III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Occupational exposure to ultraviolet radiation occurs from both natural and artificial generation of ultraviolet. The sun is the principal natural source. Artificial sources either produce ultraviolet as a byproduct, or are designed to generate ultraviolet to utilize its properties. Some industrial processes in which ultraviolet energy is a byproduct are welding, plasma torch operations, photoelectric scanning, and hot metal operations. Because of the germicidal properties of certain portions of the ultraviolet spectrum, artificial sources are used in hospitals, biological laboratories, schools, and in 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 of these occupations are listed in Table X-1.[1] New sources, such as ultraviolet lasers and fluorescent panels, are being developed.

Table X-2 shows the best available estimate of the number of workers with industrial exposure to artificial sources of ultraviolet radiation.

Historical Reports

The light-induced, acute inflammatory reaction of the eye has been known since early times, as indicated by Xenophon's mention of "snow-blindness" in his treatise Anabasis (ca. 375 BC), quoted by Duke-Elder.[2] Although more energetic than the visible portion of the electromagnetic

spectrum, most ultraviolet radiation is not detected by the visual receptors in mammals, including man. Thus, exposure to ultraviolet may result in ocular damage without the subject's being aware of the potential danger. Cases of keratinization of the cornea and cataracts of the lens have been observed since the early part of this century[2,3] from ultraviolet radiation levels associated with welding arcs, high-pressure pulsed lamps, and reflection of solar radiation from snow, desert and water.

Effects on Humans

Reviews of the literature on the biologic effects of ultraviolet radiation have been compiled by Verhoeff et al.,[4] Buchanan et al.,[5] Christner et al.,[6] and Duke-Elder.[2] Verhoeff and his colleagues included extensive research data in their report and formulated some of the basic hypotheses regarding ocular damage by ultraviolet radiation.

The International Commission on Illumination[7] has separated the ultraviolet spectrum into 3 different wavelength bands, 315 to 400 nm, 280 to 315 nm, and 200 to 280 nm, for convenience in classification. These ranges, with slight variations, are also referred to as near, midrange, and far ultraviolet, respectively. Wavelengths below 200 nm are of little biological significance since radiation in this region (vacuum ultraviolet) is absorbed in very short pathlengths in air with associated production of ozone.[8] Ozone is produced principally at wavelengths less than 220 nm.

1. Effects on eyes

Ordinary clinical photokeratitis has been described by Pitts and Gibbons[9] as 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 minutes or as long as 24 hours, but is usually 6 to 12 hours. Conjunctivitis follows, often accompanied by erythema of the facial skin surrounding the eyelids. There is a sensation of a foreign body or "sand" in the eyes and varying degrees of photophobia, lacrimation, and blepharospasm. These acute symptoms usually last from 6 to 24 hours with nearly all discomfort disappearing within 48 hours. The individual is visually incapacitated for varying periods of time. It is important to note that the ocular system, unlike the skin, does not develop tolerance to repeated ultraviolet exposure.[9]

Quantitative dose-response studies on eyes have been conducted in man and animals, and the two approaches have complemented each other; some of the following comments on effects on the human eye are amplified and compared with studies on animals in the section on Animal Toxicity.

Pitts and Tredici[10] studied threshold intensities for production of photokeratitis. From animal studies, they predicted maximal sensitivity of humans to occur at 280 nm and exposed a few humans at this wavelength. From the limited results, they estimated a threshold at 280 nm of 0.05×10^{6} ergs/cm^{2}; however, while there were no symptoms reported until the light intensity was about 15% greater than this threshold, there was a reduction in visual acuity to as much as 20/40 at the "threshold". They concluded that ultraviolet induced photokeratitis is insidious and incapacitating. Most symptoms of photokeratitis did not appear for about 4 to 12 hours; it took about

8 hours for visual incapacitation to be evident.

A later report by Pitts and Gibbons[9] showed that the human threshold of response was similar to that of rabbits and primates at 260 nm and longer, while at 250 nm and shorter the human was more sensitive than animals. At 270 nm the human threshold was 0.04×10^6 ergs/cm^2.

As a result of observations at above-threshold intensities, it was felt that the reaction of the cornea to wavebands from 220 to 250 nm was different from those found with exposures from 250 to 310 nm. For exposures below 250 nm, signs and symptoms occurred soon after exposure, and subjective symptoms always returned to normal prior to completion of the experiment, approximately 14 hours later. For exposures above 250 nm, symptoms did not occur until late in the experiment, generally 9 to 11 hours after exposure, and visual acuity remained below normal for 24 hours after exposure. The observed differences were attributed to the difference in the absorption of the different wavebands. The lower wavebands were absorbed in the outer corneal epithelial layers and underwent rapid change whereas the higher wavebands were absorbed in the deeper epithelial layers and showed delayed changes because these cells were more viable. Thus, the response at shorter wavelengths was rapidly revised while at the longer wavelengths there was a delayed and more serious response.

Kinsey et al.[11] studied the production of eye damage from arc-produced ultraviolet radiation and Rieke[12] considered it to account for 40% of all injuries in engineering shops. Grim and Kusnetz[13] reported

severe pain in workers several hours after a brief (10-second) exposure to radiation from an arc torch that generated an intense flame 8 to 12 inches long. Powell et al.[14] studied hazards from both laboratory and industrial plasma torches and found the output of these sufficient to cause eye and skin irritation on long exposure. Erythema on unprotected forehead and forearms developed within an hour after exposure began.

Schall et al.[15] observed no eye lesions or erythema in "Go-Go dancers" exposed to the following maximum levels of UV energy from fluorescent "black" light bulbs: 0.2 $\mu W/cm^2$ at 253.7 nm; 1.4 $\mu W/cm^2$ at 296.7 nm; and from less than 20 to 210 $\mu W/cm^2$ at 365 nm.

2. Effects on skin

Erythema is the most conspicuous change in the skin brought about by ultraviolet radiation.[16] Erythema has been evaluated by varying the amount of ultraviolet energy to produce a different biological response and is most commonly expressed as the Minimal Erythema Dose (MED).[17]

Methods to quantitate the erythemal response have involved use of both a series of red-stained slides or color-graded modifications to which the reaction could be compared and graded[18,19,20,21] and reflectance spectrophotometry.[22,23,24]

In an attempt to standardize the definition of minimal erythema, Van Der Leun[25] prepared a conversion table for various forms of MED determinations to what he thought more likely to be a true MED.

determinations to what he thought more likely to be a true MED.

Through a series of graded determinations ranging from - to + +, the first + reaction is taken to be the MED.

Action spectra (Figure X-1) for the erythemal response have been developed by a number of investigators.[26,27,28,29] These spectra were based on data showing the relative effectiveness of equal amounts of energy at different wavelengths in producing erythema. The different curves showed close agreement from approximately 270 nm to 310 nm. From these reports, a "standard erythemal curve" (Figure X-2) was formulated in 1934 by Coblentz and Stair[30] which plotted relative erythemal effectiveness against wavelength. This standard erythemal curve has been accepted for a number of years, and shows maximum erythemal effectiveness at approximately 297 nm, least at 280 nm, and intermediate at 254 nm. Hausser and Vahle demonstrated[27] that erythema develops more slowly at 260 nm than at 300 nm. From this observation it was concluded that a true action spectrum for a simple response such as vasodilatation cannot be obtained by comparing the energy requirements of different wavelengths to elicit a given intensity of reaction.[31] Everett et al.[32] developed a spectral curve (Figure X-3) considerably different from the standard curve and showing maximum erythemal effectiveness at about 254 nm with an intermediate plateau between 280 and 300 nm, at which point it coincided with the standard curve for the higher ultraviolet wavelengths. Freeman et al.,[33] in 1966, reported a spectral curve (Figure X-3) which was intermediate

between that which was reported by Everett and co-workers and the standard curve. Berger et al.,[34] in 1967, demonstrated that different choices of time after irradiation, and whether minimal or moderate erythema was used as the endpoint, would produce action spectra (Figure X-4) resembling those reported by Everett et al. and Freeman et al. Furthermore, their results confirmed the original observations of Hausser and Vahle[27] and indicated that disagreements were due to differences in time of evaluation (8 hours vs. 24 hours) and the difficulties inherent in the delineation of "minimal erythema".

Melanin, the pigment responsible for varying degrees of skin coloration, is present in the epidermis of the skin.[35] When it is present in high concentrations, the deeper levels of the skin are protected from damaging effects of ultraviolet radiation, the melanin acting somewhat as a supplementary epidermal biological filter. The process of melanin pigmentation in the skin is believed to be initiated from pigment granules present in melanocytes with transfer of the granules to neighboring cells in the basal layers of the skin.[36] The number of melanocytes in Negro and Caucasian skin is about the same,[37] so that differences in degree of skin pigmentation result from differences in cell activities. Longer wavelengths than those required for erythema produce some suntanning, even wavelengths extending well into the visible range.[38,39]

Miescher[40] showed that the ratio of thresholds for mild sunburn was about 8 times as great for Negro skin as for Caucasian skin, and about 120 times as great for severe sunburn. Thus, though skin pigmentation does afford protection from sunburn, Fitzpatrick[41]

demonstrated that erythema nevertheless does occur in deeply pigmented skin even though it is extremely difficult to measure.

The manner in which melanin affords protection is not entirely understood. Daniels,[42] in reviewing the relation between pigment and human adaptation to environmental radiation, stated that it was unlikely that a darkly pigmented skin was required solely as a shield against the ultraviolet radiation of sunlight.

The epidermis of the skin which has been exposed to mild doses of ultraviolet radiation becomes thickened, initially due to inter- and intra-cellular edema. After approximately 72 hours, the mitotic rate has accelerated and increased cellular production contributes to the epidermal thickening. All layers of the epidermis, except for the basal layer, are thickened and remain so with further stimulation. The thickened epidermal layer affords protection against damage by ultraviolet radiation. The potential protection afforded by the thickened epidermis is illustrated by the practical impossibility of eliciting an ultraviolet erythema in the palms of the hands or soles of the feet. Calculations based on the thickness of the horny layer have shown that a dose many thousandfold that of the MED for trunk skin would be required to produce erythema in such areas as the palms of the hands.

Worthy of brief mention is Vitamin D production and two genetically inherited diseases, xeroderma pigmentosum and congenital erythropoietic porphyria. These are mentioned primarily because of the unique role played by ultraviolet radiation in their development.

The photochemical conversion of provitamin D to the active compound by ultraviolet radiation is a well established reaction. Johnson et al.[16] compared the ultraviolet energy requirement for Vitamin D synthesis to that of the MED. Gorter[43] found that with 297 nm radiation, a daily dose of 0.1 calories (4.2×10^6 ergs) was required to cure rickets in children. The radiation covered 200 cm^2 of skin and was, therefore, 2.1×10^4 ergs/cm^2. According to Coblentz et al.,[44] the MED at 297 nm, 4×10^4 ergs/cm^2, on the average, the daily dose effective in curing rickets, amounted to 5% of the MED over a skin area as small as 200 cm^2.

Xeroderma pigmentosum presents an unusual example of the effects of ultraviolet radiation on normal skin. At an early age, the victims of this disease develop freckling, depigmentation, precancerous tumors, basal and squamous cell cancers, and malignant melanomas which cause early death. When this occurs in African Negroes, the course is the same in spite of very dark pigmentation,[45] so that melanin per se cannot entirely account for the protection of skin from ultraviolet carcinogenesis.

Congenital erythropoietic porphyria is a rare disease in which red teeth and red urine are characteristic. Photosensitization of the skin leads to blisters, hyperpigmentation, increased hair growth, and progressive scarring and deformity of the fingers, ears, nose, eyelids, and face. The picture of a hairy scarred face, clawlike hands, and blood-red teeth in people who avoided daylight and went about by moonlight, led to the idea of werewolves.[46]

The topical application or the oral or parenteral administration of certain drugs and chemicals causes the skin to become hypersensitive to ultraviolet and visible light. In many cases, the photosensitizing

ability of a drug has been discovered only after its acceptance for clinical use. Pathak[47] listed various agents implicated in the photosensitivity reactions of skin and showed their therapeutic uses and their effect on skin in the presence of light. For specific agents, he also gave the biologic spectrum, i.e., the band of wavelengths that effectively induced erythemal response, edema, photo-allergic manifestations, and other biologic changes .

The chronic effects of repeated ultraviolet exposure in individuals not adequately protected by pigmentation or other skin mechanisms are basophilic degeneration of the connective tissue, fragmentation of the elastic tissue (senile elastosis), and carcinogenesis.[48] Sunlight, but more specifically wavelengths from about 290 nm to 325 nm,[49] is far more important than aging in producing skin changes.[50] Solar-damaged skin has markedly increased ground substance, increased elastic fibers associated with a diminution of collagen,[51,52] and epidermal atrophy with many abnormal cells in a disorderly pattern.[53]

Epidemiologic, clinical, and tumor distribution studies have clearly implicated solar ultraviolet radiation as a factor in the etiology of human skin cancer. Brodkin et al.[54] present many early findings relating the incidence of basal-cell epithelioma to specific geographic regions, areas of the body, and complexion characteristics in individuals. The following arguments have been proposed to support the belief that sunlight is a causal factor in human skin cancer:

(1) Skin cancer occurs most frequently on exposed areas of the body;[55]

(2) Pigmented races have less skin cancer than do people with white skin [42];

(3) Among Caucasians, those having outdoor work activities appear to have a greater prevalence of skin cancer than those who work indoor[56,61];

(4) Skin cancer is more common in light-skinned people living in areas where solar radiation is greater.[56,59]

The histologic and cytologic changes induced by ultraviolet radiation have been reviewed by Blum[49] and Daniels.[48] The erythema noted after exposure of the skin to ultraviolet radiation is accompanied by glycogen deposition in the basal-cell layer. Approximately 24 hours after initial exposure, the upper portion of the Malpighian layer contains pycnotic, densely nucleated cells and a glassy homogenous cytoplasm shrunken around the nucleus, leaving a clear area outside.[62] In the normal skin, the cells in the upper Malpighian layer undergo changes leading up to nuclear disappearance. It has been suggested that the latent period of ultraviolet effects is partly related to mitotic interval delays.[48] Later, the outer portion of the Malpighian layer becomes hyalinized and concentrated rather than dissolved and broken down. Mature cells seem to be withdrawn from biochemical activity, particularly the production of organ-specific mitotic inhibitors to the basal-cell layer. Thus, interrupted feed-back aspects of carcinogenesis appear to be associated with genetic changes produced in germinal cells.[48]

Lysosomes, which contain a number of hydrolytic enzymes, have been implicated by Novikoff[63] in keratinization processes and squamous

metaplasia. These lysosomal enzymes, when released, are capable of breaking down the major components of cells.

The Langerhans' cells, containing light-sensitive organelles, are considered among the melanocyte series.[64] These Langerhans' cells are accessible in basal-cell locations in vitiligo (failure of the skin to form melanin), possibly suggesting a feedback inhibition of the activity of melanocytes. Damage to this feedback mechanism would then be consistent with the upward melanin migration and increased melanization after sunburn.[48]

Evidence for feedback regulatory mechanisms in cancer production has been demonstrated by a number of reports and mathematical models.[65-70] The predisposition of an atrophic skin to cancer formation is more consistent with a decrease in regulatory factors produced by an inadequate supply of normal tissues and cells than it is with an irritation of hyperplasia phenomenon.[48]

Epidemiologic Studies

Epidemiologic studies clearly implicate solar ultraviolet radiation as a factor in the etiology of human skin cancer.[49,56,57,71-73] In addition, the role of sunlight in skin cancer has been documented in a number of clinical investigations and tumor distribution studies.[54,55,60,74]

Gellin et al.[57,75] demonstrated a statistically significant tendency for patients with light complexions, light eyes, blond or red hair, and who spend a greater amount of time outdoors to have

a greater incidence of basal cell epithelioma and malignant melanoma than control groups. There was a 25 percent greater incidence of basal cell epithelioma among men than among women, most likely because men spend more hours outdoors for work or sport. Ninety-one percent of the basal cell epitheliomas were on sun-exposed parts.

Silverstone and Searle [58] studied the influence of age, sex, susceptibility to sunburn, complexion, eye color, ancestry, occupation, clothing habits, and residential district in the etiology of skin cancer and solar keratosis in Queensland, Australia. These investigators reported that genetic factors, as reflected in susceptibility to sunburn, complexion, etc., were of much greater importance than environmental factors such as district and occupation. With reference to susceptibility, they concluded that it is better to make a detailed investigation of a patient's response to sunlight, such as erythemal reaction, degree of burning, and ability to produce pigmentation, than simply to ask questions about ancestry or observe skin, eye, and hair coloration. Silverstone [73] had earlier observed a significant excess of tumors in Celtic people in three areas of Queensland over that expected on the basis of distribution of the local population.

MacDonald[59] found that the prevalence of carcinoma in El Paso County, Texas, where the sun shines during 80 percent of the daylight hours, was eight times higher than in Hartford, Conn., where the sun shines 50 percent of the daytime. While concluding that the incidence of skin cancer in Rhode Island is less than in Southern states, Winkler[76]

found that the sun also plays a role in the North--particularly in individuals with light eyes, light skin, and inability to tan. Similarly, Jakac[77] observed that the majority of skin cancers in Yugoslavia occurred in light-skinned persons.

Swanbeck and Hillstrom[60] analyzed the distribution of squamous cell carcinoma on the arm and hand from medical records of the 154 cases reported in Sweden during the period 1958-1965. There were 129 patients with skin cancer on the hands (mainly dorsal parts) and only 24 with cancer on the arm. Outdoor workers formed the largest group with squamous cell carcinoma on the hands, and the incidence of this cancer was higher for subjects in southern than in northern Sweden. The amount of ultraviolet radiation reaching the ground is greater in the southern part of the country.

Studies by Davis and Herron[78] produced conflicting evidence on the role of sunlight in malignant melanoma. The tumor was more common in persons spending long periods of time outdoors and in those who burn easily on exposure to the sun. Against this evidence was the fact that the distribution of melanoma on the body was vastly different from that of squamous carcinoma. These findings led the investigators to conclude that sunlight may exert both a direct and indirect effect on Caucasians.

In investigations in Rumania, Nicolau and Balus[61] observed that chronic actinic cheilitis was the precancerous disorder responsible for most of the epitheliomas occurring on the lower lip.

A large number of his subjects spent most of their time outdoors, and all were from areas with long summers and a high rate of exposure to sunlight. Monnich[79] reported a high incidence of skin cancer among agricultural workers in Potsdam due to actinic radiation.

Animal Toxicity

The experimental evaluation of ultraviolet-induced keratitis has been conducted mainly by animal experimentation, primarily in rabbits and guinea pigs.[80-82] Pitts and Tredici,[10] and Pitts and Gibbons[9] included human subjects along with rabbits and primates to establish a comparative experimental threshold for photokeratitis.

Cogan and Kinsey[82] determined the threshold dose necessary to produce keratitis in the eyes of albino rabbits. Utilizing a double monochromator and 1 mm entrance and exit slits, the spectral region from 240 to 316 nm was evaluated with band widths approximately 20 nm wide. Threshold response was determined by a granular appearance (50 to 200 individual granules) within the corneal epithelium. The granules were of uniform size, each being approximately the size of a single epithelial cell. With severe reactions above threshold, the number of granules increased, ultimately forming a mosaic. The peak sensitivity to ultraviolet radiation was reported to be about 288 nm with a corneal threshold reaction of 0.15×10^6 ergs. This compared with 2.0×10^6 ergs as reported by Duke-Elder[2] utilizing a broad ultraviolet spectrum.

Quantitative determinations of ultraviolet absorption by different structures of the eye were reported by Kinsey[80] to clarify

questions concerning various pathologic conditions such as cataract,[83] retinal damage,[84] and functional visual disturbances.[85] The limit of ultraviolet transmission for the whole eye was found to be approximately 330 nm; that for the lens, 310 nm, and approximately 280 nm for the aqueous and vitreous humors and cornea. It was concluded from calculations that the eye would have to be exposed to three times the dose necessary to produce minimal damage to the cornea before minimal injury to the lens could be encountered. This finding confirmed the conclusions of Verhoeff and co-workers[4] from studies of men and animals, that damage to the lens could result only after severe injury had been produced to the cornea.

Bachem,[81] using low pressure and medium pressure mercury arc ultraviolet sources on the eyes of albino rabbits and guinea pigs, concluded that (1) the ultraviolet radiation most effective in causing eye irritation is that near 300 nm; 288 nm for the cornea and 297 for lens; (2) shorter wavelengths of ultraviolet radiation are relatively harmless to the eye (they produce no lens injury, but may cause corneal and conjunctival inflammation) and (3) ultraviolet radiation of longer wavelengths can cause cataracts through the cumulative effect of repeated excessive dosage.

Pitts and Tredici[10] sought to establish experimental thresholds for photokeratitis in rabbits, monkeys, and humans. Ocular changes were determined in the animals from ultraviolet exposures at 10 nm waveband steps from 210 to 320 nm. Observations were made 12 to 18 hours after exposure since previous work had shown that threshold signs were just as evident as observations made directly after the

the latent period. Procedures for determining the threshold in human subjects were identical to those used for the animal experiments except that, after exposure, the subjects were examined at 30 minute intervals for the first 6 hours and hourly thereafter and asked to describe verbally any symptoms which they had experienced.

To describe clinical photokeratitis at least 9 criteria were used: tearing, stippling, hyperemia, haze, photophobia, discharge, pain, blepharospasm, and exfoliation. The criteria used to determine the photokeratitic threshold were the production of granules and epithelial haze for both animals and humans. Threshold exposure was defined as the presence of 50 to 200 granules as used in the study reported by Cogan and Kinsey.[82]

The photokeratitic threshold (maximum sensitivity) for both rabbits and monkeys occurred at 270 nm, being 0.05×10^6 erg/cm^2 for rabbits and 0.04×10^6 ergs/cm^2 for monkeys.

The ultraviolet photokeratitic thresholds for the cornea were felt by the authors to be accurate to $\pm$10%. Human and primate data corresponded surprisingly well.

In experiments with chinchilla rabbits, Sherashov[86] studied the spectral sensitivity of the cornea to ultraviolet radiation by measuring the ultraviolet pulses with a semiconductor thermoelectric calorimeter. His report indicates that there are two clearly defined maxima of sensitivity of the cornea. The first peak corresponds to the wavelength 289.4 nm and the second is in the region of 253.7 nm.

Between them only an insignificant fall in sensitivity was observed. Ultraviolet radiation at wavelengths greater than 330 nm had practically no photochemical effects.

Studies on ultraviolet absorption in nucleopeptides and ultraviolet-induced alteration of RNA and DNA synthesis[87-90] indicate that ultraviolet effects on corneal tissue are caused by absorption within the nucleoprotein.

The experimental production of cancer by ultraviolet radiation has been reviewed by Blum[49] and Epstein[89] in 1966. According to Epstein,[89] although there is some question about the carcinogenic spectrum in human skin cancer, there is no controversy about experimental cancer produced by ultraviolet radiation. Action spectrum studies have established that carcinogenic effects are limited to wavelengths shorter than 320 nm[49,90] and are significantly more effective between 280 nm and 320 nm.[91-93] This is the same wavelength spectrum in which solar radiation induced phototoxic sunburn responses. Under ordinary conditions, longer ultraviolet radiation and visible light are not carcinogenic; however, repeated long wavelength exposures in the presence of photosensitizers, which include many chemical carcinogens, have resulted in a high incidence of cancer.[49,94,95]

Action spectrum studies involving monochromatic radiation have shown that solar radiation at the wavelengths evoking sunburn response in man, 290 nm to 320 nm, also induces cancer in mice. However, Freeman et al.[90] determined that the wavelengths between 290 nm and 320 nm are not equally effective in inducing skin cancers. A weekly dose of 1 x 10 $\mu W\ sec/cm^2$ was given to two groups of albino mice. Tumors developed in

the group exposed to 300 nm radiation but not in the group exposed to 310 nm. Winklemann[96] found that 280 nm to 310 nm induced squamous cell carcinoma in the skin of hairless mice.

Prior to 1960, sarcoma was the primary tumor produced experimentally by ultraviolet radiation on the ears of albino mice and rats.[49] With the development of hairless mice, squamous cell carcinomas were reported[97] and further studies established that squamous cell carcinomas could be produced almost to the exclusion of connective tissue (sarcoma) growths.[96,98] The hairless mouse has also provided an experimental model for demonstrating that benign pigmented lesions could be stimulated to develop into malignant melanomas by ultraviolet radiation.[99] This further emphasizes that exposure to the sun may play an important role in human malignant melanoma formation.[100]

Although one cannot make quantitative extrapolation from the induction of cancer in laboratory animals to the environmental situation of men exposed to ultraviolet radiation, it seems likely that the mechanism of cancer induction in the mouse is basically similar to that of cancer induction in man.[101] Ultraviolet exposure alone must be repeatedly applied in order to induce an observable cancer. Blum[49,101] suggests from a series of calculations and experimental observations in mice that the rate of growth of a tumor is increased with each dose of ultraviolet radiation. It has been shown by using croton oil, a substance which increases the rate of proliferation of cells but does not by itself cause cancer, that a single dose of ultraviolet light may suffice to produce a tumor. That tumors are not observed follow-

ing single doses of ultraviolet radiation may be explained by the postulate that a single dose produces some fast growing, genetically changed clones but not in sufficient quantity to form a tumor within the lifetime of a mouse. Successive doses of ultraviolet radiation progressively expand and accelerate the tumorigenic process. Cancer induction depends not only upon somatic mutations from each dose, but also upon a progressive acceleration which is speeded up by each successive dose of ultraviolet radiation. The important bearing to the problem of ultraviolet-induced human cutaneous cancer is that the process of cancer induction is cumulative and hence the total amount of exposure is the important factor rather than a single or a few severe exposures. The induction of cancer by ultraviolet radiation is inferred to be irreversible in that there is no evidence for a "precancerous" condition.[49,101,102]

Correlation of Exposure and Effect

A summary of threshold values, presented as the minimum erythema dose (MED) in humans for six independent investigations, is listed in Table X-3. The MED's were determined at approximately 300 nm, the wavelength region of maximum erythemal effectiveness according to the standard erythema curve (Figure X-2). Differences existed between investigators as to the skin site, duration, and endpoint for erythemal testing which resulted in reported MED values ranging from 1.14 to 6.4 x 10^4 μWsec/cm^2. If the value reported by Olson et al.[103] of 2.42 x 10^4 μWsec/cm^2 is considered to be representative of a minimum erythema dose, then the value, converted to 24.2 mJ/cm^2, is shown

to be 2.4 times that of 10 mJ/cm^2 at 300 nm proposed as a minimum hazard level by Sliney[8] in 1972. This indicates a 2.4-fold safety factor at 300 nm from the minimum hazard level for the production of minimum erythema as determined by Olson et al.[103] If the lowest MED from Table X-3 is considered, 1.14×10^4 $\mu W/cm^2$ (11.4 mJ/cm^2), the proposed minimum hazard level of 10 mJ/cm^2 still seems acceptable.

The dose of ultraviolet radiation necessary to give a threshold erythema reaction at 253.7 nm wavelength is only about 50% of that necessary at 300 nm. A limit of 0.1 $\mu W/cm^2$ (8.6 mJ/cm^2) for 24 hours has been established.[104] Again, the proposed minimum hazard level is satisfactory at the 254 nm wavelength (6.0 mJ/cm^2).

The comparative photokeratitic thresholds for the cornea shown in Figure X-5 generally indicate a greater sensitivity in the human than in the rabbit or primate over the ultraviolet spectrum from approximately 220 to 310 nm. At 270 nm, the point of peak absorption, thresholds are about equivalent, 0.4×10^{-2} $\mu W/cm^2$ (4 mJ/cm^2) for humans and primates, and 0.5×10^{-2} $\mu W/cm^2$ (5 mJ/cm^2) for rabbits.[9,10] These data are in general agreement with those reported by Cogan and Kinsey[82] from studies of the rabbit. At the extremes of the ultraviolet spectrum studied, the human photokeratitic threshold is 4.6 times lower than that for the rabbit and 3.4 times lower at 310 nm. Interestingly, the human photokeratitic threshold appears to show a rather straight-line relationship through the ultraviolet spectrum studied from 220 to 300 nm. Above 300 nm, a trend toward decreased sensitivity is noted and would be expected to be quite marked as seen in the rabbit. The photo-

[illegible] nm, a trend toward decreased sensitivity is noted and would

keratitic thresholds for both animals and humans show good agreement with the proposed minimum hazard level curve.

Hart[105] reported the extensive use of bactericidal ultraviolet radiation in hospital rooms. Ultraviolet radiation at 253.7 to 290.0 nm was delivered at the operating site with an intensity of 18 to 30 $\mu W/cm^2$. A subsequent report[106] described lamp installations in which the upper portions of operating rooms were exposed to an average irradiance of 50 $\mu W/cm^2$ while maintaining the desired intensity at the operative site (24 to 30 $\mu W/cm^2$). These levels of ultraviolet radiation reduced post operative infections by as much as 85%[106] but required personnel to have skin and eye protection to prevent erythema and photokeratitis.

Schall and co-workers[15] reported the maximum energy level recorded at the working level for entertainers exposed to black-light radiation was 210 $\mu W/cm^2$ at 365 nm. In addition, small exposures of 1.4 and 0.2 $\mu W/cm^2$ were reported for 296.7 nm and 253.7 nm, respectively. No significant clinical evidence was revealed of skin or eye damage from the exposures studied. It was felt, however, that exposures for several hours at short distances from black-light sources could conceivably cause erythema and dermatitis as well as eye irritation.

High pressure arcs and plasmas produce ultraviolet-induced ocular damage considered by some investigators[11,12] to be the most common accident in engineering shops, accounting for 40% of all injuries. Irradiance in excess of 250 $\mu W/cm^2$ at 253.7 nm have been reported.[13] A 10-second exposure to this intensity produced severe ocular pain which required strong analgesics. Powell and co-workers[14] reported development of

sunburn reactions on unprotected forehead and forearms in plasma torch operators within an hour after exposure to levels sometimes in excess of 1000 $\mu W/cm^2$ at 253.7 nm and 400 $\mu W/cm^2$ at 365.0 nm. The sunburn was followed by desquamation and pigmentation.

Cases of dermatitis and erythema have been reported from ultraviolet radiation below 320 nm produced by fluorescent lamps used for general lighting purposes.[107,108] Irradiance levels were not known.

IV. ENVIRONMENTAL DATA

Although there is much information on industrial applications of ultraviolet energy, there is little information on exposure levels. The following discussion relates various ultraviolet-emitting devices with several parts of the ultraviolet spectrum, and thereby offers an impression of the nature of the hazards.

Low-pressure mercury vapor lamps emit several narrow bands; the lower the pressure of mercury vapor the fewer lines emitted. Much of this energy is of 253.7 nm wavelength, which is near the peak of germicidal effectiveness of 265 nm, hence its usefulness in control of microorganisms in operating rooms,[105,106] in control of airborne infection,[109,110] in control of bacteria in meat processing,[111] in the prevention of product contamination in pharmaceutical houses and biological laboratories,[112] in irradiation of air-conditioning ducts,[113] and in making water potable.[114]

High-pressure mercury vapor lamps are used in photochemical reactions, mineral identification, to produce fluorescence, and for diagnosis of dermal and scalp disorders, including porphyria.

Quartz-mercury arcs emit radiation over much of the ultraviolet spectrum, and can cause erythema and conjunctivitis from radiation over the range of 200 to 320 nm.

Fluorescent-type ultraviolet lamps also emit germicidal radiation similar to low-pressure mercury vapor lamps. While there is little evidence that they are significant sources of ultraviolet-induced injury,

it is believed that they may cause skin and eye effects, since a small part of their output is below 320 nm.[15,115] Fluorescent lamps used for general lighting purposes emit a negligible amount of energy below 320 nm. Although rare, skin photosensitization from these lamps has been reported.[107,108]

High-pressure xenon arcs emit a spectrum like that of sunlight in a continuous spectrum. Carbon arcs emit a continuous spectrum from the incandescent electrodes, upon which a broad-band spectrum from the luminous gases is superimposed.

Incandescent sources emit very little ultraviolet energy except at temperatures above 2500 K.[116] Open oil and gas flames are normally less than 2000 C. Oxyhydrogen and oxyacetylene flames are much hotter, so solids heated by these two flames may radiate ultraviolet.

The plasma torch can produce temperatures over 6000 K, the temperature at the surface of the sun, and intense ultraviolet radiation can result. Exposure to radiation from plasma torches can result in keratoconjunctivitis and sunburn if skin and eyes are not protected.[14]

Welding produces ultraviolet radiation in broad bands which often appear as a continuous spectrum. The intensities of the various bands depend on many factors; materials used in the electrodes, discharge current, gases surrounding the arc.[117] A common source of ultraviolet damage is from arc welding.[118,119]