVR dose and the production of skin cancer has been thoroughly explored; tumour incidence in this experimental model is proportional to the square root of the number of doses, the dose size, and the interval between doses.

In man, there is ample evidence that a latitude gradient exists for the incidence of skin cancer in sensitive, fair-skinned populations, and that this gradient is non-linear. There is obviously a relationship between latitude and the intensity of solar radiation, and this gradient is exaggerated in the UVR portion of the spectrum. Although the shape of this relationship is relatively complex and depends on a number of variables, for a range of mid-latitudes (30°—50°), both the theoretical form and that obtained from actual field measurements closely approximate a straight line. It is generally accepted that latitude-related climatic and environmental conditions and behavioural effects must modify the UVR dose actually reaching a population. The factors involved, and their magnitude are largely speculative.

A series of mathematical models relating human skin cancer incidence to solar UVR has been proposed at various times in the past few years, because of concern about alteration of the stratospheric ozone layer (Green et al., 1978; Rundel & Nachtwey, 1978). While the uncertainties are very great, the best accepted model data suggest that a 5% increase in erythema-effective solar UVR may result in a 15% (range 7.5—25%) increase in skin cancer in a susceptible population after about 60 years, when a steady state has been reached. As far as the relative risk is concerned in susceptible white-skinned populations, people in older age groups, with fair skin that sunburns easily and with a high life-time solar exposure, run 10—20 times more risk of developing skin cancer than their contemporaries, who tan easily and have a low life-time solar exposure (Vitaliano, 1978). Incidences of nonmelanoma skin cancer as high as 350/100 000 population per year have been observed in elderly, white-skinned males in Queensland, Australia, and Texas, USA. Populations with constitutionally, heavily pigmented skin run only a minimum risk of developing skin cancer in their lifetime.

7. GUIDELINES FOR HEALTH PROTECTION

The development of criteria for both upper and lower limits of exposure to either natural or artificial UVR is extremely difficult because of such problems as:

(a) the variation in both the acute and chronic effects of UVR of different wave lengths;

(b) the considerable differences in the spectral composition of light from different sources and particularly of sunlight at different latitudes;

(c) the great differences in cutaneous sensitivity to UVR due to genetic, environmental, and adaptive effects, and the considerable variation in sensitivity in the same person at different times; and

(d) the difficulty of differentiating between the necessary dose of UVR compatible with the upkeep of life, and the lowest dose that results in serious detrimental effects.

7.1 Range of Exposure Limits

7.1.1 Exposure to solar ultraviolet radiation

As described in section 6, two thirds of the daily amount of solar UV-B radiation reaches the earth between 10h00 and 14h00. Thus, exposure should be reduced to a miminum during these hours. After a period of acclimatization, most people can tolerate several hours of outdoor exposure in the morning and afternoon, but shielding in the near noon hours should always be considered. In general, exposure during this very important period of acclimatization should not exceed 4 minimal erythema doses per day without some protection (either clothing or sunscreens, section 7.3). This would correspond to 1 h of exposure in the tropics. A dose of 1/8 MED per day appears to be sufficient to prevent UVR deficiency.

7.1.2 Occupational exposure to artificial ultraviolet radiation

No internationally agreed limits exist at this time for occupational exposure to UVR, which take into consideration the acute effects and the risk of late cancer development. So far, the only limits available, which could be used in the preparation of guidelines, have been proposed by the National Institute of Occupational Safety and Health in the USA (NIOSH, 1975).

The limits are based on the minimal erythema dose (MED) and the minimal photokeratitic dose, which means that only acute effects have been taken into consideration. For the UVR 200—315 nm region, it is stated that radiant exposure in any 8-h period must not exceed the values given in Table 11. For the wavelength range 315—400 nm, the total irradiance on unprotected skin or eye must not exceed 10 W/m^2 for periods exceeding 10^3 seconds. For radiant exposure of shorter durations, it should not exceed 10 000 J/m^2. The

Table 11. Total permissible 8-h doses and relative spectral effectiveness of some selected monochromatic wavelengths [a]

Wavelength (nm)	Permissible 8-h dose (J/m^2)	Relative spectral effectiveness ($S\lambda$)[b]
200	1000	0.03
210	400	0.075
220	250	0.12
230	160	0.19
240	100	0.30
250	70	0.43
254	60	0.50
260	46	0.65
270	30	1.00
280	34	0.88
290	47	0.64
300	100	0.30
305	500	0.06
310	2000	0.015
315	10 000	0.003

[a] From: NIOSH (1975).

Table 12. Maximum permissible exposure times for selected values of I_{eff} [a]

Duration of exposure per day	Effective irradiance, I_{eff} (W/m^2)[b]
3 h	1.0
4 h	2.0
2 h	4.0
1 h	8.0
30 min	17.0
15 min	33.0
10 min	50.0
5 min	100.0
1 min	500.0
30 sec	1000.0

[a] From: NIOSH (1975).

[b] Effective irradiance = action spectrum weighted irradiance.

limit for 315—400 nm is probably much too low and could be revised to a higher level.

However, these values only apply to sources emitting essentially monochromatic UVR. The maximum permissible exposure for a broad band source should be calculated by summing up the relative contributions from all its spectral components, each being weighted by the relative spectral effect S_L, as given in Table 12. In addition, these guidelines for determining exposure limits should not be used for photosensitive individuals.

So far, none of the guidelines has included an evaluation of the carcinogenic risk, as neither the action spectrum nor the dose-

response curve is known for man. It is hoped that this will be obtained by comparison of cancer incidence and UV irradiance as measured by the Robertson-Berger method.

7.1.3 Exposure of the general population to artificial ultraviolet radiation

The exposure of the general population to artificial UVR is primarily for hygienic and for cosmetic purposes. The use of UVR for health purposes is discussed in sections 7.2 and 7.3.

The use of UVR for cosmetic purposes generally involves a requirement for the development of skin pigmentation. For this reason, it is unrealistic to follow the occupational standards, since they would not allow the desired effects to be obtained.

Doses of UVR sufficient to produce slight erythema in 24 hours are usually adequate for cosmetic purposes. Significant overdoses and repeated UVR exposures for prolonged periods should be avoided. The eyes must be properly shielded during each exposure. The risk of the development of skin cancer due to chronic exposure to UVR for cosmetic purposes is not known.

A number of devices available to the general population emit significant amounts of UVR, or will do so if the protective envelope of the device is damaged, and may cause acute UVR-induced eye and skin damage. Such devices include Wood's lights, sterilizing and ozone-producing lamps, and high power mercury and xenon arc lamps used for illumination.

7.1.4 Measurement of natural and artificial ultraviolet radiation

Measurement of solar UVR involves serious difficulties, because of the need for accurate spectral discrimination at the shortest end of the solar spectrum. This is necessary because of the considerable variations in the biological effectiveness of UVR shorter than 320 nm. Few really practical, accurate, stray light-free spectroradiometers have been developed so far, for use in the middle UVR region (UV-B) and the use of action spectrum weighted, integrating analogue UVR meters has been found to be much more practical.

The few practical prototypes of integrating chemical UVR dosimeters that have been developed are still in the experimental stage. If they can be perfected, such personal UVR dosimeters would be of the greatest use (Challoner et al., 1976; Davis et al., 1976).

Basically, the same problems pertain to monitoring of artificial UVR, although measurements are somewhat easier in a laboratory setting.

The exposure criteria recommended in section 7.1.2 have not been put to practical use, because it is still not technologically possible to measure UVR adequately for compliance.

Thus, working practices are recommended for the control of exposure in situations where sufficient measurement or emission data are not available. A frequently practiced method of protection consists of adequate containement of UVR-producing light sources.

7.2 Health Effects of Solar Ultraviolet Radiation in the General Population

Two aspects of health protection in the general population are of interest. One is the prevention of UVR deficiency that can occur in populations living near the north and south poles (generally at latitudes of 60° or more). The other deals with the protection of pale-skinned people from excessive UVR in subtropical and tropical areas (generally between latitudes 35° N and 35° S).

The zoning of the USSR for UVR is particularly interesting from a health point of view (Belinskij, 1971). In the "UVR-deficit zone" it appears essential to use irradiation from artificial sources, during certain months, to compensate for UVR deficiency. In the "UV comfort zone", artificial irradiation is unnecessary. In the "UVR excess zone", it is essential to undertake measures for protection against solar UVR, in order to avoid skin cancer. It has also been proposed that, in order to prevent skin tumours among town dwellers in whom light starvation has caused depigmentation of the skin, preventive UVR should be carried out to increase skin pigmentation.

7.3 UVR Deficiency and its Prevention

7.3.1 Insolation and UV irradiation of built-up areas

It is well known that solar energy entering a room illuminates, warms, dries, and particularly important, disinfects it, thus having a beneficial, physical and psychological effect. The sanitation standards and regulations for the insolation of dwellings and public buildings and built-up areas, which are in force at present in the USSR, are based on the requirement that premises should receive three hours' uninterrupted insolation on cloudless days during the period 22 March—22 September and that protection should be given to limit the thermal effect of solar radiation in the southern regions, below latitude 55°N (State Standards, 1976b).

This health requirement is evident from a number of reviews (Dancig, 1971; Galanin & Pirkin, 1971; Aleksandrov et al., 1975). Solar UVR has a particularly valuable health-effect in that, *inter alia*, it speeds up the processes of environmental selfpurification (Belikova, 1960; Gluscenko et al., 1975). Therefore, town planning tasks should include the rational use of UVR from the sun and sky (Davidson, 1970; Gusev & Dunaev, 1971).

Since window glass cuts off the most biologically active component of natural UVR, research to increase the UVR transparency of window glass has been of particular concern to health workers in the most northern latitudes (Belikova, 1964).

7.3.2 Sunbathing and air-bathing in the prevention of UVR deficiency

In addition to measures ensuring the maximum possible penetration of natural UVR into working and dwelling places, prevention of UVR deficiency can also be ensured by organizing solaria, beaches, and sports areas attached to children's establishments (kindergartens and pioneer camps), and to factories and mills. A schedule for the UV irradiation of children and adults, for sun and sun-and-air baths at different geographical latitudes, at different seasons of the year, and at different times of the day has been developed (Generalov, 1971). At present, the effects of such solar radiation schedules cannot be extrapolated to potential late effects.

7.3.3 Artificial ultraviolet radiation in the prevention of UVR deficiency

Effective principles for the use of artificial UVR in the prevention of UVR deficiency and "light starvation" in man have been developed in the USSR. The recommended levels consist of a daily dose of UV-B of between 0.125 and 0.75% of the threshold erythema dose (State Standards, 1964). The use of prophylactic UV irradiation has been shown to be quite effective in workers in industries lacking natural light (Bocenkova, 1971) and particularly effective in children of preschool and school age (Ronge, 1948; Zilov, 1971).

Regulations have been drawn up for the planning and operation of artificial UV irradiation devices in industrial enterprises (State Standards, 1976b).

7.4 Protection against Ultraviolet Radiation

The whole of the world population has a potential for developing skin cancer, the risk depending on the intensity and

degree of exposure to solar UVR during the life span. If all current exposure to solar UVR could be significantly reduced, the incidence of skin cancer would eventually decrease greatly.

Health and appearance can be adequately catered for by exposing only part of the body for less than half an hour per day at or near noon, except at latitudes north of 60° N.

7.4.1 Sunscreen preparations

Sunscreen preparations are usually classified as chemical or physical agents. The former include para-aminobenzoic acid and its esters, cinnamates, and benzophenones, all of which act by absorbing radiation, which is dissipated as radiation of lower energy. Physical agents act as simple physical barriers, reflecting, blocking, or scattering light. They include titanium dioxide, talc, and zinc oxide. Mainly because of cosmetic objections, the physical barriers are not often used in sunscreen formulations (Robertson, 1972).

The principle of covering the skin by spreading a layer of reliable UV absorber on the surface has proved a popular one. Providing that the thickness of the layer applied is adequate and that it adheres to the skin, it gives protection to the wearer under all conditions.

Details of the kind of chemicals and bases used are beyond the scope of this report.

7.4.2 Clothing

Covering the skin with clothing gives a sense of security that is often misleading. The most frequent sites for skin cancer are those that face upward. Thus, a hat is essential for adequate protection of the forehead, scalp, and tops of ears. However, generally, it gives only partial protection for the nose, less for the lower face, and none for the hands and arms.

Body coverings worn in hot climates are generally not complete absorbers. The average white shirt worn by men may transmit 20% of UVR, while lighter weaves favoured by women may allow 50% of UVR to reach the shoulders. Fairly complete clothing cover is more tolerable in a dry atmosphere than a humid, coastal, tropical environment.

7.4.3 Behavioural conformity with the environment

When unexpectedly detained in the sun, protective procedures available include facing in a variety of directions, hanging the head and shielding the head with the hands or with a handkerchief.

Shadows should be used whenever possible, including one's own shadow. When standing in the shadow of a building, only rays from about half the sky are received, that is, about one quarter of the harmful intensity of full daylight. This is certainly useful protection, but fair skin will still burn in about one hour; in three hours, a painful burn may be initiated, although the sufferer has not been in direct sunlight at all.

The dominant factor in the daily erythemal exposure is the angle of the sun above the horizon. This varies with latitude and with time of year. Thus, maximum exposure occurs, when the sun is almost directly overhead. The simplest means of protection is to take shelter around the middle of the day, especially in the summer months.

At least one third of the whole day's UVR exposure occurs in the hour before and the hour after noon; half the day's exposure, enough for a very disabling sunburn, occurs during the 3-hour period around noon. If shelter is taken between 10h00 and 14h00, only one third of the day's exposure remains. Outside the period from 9h00 to 15h00, only one sixth remains, permitting considerable outdoor activity even for subjects with the most sensitive skin types.

7.4.4 Occupational protection

With the exception of medically prescribed doses, exposure of both the eyes and skin to UVR should be kept to a minimum. In order to protect persons in the vicinity of artificial UVR, the following precautions are recommended:

(a) Whenever possible, prevention of excessive exposure of the eyes and skin should be ensured by proper engineering design of UVR-emitting installations and suitable enclosures, so that any UVR is either adequately contained or sufficiently attenuated.

(b) When, for justifiable reasons, such containment is not possible, protection should be afforded by providing close-fitting goggles and/or face shields accompanied, if necessary, by suitable UVR-opaque clothing and gloves to cover the skin.

(c) Adequate and appropriate instruction should be given, to any person liable to be excessively exposed to UVR, concerning the hazards involved and the precautions to be observed to avoid excessive exposure.

(d) For artificial UVR sources that do not emit significant visible light, a visible or audible warning signal may be required to show when the UVR is being emitted.

(e) Powerful short wavelength UVR sources may generate ozone. This additional hazard should be avoided by providing either adequate ventilation or an adequate ozone removal system in the workplace.

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