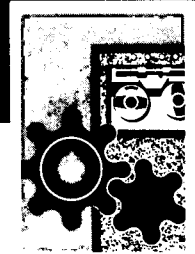*Glaser*

NIOSH

TECHNICAL REPORT

Carcinogenic Properties of Ionizing and Nonionizing Radiation

Volume I – Optical Radiation

A CURRENT LITERATURE REPORT ON THE CARCINOGENIC

PROPERTIES OF IONIZING AND NON-IONIZING RADIATION

I.   OPTICAL RADIATION

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The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the Division of Biomedical and Behavioral Science of the National Institute for Occupational Safety and Health conducts a formal program of research and information dissemination. The users of this information include basic and clinical researchers, legislators, research and biohazards administrators, occupational safety and health professionals, teachers, and students.

In keeping with its mandate, the Division of Biomedical and Behavioral Science requested The Franklin Institute Research Laboratories' Science Information Services to review the world's biomedical literature and to prepare a general reference document on the known or potential carcinogenic hazards of occupational exposure to ionizing and non-ionizing radiation. The purpose of the study was four-fold:

1. to identify and document radiation types which have been shown to be actual or potential carcinogens;

2. to review recent findings regarding (a) current substantive issues and (b) impressions of distinguished investigators regarding the types of cancer induced by radiation, carcinogenic dose-response relationships, radiocarcinogenic mechanisms, and synergistic (co-carcinogenic) effects;

3. to predict the expected excess of cancers (or, for potentially carcinogenic types of radiation, the potential risk of cancer) either under commonly encountered conditions of occupational exposure or at the currently accepted maximum permissible dose limits; and

4. to identify specific gaps in the present knowledge of radiation carcinogenesis, and to recommend specific areas in need of further investigation.

In the course of the Franklin Institute study, five types of radiation were examined: ionizing, ultraviolet, visible, infrared, and microwave/radiofrequency radiation. The range of energies, frequencies, and wavelengths for each of these is as follows:

Type of Radiation	Energy Range	Frequency Range	Wavelength Range
Ionizing	above 12.4 eV	above 3,000 THz	below 100 nm

Type of Radiation	Energy Range	Frequency Range	Wavelength Range
Ultraviolet	6.20-3.10 eV	1,500-750 THz	200-400 nm
Visible	3.10-1.77 eV	750-429 THz	400-700 nm
Infrared	1.7[7] eV-1.24 meV	429 THz-300 GHz	700 nm-1 mm
Microwave	1.24 meV-1.24 μeV	300 GHz-300 Mhz	1 mm-1 m
Radiofrequency	1.24 μeV-1.24 neV	300 MHz-300 kHz	1 m -1 km

Due to the volume of material, the study was limited to literature published since 1970, with only brief supplemental use of older materials when needed. The study is being published in three volumes:

I   -- Optical Radiation (Ultraviolet, Visible, and Infrared);

II   -- Microwave and Radiofrequency Radiation; and

III -- Ionizing Radiation.

The present volume documents the current status of knowledge regarding the carcinogenic hazards of occupational exposure to optical radiation. A sub-classification of the different biologically active regions of ultraviolet and infrared radiation is given below:

Region	Energy Range	Frequency Range	Wavelength Range
UV-A	3.84-3.08 eV	938-750 THz	320-400 nm
UV-B	4.39-3.84 eV	1,071-938 THz	280-320 nm
UV-C	6.15-4.39 eV	1,500-1,071 THz	200-280 nm
IR-A	1.77 eV-866 meV	429-214 THz	700 nm-1.4 μm
IR-B	886-413 meV	214-100 THz	1.4 μm-3.0 μm
IR-C	413-1.24 meV	100 THz-300 GHz	3.0 μm-1.0 mm

For the most part, the information reported has been gathered from the original literature. The authors' intent is to present a general non-technical overview with selective follow-ups. Independent judgement regarding the validity of the reported findings and interpretations has been avoided.

MKS units of measurement are employed throughout the present volume. Radiant energy is expressed in joules (J), and doses are given in J/m^2. Irradiance (the exposure dose rate) is measured in watts/m^2 (W/m^2). Conversion factors for other commonly used units of measurement are listed in Appendix I. A glossary of frequently used technical terms is given in Appendix II.

ABSTRACT

This report presents a general overview of the known and potential carcinogenic hazards of occupational exposure to ultraviolet, visible, and infrared radiation based on a literature review of original investigations published since 1970. Recent findings are reported, and current substantive issues and the impressions of distinguished investigators regarding the types of cancer induced by optical radiation, proposed radiocarcinogenic mechanisms, dose-response relationships, wavelength-dependence, and synergistic (cocarcinogenic) effects are identified. The risk of excess radiation-induced cancer under commonly encountered conditions of occupational exposure is estimated, and specific gaps in the present knowledge of radiation carcinogenesis are identified. Specific areas in need of further investigation are recommended.

CONTENTS

ACKNOWLEDGMENTS

CHAPTER ONE

ULTRAVIOLET RADIATION CARCINOGENESIS

Skin cancer accounts for about 40% of all malignant lesions in the United
States (Urbach, 1977) and for approximately 50% of all cancer in Australia
(Belisario, 1972 a). It is the most common form of cancer occurring in
light-skinned populations (Emmett, 1973; Urbach, 1971; Elwood et al., 1974;
Macdonald, 1975).

A causal relationship between chronic exposure to sunlight and skin pathology,
including the development of skin cancer, was first documented by Unna (1894).
Since then, the following evidence implicating solar radiation in the etiology
of human skin cancer (Urbach et al., 1974; Emmett, 1973; Gordon and Silverstone,
1975) has accumulated:

1. The incidence and prevalence of skin cancer correlate with decreasing
   geographic latitude, hence with the degree of insolation.

2. Over 90% of skin cancers occur on parts of the body exposed to
   sunlight.

3. The amount of pigmentation affects the incidence and prevalence
   of skin cancers.

4. Skin cancer is more prevalent in people who spend more time out
   of doors.

The extreme sensitivity of xeroderma pigmentosum patients to the ultraviolet (UV)
rays of the solar spectrum, and the neoplastic transformation characteristic of
the disease provide further evidence of the association between sunlight and
skin cancer (Gianelli, 1976; Epstein, 1974; Robbins et al., 1974; Mascaro, 1976).

The portion of the electromagnetic spectrum from 200 nm to 400 nm is defined
as UV radiation. Ozone in the earth's atmosphere absorbs all UV radiation
with wavelengths shorter than 290 nm. The UV component of solar radiation
at Earth's surface is therefore that portion of the spectrum with wavelengths
greater than 290 nm.

TYPES OF MALIGNANCIES OBSERVED IN MAN

Cutaneous neoplasms in man associated with exposure to sunlight are predomi-
nantly epithelial. Basal cell carcinomas are the most common type of skin
malignancy in Caucasians, followed by squamous cell carcinomas. Basal cell
carcinomas are derived from epidermal or adnexal basal cells and show differ-
entiation toward primitive appendegeal structures (the hair follicles,

sebaceous glands, and sweat glands). The lesions invade locally, but rarely metastasize. Squamous cell carcinomas also arise in surface epidermal cells but show differentiation towards keratinizing surface epidermis. They present as a relatively slow growing tumor which may metastasize to draining lymph nodes (Emmett, 1973; Robbins et al., 1974).

In a study of 200,000 individuals with cancers of all sites in Texas in the period 1944-1966, Macdonald (1975) identified 45,563 with cancer of the skin, excluding melanoma. Of the skin cancers, 68% were basal cell carcinomas, 28.9% were squamous cell carcinomas, and 3.1% were other histologic types. Table 1 shows skin cancer lesions, excluding melanoma, by histologic type.

Urbach et al. (1974) investigated a group of 456 consecutive patients with skin cancer seen in the Tumor Clinic of the Skin and Cancer Hospital, Philadelphia, Pennsylvania, between 1967 and 1969. There were 392 (nearly 86%) patients with basal cell carcinoma, 59 (nearly 13%) with squamous cell carcinoma, and 5 with carcinoma of the lip.

Scotto et al. (1974) conducted a survey of the incidence of non-melanoma skin cancer in Caucasians in four areas of the United States. Table 2 presents the annual age-adjusted skin cancer incidence rates by cell type and sex for both patients and cancers. The incidence of basal cell carcinoma exceeded that of squamous cell carcinoma by a factor of three to four in the Dallas-Ft. Worth and Iowa areas, and by a factor of five to six in the Minneapolis-St. Paul and San Francisco-Oakland areas.

Frequency of skin cancer was surveyed in a rural area of western Tennessee by Zagula-Mally et al. (1974). Forty-three persons with clinical skin cancer were found in the sample population of 978 Caucasian adults. The prevalence of basal cell carcinoma was 3.4% while that of squamous cell carcinoma was 1%.

Basal cell carcinomas are rare in deeply pigmented races. Gordon and Silverstone (1975) reviewed earlier studies on the effect of skin pigmentation on skin cancer incidence and prevalence and concluded that in darkly pigmented populations the overall pattern with respect to skin cancer is one of low incidence, complete reversal of the usual basal cell carcinoma to squamous cell carcinoma ratio and no particular predilection for areas exposed to sunlight. Conversely, in white-skinned populations, skin cancer occurs predominantly on body sites which are exposed to sunlight, e.g., the face, neck, dorsa of the hands, and forearms (Belisario, 1972 b). Scotto et al. (1974) also found that 80% of all malignant skin lesions occurred on the head, face, and neck; the next most common anatomical site was the trunk for basal cell carcinoma and the upper extremity for squamous cell carcinoma.

Macdonald (1975) studied the distribution of basal and squamous cell cancers by area of the body (Table 3). Lesions of the head and neck constituted 70% of the squamous cell carcinomas and 90% of the basal cell carcinomas. Basal cell cancers of the upper extremity accounted for 5% and squamous cell cancers for 22.6% of the total lesions. Squamous cell cancers of the lower extremity accounted for 1.5% of the total lesions.

Urbach (1971) analyzed the prevalence of basal skin carcinoma and squamous

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Table 1

Cancer of the Skin, Excluding Melanoma
Total Lesions by Histologic Type
Six Regions in Texas
1944-1966*

Type	Number of Lesions
Basal cell carcinoma	30,912
Squamous cell carcinoma	13,055
Subtotal	43,967
Adenoacanthoma	78
Adenocarcinoma, sweat gland or duct origin	52
Adnexal carcinoma, type not specified	53
Carcinoma-in-situ	378
Carcinoma-in-situ, Bowen's type	273
Dermatofibrosarcoma protuberans	71
Extramammary Paget's disease	13
Fibrosarcoma arising in irradiated tissue	9
Kaposi's sarcoma	19
Malignant lymphoma	24
Mycosis fungoides	24
Sebaceous gland carcinoma	16
Squamous cell carcinoma arising in radiation scar	2
Squamous cell carcinoma, Marjolin's ulcer	14
Squamous cell carcinoma, spindle cell variant	12
Unclassified carcinoma	307
Unclassified malignant neoplasm	236
Unclassified sarcoma	15
Subtotal	1,596
GRAND TOTAL	45,563

*From Macdonald (1975)

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Table 2

Annual Age-Adjusted Skin Cancer Incidence Rates* for Caucasians
Sex, Cell Type, and Area
1971 - 1972 **

AREA:	Dallas-Ft. Worth			Iowa			Minneapolis-St. Paul			San Francisco-Oakland		

A. Patients

Cell Type	T	M	F	T	M	F	T	M	F	T	M	F
All patients	379	539	259	124	174	83	151	201	115	184	250	133
Basal cell	286	394	205	93	123	69	129	165	103	153	198	117
Squamous cell	83	124	51	28	47	13	21	35	12	28	45	15
Both basal and squamous	10	21	3	3	4	1	1	1	0	3	7	1

B. Cancers

Cell Type	T	M	F	T	M	F	T	M	F	T	M	F
All cancers	439	643	286	133	189	87	164	223	123	206	287	145
Basal cell	338	485	230	102	137	73	141	183	110	173	232	128
Squamous cell	101	158	56	31	52	14	23	40	13	33	55	17

*Per 100,000 population standardized to the population of the United States for 1970
**From Scotto et al. (1974)

Table 3

Cancer of the Skin Excluding Melanoma
Distribution of Total Lesions by Anatomic Site
Six Regions in Texas
1944-1966 *

	Head and Neck	Upper Ext.	Trunk	Lower Ext.	Gen. or no Prim. Found	Total
BASAL–MALE						
White	16015 (87.3%)	875 (4.8%)	688 (3.7%)	100 (0.5%)	674 (3.7%)	18352
Nonwhite	33 (84.6%)	1 (2.6%)	3 (7.6%)	1 (2.6%)	1 (2.6%)	39
Spanish surnamed	673 (88.0%)	16 (2.1%)	39 (5.1%)	9 (1.1%)	28 (3.7%)	765
Total	16721 (87.3%)	892 (4.7%)	730 (3.8%)	110 (0.5%)	703 (3.7%)	19156
BASAL–FEMALE						
White	9218 (84.8%)	557 (5.1%)	506 (4.7%)	178 (1.6%)	418 (3.8%)	10877
Nonwhite	32 (86.5%)	– (–)	4 (10.8%)	– (–)	1 (2.7%)	37
Spanish surnamed	730 (86.7%)	22 (2.6%)	35 (4.2%)	11 (1.3%)	44 (5.2%)	842
Total	9980 (85.0%)	579 (4.9%)	545 (4.6%)	189 (1.6%)	463 (3.9%)	11756
BASAL–TOTAL	26701 (86.4%)	1471 (4.8%)	1275 (4.1%)	299 (0.9%)	1166 (3.8%)	30912
SQUAMOUS–MALE						
White	6091 (69.6%)	1979 (22.6%)	185 (2.1%)	130 (1.5%)	368 (4.2%)	8753
Nonwhite	31 (51.7%)	8 (13.3%)	3 (5.0%)	13 (21.7%)	5 (8.3%)	60
Spanish surnamed	254 (65.8%)	63 (16.3%)	24 (6.2%)	17 (4.4%)	28 (7.3%)	386
Total	6376 (69.3%)	2050 (22.3%)	212 (2.3%)	160 (1.7%)	401 (4.4%)	9199
SQUAMOUS–FEMALE						
White	2052 (58.1%)	974 (27.6%)	126 (3.6%)	177 (5.0%)	201 (5.7%)	3530
Nonwhite	15 (29.4%)	6 (11.8%)	13 (25.5%)	12 (23.5%)	5 (9.8%)	51
Spanish surnamed	158 (57.4%)	42 (15.3%)	22 (8.0%)	14 (5.1%)	39 (14.2%)	275
Total	2225 (57.7%)	1022 (26.5%)	161 (4.2%)	203 (5.3%)	245 (6.3%)	3856
SQUAMOUS–TOTAL	8601 (65.9%)	3072 (23.5%)	373 (2.9%)	363 (2.8%)	646 (4.9%)	13055

*From Macdonald (1975)

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cell carcinoma by body area, and found that 88% of all basal cell carcinomas occurred on the head and neck. A very close correlation was noted between sun exposure of selected anatomical sites of the head and neck and the relative distribution of squamous cell carcinoma. However, the distribution of basal cell carcinoma on the head and neck did not always correspond with sites of greatest exposure to solar radiation, suggesting that factors other than sun exposure must play a role in the development of this type of skin cancer, and that the relationship with solar radiation is not as direct as that for squamous cell carcinomas.

Malignant melanomas appear to have an even more indirect association with exposure to sunlight. Melanoma is a relatively uncommon neoplasm with an incidence which ranges from less than 1 per 100,000 among heavily pigmented ethnic groups to 16 per 100,000 in northern Australia (Gordon and Silverstone, 1975). Melanomas metastasize frequently and cause much greater mortality than the more common skin malignancies (Robbins et al., 1974; Emmett, 1973). Approximately four of every ten patients diagnosed will die from melanoma within five years (Gordon and Silverstone, 1975).

Three types of melanoma are recognized which differ in clinical appearance, biological behavior, and prognosis (Bakos and Macmillan, 1973; Emmett, 1973; Lee and Merrill, 1970). Table 4 shows the distribution of these three malignant melanoma by site and histological type. Of the three types, lentigo maligna melanoma has the lowest mortality. It is found almost exclusively in elderly, lightly pigmented individuals on skin which has been exposed to sunlight. Lentigo maligna melanoma is characterized by a linear proliferation of pleomorphic, often spindle cell, melanocytes in the basal layer of the epidermis. Superficial spreading melanoma may occur on both exposed and unexposed skin; it is the dominant melanoma of the female lower limb. The tumor shows Pagetoid invasion of epidermis and often stratum corneum by large malignant melanocytes, usually epithelioid. Nodular melanoma may also occur anywhere on the body. It shows malignant melanocytes confined to the dermal tumor and appearing in some instances in the epidermis. There is no intraepidermal growth without associated dermal invasion. Nodular melanoma has the worst prognosis (Bakos and Macmillan, 1973; Emmett, 1973; Lee and Merrill, 1970).

Although the relationship between solar radiation and the incidence and prevalence of malignant melanoma is unclear, several epidemiological studies provide evidence implicating sunlight as an important factor in the etiology of malignant melanoma. The following studies substantiate the hypothesis that exposure to sunlight is related to the development of malignant melanoma.

Magnus (1976) reviewed over 3,000 case reports of malignant melanoma submitted to Norway's Cancer Registry in the period 1955-1973, and found that the number of new melanoma cases reported annually had tripled in that period. The rate of incidence had also increased by a factor of over three from about 2 per 100,000 population to nearly 8 per 100,000. The greatest increases occurred in those body sites where, because of changing life style, clothing, attitudes toward tanning, and increased out-of-doors leisure time, exposure to the sun had increased, i.e. the neck and trunk in males and the lower limbs (excluding the foot) in females. Melanoma incidence increased with age suggesting that total accumulated exposure to sunlight was a factor. Magnus (1976) also found that the incidence of melanoma increased with decreasing latitude, indicating a positive correlation between degree of insolation and melanoma incidence.

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Table 4

Distribution of Malignant Melanoma by Site, Histological Type,

and Ratios of Types by Site*

Site	Lentigo Maligna Melanoma	Superficial Spreading Melanoma	Nodular Melanoma	Ratio Lentigo Maligna to Nodular Melanoma	Ratio Superficial Spreading to Nodular Melanoma
Female lower leg	2	19	6	0.3:1	3.2:1
Head and neck	25	22	9	2.8:1	2.4:1
Chest, back and upper arm	0	30	13	–	2.3:1
Male lower leg	0	3	2	–	1.5:1
Foot	0	19	13	–	1.5:1
Forearm, hand	2	13	9	0.2:1	1.4:1
Abdomen, lower back, genitals, thigh	0	11	11	–	1.0:1

*From Lee and Merrill (1970).
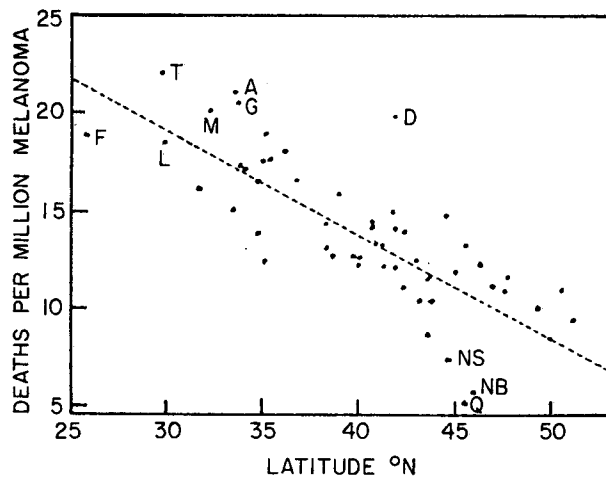
Figure 1:

Age-standardized male mortality from melanoma, 1950-1967, for
each U.S. state and Canadian province plotted against latitude
of largest city. F = Florida; A = Alabama; NB = New Brunswick;
D = Delaware; Q = Quebec; T = Texas; G = Georgia; L = Louisi-
ana; M = Mississippi; NS = Nova Scotia. (Newfoundland not shown:
mortality = 1.93, latitude = 47.6.) (From Elwood et al., 1974.)

Elwood et al. (1974) examined age-standardized mortality rates from malignant melanoma and other skin tumors for each state in the United States and each Canadian province over the period 1950–1967. He found that the main factor affecting both melanoma and non–melanoma mortality rates is the latitude of residence with mortality rates increasing as latitude decreases. Figure 1 shows age-standardized male mortality from melanoma plotted against the latitude of the largest city in the state or province. The relationship of female mortality rates with latitude was similar to that of males. Elwood et al. (1974) suggest that further study will show a similar relationship with melanoma incidence.

Fears et al. (1976) plotted non–melanoma incidence, and melanoma incidence and mortality in the United States against latitude (Figures 2 & 3) and found that latitude decreases with both increasing incidence and mortality. Table 5 summarizes the regressions of incidence and mortality rates on latitude.

Bakos and Macmillan (1973) reviewed a series of 137 patients with primary malignant melanoma of the skin in the Cambridge area of Great Britain in 1961–1971, and compared the type, site and incidence of melanoma with previously reported series from the United States (Boston) and Australia (Sydney). Incidence and mortality figures in all three series supported the hypothesis that, in populations of European descent, incidence of melanoma is inversely related to latitude of residence.

Movshovitz and Modan (1973) studied reports of all 390 newly diagnosed malignant melanomas in Israel in the period 1961–1967 to determine whether different ethnic groups exhibited different rates of incidence. Among foreign-born residents, melanoma incidence was much higher among the European-born than among natives of Africa or Asia; among the European-born, incidence was highest in those with the longest period of residence in Israel. Melanoma incidence among the Israeli-born, most of whom were of European extraction, was higher than any of the foreign-born groups. These data corroborate the evidence for the cumulative influence of sun exposure on the development of malignant melanoma as well as the protective mechanism of darkly pigmented skin.

Pantoja et al. (1976) studied the anatomical distribution of malignant melanoma of the lower extremities in native Puerto Ricans. While most melanomas observed in predominantly white populations occur above the ankle, 86% of the primary lesions studied occurred in the foot, particularly in the minimally pigmented zones, a distribution similar to that reported in black patients. They suggested that this distribution may be an indication of the etiologic role of sunlight in melanoma.

Despite the epidemiological evidence, the relationship between malignant melanoma and sunlight remains somewhat paradoxical. Ultraviolet radiation (UVR) is implicated in melanomas occurring in areas which are directly exposed to the sun; an as yet unknown systemic agent has been postulated to account for a possible indirect effect of solar radiation on the development of melanoma in unexposed areas of the body. Lee and Merrill (1970) have proposed that a substance produced in exposed skin by the
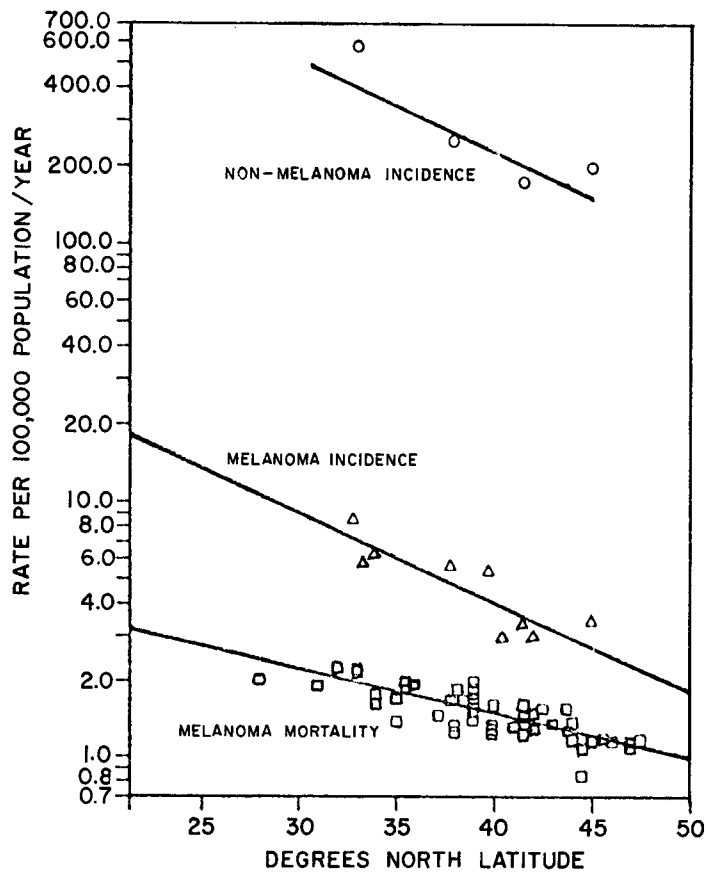
Figure 2:

Age adjusted skin cancer rates, white males.
(From Fears et al., 1976)
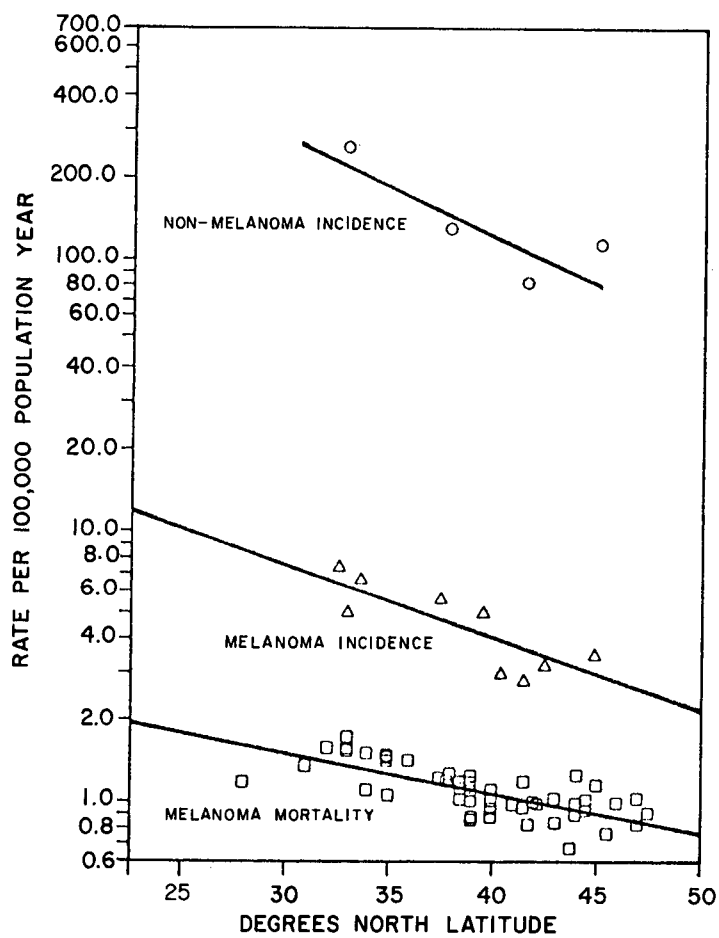
Figure 3:

Age adjusted skin cancer rates, white females.
(From Fears et al., 1976)

Table 5

Summary Statistics for Regressions of Skin Cancer Incidence and Mortality on Latitude*

	MALES			FEMALES		
	Correlation Coefficient	Regression Slope ± S.D.	Doubling Latitude	Correlation Coefficient	Regression Slope ± S.D.	Doubling Latitude
Non-Melanoma Incidence	−0.89	−0.037 ± 0.013	−8.1°	−0.83	−0.033 ± 0.016	−9.2°
Melanoma Incidence	−0.86	−0.031 ± 0.007	−9.8°	−0.83	−0.028 ± 0.007	−10.7°
Melanoma Mortality	−0.81	−0.017 ± 0.002	−19.9°	−0.71	−0.014 ± 0.002	−21.2°

*From Fears et al. (1976)

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action of sunlight and circulating in the blood stream could induce malignant change in melanocytes in other parts of the body. They called this substance a "solar circulating factor" and suggest that melanocyte chalone, a material which is extractable from epidermis and controls melanocyte mitosis, could produce such as effect.

More recently, Blum et al. (1975) demonstrated the existence of a hyperplasia-inducing diffusible factor in albino mouse epidermis exposed to UVR, and suggested that such a factor could be implicated in the development of malignant melanoma in areas not directly exposed to sunlight.

The role of sunlight in the development of cutaneous changes and neoplastic transformation which is characteristic of xeroderma pigmentosum (XP) has been established by clinical observation and by experimental studies (Epstein, 1974). Xeroderma pigmentosum is a rare hereditary process which occurs in approximately 1 person in 250,000 in the general population; patients have been found worldwide and in all races (Robbins et al., 1974). It is a systemic disease which manifests itself primarily through cutaneous symptomatology, or shows itself as a complex cutaneo-neuroendocrine-somatic expression (Robbins et al., 1974; Epstein, 1974; Gianelli, 1975; Mascaro, 1976). The cutaneous manifestations of XP are due to hypersensitivity to UVR (Robbins et al., 1974; Epstein, 1974; Gianelli, 1976; Mascaro, 1976). The clinical manifestations of XP can be delayed by the avoidance of exposure to sunlight (Robbins et al., 1974).

Many, but not all, XP patients exhibit an acute erythemal and edemal reaction to sunlight in early infancy which subsides later in life (Robbins et al., 1974). Mascaro (1976) and Gianelli (1976) described the subsequent progression of the disease. Intense freckling develops on sun-exposed areas early in life, and skin on the exposed areas becomes dry and scaly. Later, dystrophic and atrophic changes in the skin of XP pa-

Table 6

Cutaneous Manifestations of Xeroderma Pigmentosum *

Erythema and bullae (acute sun sensitivity in infancy)
Freckles
Xerosis (dryness) and scaling
Hypopigmentation
Telangiectasia
Atrophy
Tumors
   Actinic keratoses
   Basal and squamous cell carcinomas
   Malignant melanomas
   Others (keratoacanthomas, angiomas, fibromas, sarcomas)

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*From Robbins et al. (1974)

tients following repeated exposure to sunlight are accompanied by the appearance of benign and malignant lesions at several independent sites, usually in those anatomical areas most exposed to sunlight. The skin of unexposed areas remains normal. The malignant tumors are predominantly basal and squamous cell carcinomas, keratoacanthomas and adenocarcinomas, and, more rarely, malignant melanomas, neurinomas, sarcomas, and angiosarcomas. Table 6 outlines cutaneous manifestations of xeroderma pigmentosum.

TYPES OF MALIGNANCIES OBSERVED IN LABORATORY ANIMALS

The association between solar radiation and skin cancer has been confirmed by experimental studies which have demonstrated the carcinogenicity of UVR in laboratory animals. The skin of albino and hairless mice, rats and of other rodent species, has been used for the experimental production of tumors.

Skin tumors were first induced in laboratory animals by UVR nearly 50 years ago. In 1928, Findlay reported that daily exposure of mice to UVR from a mercury arc lamp produced skin cancer. In 1933 and 1934, Roffo demonstrated that skin cancer could be induced in rats by exposure to natural sunlight as well as by mercury arc. A series of experiments on UV carcinogenesis in albino mice conducted in 1941-1944 by Blum and his co-workers obtained highly reproducible cancers, and Blum (1974, 1976) and Blum et al. (1975) have based the formulation of systems models of carcinogenesis on the results of those early experiments.

Whereas cutaneous neoplasms associated with UV light exposure in man are predominantly epithelial, tumors induced by artificial light sources in laboratory animals derive both from the epidermis and the dermis.

Repeated exposures have produced papillomas, keratoacanthomas, spindle cell tumors, hemanigiomas, squamous cell carcinomas, myxosarcomas, angiosarcomas, fibromas, and fibrosarcomas in C3Hf/Sm, A/J. albino, Swiss and hairless mice and NMR strain rats (Kripke, 1974; Kripke and Fisher, 1976; Zigman et al., 1976; Urbach et al., 1974; Freeman, 1976; Stenback, 1975 b).

Hsu et al. (1975) reported the induction of benign and malignant skin tumors in hairless mutant mice following a single exposure to UVR. No exogenous chemical agents were used to promote tumor induction. The UVR was delivered in single doses ranging from 3 to 24 x 10^4 J/m^2 in 3 hours or less. Tumors were first noted as early as 7 weeks following irradiation; the greatest number of tumors was present 25-30 weeks after irradiation. Of the 98 tumors observed, 92 were papillomas and 4 were squamous cell carcinomas. Tumor production was preceded by erythema, inflammation, desquamation, ulceration and cicatrization (scarring). Higher UV dose levels resulted in more severe acute damage as well as greater tumor yield. Hsu et al. concluded that the induction of malignant growths by a single exposure to UV light is an event of low probability which depends on the magnitude of the UV dose and the severity of resulting tissue damage.

In an attempt to find an animal model with cutaneous neoplasms comparable to those induced by UVR in man, Stenback (1975 b) studied the reaction of

animal skin to repeated exposure to carcinogenic wavelengths of UV light.
Swiss mice, NMR strain rats, Syrian golden hamsters, and guinea pigs were
exposed to four 40-W sunlamps emitting 1.8×10^4 J/m^2/hr for 3 hours
once or twice a week for 60 weeks. The studies showed that when animal
skin was exposed repeatedly to UVR both the epithelium and connective tissues
exhibited continuous irritation and disorganization which could finally
result in tumor formation. The ultimate effect was, however, dependent
upon the animal species. The mouse and rat were sensitive, but the
guinea pig was resistant to tumorigenesis. Tumor formation occurred
only on those animal species initially showing ulceration and cicatri-
zation. Tables 7 and 8 show UVR-induced tumors and tumor bearing animals
in different species.

In Swiss mice, Stenback (1975 b) observed UV-induced necrosis, and ulcera-
tion, followed by fibrosis. The development of a disorderly epidermal
hyperplasia was closely linked with the alterations. Tumors were composed
of anaplastic, densely packed cells. Vascular alterations were common,
destructive, and proliferative, and consisted of necrosis and inflammation
which ranged from hyperplasia to malignant tumors. The neoplastic response
in Swiss mice was almost exclusively of subcutaneous origin, with formation
of fibromas and fibrosarcomas in 17 of 20 tumor bearing mice.

Table 7

UVR-Induced Tumors in Different Animal Species*

	Rat	Guinea Pig	Syrian Golden Hamster	Swiss Mouse
Total animals	40	25	40	40
Tumor-bearing animals	16	2	14	20
Ear tumor-bearing animals	15		1	16
Animals with dorsal skin tumors	2	2	14	10
Histologically verified skin tumors	25	2	30	27

*From Stenback (1975 b).

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Table 8

Skin and Ear Tumors Induced by UVR
in Different Animal Species*

	Rat	Guinea Pig	Syrian Golden Hamster	Swiss Mouse
Skin Tumors				
Papillomas	2/1	–	22/14	1/1
Keratoacanthomas	–	–	4/3	–
Squamous cell carcinomas	–	–	1/1	–
Fibromas	–	1/1	–	1/1
Fibrosarcomas	1/1	–	–	8/8
Trichofolliculomas	–	1/1	–	–
Ear Tumors				
Papillomas	10/7	–	3/1	2/2
Keratoacanthomas	5/2	–	–	–
Squamous cell carcinomas	3/2	–	–	3/3
Fibromas	1/1	–	–	3/3
Fibrosarcomas	–	–	–	7/6
Hemangiomas	1/1	–	–	1/1
Angiosarcomas	2/1	–	–	1/1

*From Stenback (1975 b)

Repeated UV irradiation of NMR rats caused necrosis, ulceration, cicatrization, hyperplasia, and eventually, epithelial tumors including papillomas, keratoacanthomas and squamous cell carcinomas. The latter were composed of atypical keratinized cells and horn cysts. In 15 of the 16 tumor-bearing rats, the tumors were located in the ear. Tumors of dermal origin were found in 10% of the rats; these were a fibroma, a fibrosarcoma and three tumors of vascular origin.

Guinea pigs presented minimal evidence of neoplastic transformation. A slight hyperkeratosis and dermal fibrosis were observed in some animals; only 2 of 25 animals developed tumors (a fibroma and a tricho-folliculoma).

Hamsters displayed localized epidermal hyperplasia, which gradually became papillomatous in character and ultimately led to the formation of fully developed tumors. Papillomas and keratoacanthomas developed primarily on the dorsal skin; only one ear tumor was noted. No tumors of dermal or subcutaneous origin were found.

Stenback (1977) discussed the life history and histopathology of tumors induced in mice, Syrian golden hamsters, and rats by exposure to UVR. The results, which show the sensitivity of animal skin to UV irradiation, and the species-specificity of the neoplastic response, confirm the findings of his 1975 study.

PROPOSED MECHANISMS FOR THE CARCINOGENIC PROCESS AT THE MOLECULAR AND CELLULAR LEVEL.

Ultraviolet radiation from sunlight and from artificial light sources induces a variety of chemical modifications in cells. The photochemical effects of UVR are due to electron excitation in the absorbing atoms and molecules which produces damaging biochemical reactions (Albert, 1976). DNA appears to be the main target.

Although UVR induces a number of photoproducts in DNA, a major cause of damage is the cyclobutyl pyrimidine dimer, produced by covalent addition at the 5- and 6-positions of two adjacent pyrimidines on the same DNA strand (Gianelli, 1976). The presence of pyrimidine dimers in the cell's DNA interferes with its semiconservative replication (Robbins et al., 1974). Figure 4 illustrates the UV induced formation of a pyrimidine dimer. Unrepaired damage to DNA can result in cell death, mutant formation, and neoplastic transformation (Epstein, 1974; Setlow, 1974, 1975). Most cells can repair photochemical lesions in their DNA by either removing, reversing, or bypassing the damage, that is, by excision repair, photoreactivation and post-replication or recombination repair. Pyrimidine dimers induced in human skin by solar radiation may induce skin cancer either if the dimers are not excised or if they are replicated in a defective manner (Lehmann, 1974).

In eukaryotic and prokaryotic cells, DNA damaged by UVR is restored to a functionally normal state by an excision repair process (Cleaver, 1974; Robbins et al., 1974; Gianelli, 1976; Epstein, 1974). The model for the operation of excision repair has been provided by studies in bacteria where the enzymes involved in the process have been isolated and characterized (Gianelli, 1976; Cleaver, 1974). Repair is carried out by the sequential
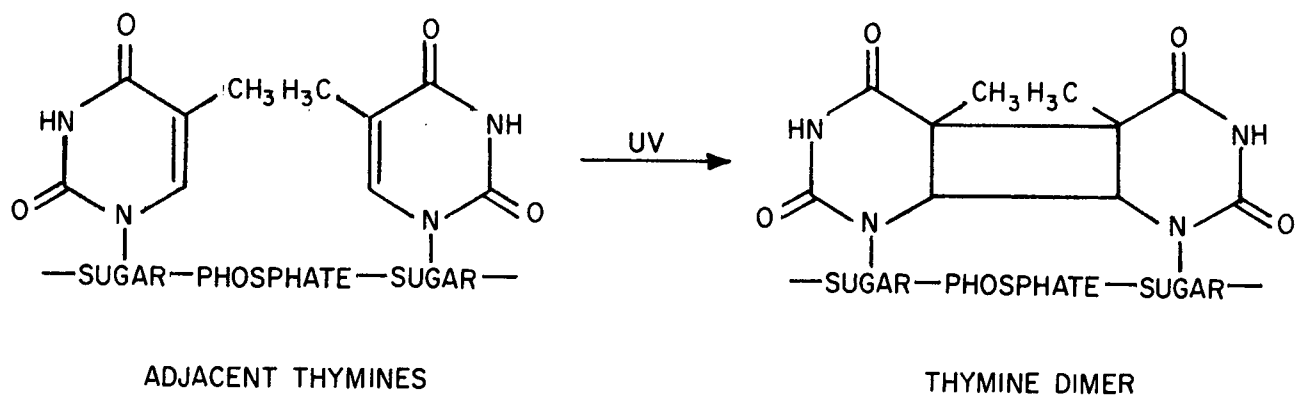
ADJACENT THYMINES   THYMINE DIMER

Figure 4:

Ultraviolet-induced formation of a thymine dimer from two adjacent
thymines on the same DNA strand. (From Robbins et al., 1974)

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operation of an endonuclease that identifies the lesions caused by UV-induced pyrimidine dimers in the DNA molecule and makes an incision in the DNA strand close to the dimer; an exonuclease that excises the segment of DNA containing the dimer; a DNA polymerase that fills in the resulting space by inserting bases by base pairing with bases on the intact opposing DNA strand (repair synthesis); and a polynucleotide ligase that re-establishes the continuity of the DNA chain (Cleaver, 1974; Robbins et al., 1974; Gianelli, 1976; Epstein, 1974).

Figure 5 illustrates the model for excision repair in bacteria. Although the human enzymes responsible for excision repair have not yet been isolated, most of the events have been observed (Gianelli, 1976). Excision processes analogous to those described for bacteria occur in mammalian cells (Robbins et al., 1974; Cleaver, 1974).

DNA synthesis can be most readily detected and measured by autoradiographic studies of the incorporation of certain exogenously supplied compounds (e.g., thymidine, bromodeoxyuridine) into the newly synthesized regions during repair synthesis, or by sedimentation techniques (Robbins et al., 1974; Gianelli, 1976). Newly synthesized DNA in UV irradiated mammalian cells is smaller than in unirradiated cells (Lehmann, 1974; Epstein, 1974). The initial formation and the final joining of single strand breaks in DNA, which precede dimer excision and follow repair synthesis, have proved the most difficult to demonstrate (Gianelli, 1976).

Studies of the excision repair process in mammalian cells are dominated by the work done on defective repair processes in the human disease xeroderma pigmentosum (XP). In 1968, Cleaver reported that skin fibroblasts from XP patients are defective in the repair of UV-damaged DNA (Robbins et al., 1974; Mascaro, 1975; Gianelli, 1976). Epstein (1974) confirmed earlier experiments demonstrating that direct inhibition of premitotic, semiconservative DNA synthesis represents one of the earliest events after UV irradiation in XP epidermal cells in vivo. While normal human cells can excise up to 80% of UV-induced pyrimidine dimers from their DNA within 24 hours of irradiation, XP cells are unable to do so (Robbins et al., 1974; Cleaver, 1974; Lehmann, 1974).

Robbins et al. (1974) studied defective DNA repair in fibroblast strains from 15 patients with XP. Of the 15 patients, 13 had had skin cancers. The authors reported that UV irradiated XP fibroblasts remove pyrimidine dimers much more slowly, if at all, than normal fibroblasts, suggesting that the enzymatic activity for the repair of UV-induced dimer damage to DNA is low or missing. Table 9 shows DNA repair rates for patients in this series.

Maher et al. (1976) showed that a strain of XP cells capable of excision repair at 15-25% of the normal rate had a mutagenesis rate about fivefold that of normal cells after irradiation with 0.5-4.5 J/m^2 UVR. Another XP strain with an excision repair rate of 2% the normal rate exhibited a mutagenic response to UV irradiation that was 16 times the normal rate. These results indicate that UV-induced mutagenicity is directly related to capacity for excision repair. Maher and McCormick (1976) postulated that the number of unrepaired lesions present in DNA during replication is responsible for both the level of mutagenesis and the cell survival.
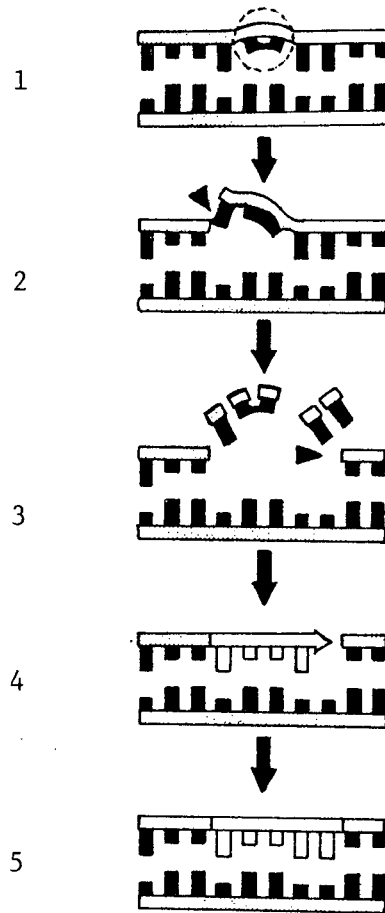
Figure 5:

Schematic representation of the excision process for repairing DNA
molecules containing thymine dimers. 1 -- A distortion in the DNA
molecule is caused by a UV light-induced thymine dimer. 2 -- A
specific endonuclease breaks the backbone of one chain near the dimer.
3 -- A small region containing the dimer is excised by an exonuclease.
4 -- 5'-3' synthesis of a new strand takes place. 5 -- Polynucleotide
ligase joins the two ends of the strand and the "repaired" molecule
is complete. (From Watson, 1970)

Table 9

Clinical Information and DNA Repair Rates for Patients in the NIH Series*

Patient	Age (yr)	Sex	Skin Manifestations			Other System Involvement			DNA Repair Rates (% of normal)
			Acute Sun Sensitivity	Neoplasms		Ocular	Nervous	Endocrine	
				Age of Onset (yr)	Number				
1	28	F	−	4	>100**	+	−	−	15-25
2	23	M	−	13	10**	+	−	−	15-25
3	24	M	+	6	>50**	+	−	−	15-25
4	27	M	−	9	>100**	+	−	−	100
5	26	F	+	18	10	+	+	−	25-55
6	20	F	+	9	25-50**	+	+	−	25-55
7	11	F	+	9	2	+	+	−	25-55
8	13	M	−	−	0	−	−	−	15-25
9	13	M	−	−	0	−	−	−	15-25
10	16	F	−	3	10-50	+	+	+	10-20
11	28	F	+	18	30	+	+	+	3-7
12	7	F	+	4	2	−	+	−	<2
13	30	M	−	16	20-30**	−	−	−	ND
14	47	M	−	22	>100**	+	−	−	15-25
15	10	M	−	4	10-20	+	−	−	ND

*From Robbins et al. (1974)
**Includes at least one malignant melanoma
− = absent; + = present; ND = not done

Andrews et al. (1976) reported that UV-irradiated fibroblast strains from XP patients exhibit decreased colony forming ability compared to normal fibroblasts, indicating that lack of adequate DNA repair is causally related to the clinical manifestations of XP.

The high susceptibility of XP patients to UV-induced cutaneous cancer is strong evidence that there is a relationship between unrepaired UV-damaged DNA, and lethal, mutagenic and carcinogenic responses to UVR (Robbins et al., 1974; Cleaver, 1974; Gianelli, 1976; Albert, 1976). Gianelli (1976) postulated that the susceptibility of XP cells to the effects of UVR may facilitate tumor growth in several different ways: by favoring the growth of clones with uncontrolled growth patterns; by affording a selective advantage to neoplastic cells which have reverted to normal repair; by producing regressive changes in skin and interfering with immunologic defenses in a non-specific way; by altering the alleged surveillance function of immunologically competent cells due, for example, to an interference with their multiplication; or perhaps, most importantly, by favoring the release of tumor associated antigens and thus the formation of enhancing factors which may block the protective activity of the immunological system in a more specific way.

The issue of the metabolic defect in XP is complicated by the finding of variant XP patients with a normal skin response to monochromatic UV irradiation and the capability for normal excision and DNA repair synthesis (Gianelli, 1976). Comparisons between the responses of XP and XP-variant cell lines to UV irradiation may permit the estimation of the relative importance of excision and post-replication repair in the correction of DNA damage.

Rudé and Friedberg (1977) compared rates of semiconservative DNA synthesis in unirradiated and UV-irradiated asynchronous XP, XP-variant, and normal human skin fibroblasts. No differences in the rates of DNA synthesis were observed in the unirradiated cells. Exposure of the three cell strains to a fluence of 5 J/m^2 led to a comparable decrease in the rate of DNA synthesis during the first 3 hours after irradiation. Recovery was absent in XP cells during a 24-hour post-irradiation period, and slower than normal in XP variant cells. Since XP cells are highly defective in the excision of thymine dimers, this result supports the hypothesis that pyrimidine dimers are very effective blocks to DNA synthesis. The slower than normal rate of recovery observed with XP-variant cells suggests that they may be defective to some extent in pyrimidine dimer excision.

When the UV fluence to XP and XP-variant cells was reduced to 0.5 J/m^2 and 2.5 J/m^2 respectively, so that survival in all three cell strains is approximately the same (25%), the kinetics and degree of recovery of the rate of DNA synthesis is the same in all three cell lines. As the fluence delivered to XP and XP-variant cells is increased, the recovery of DNA synthetic rate is progressively impaired.

The results suggest that there is no inherent defect in semiconservative DNA synthesis in either classical XP or XP-variant cells which is independent of a defect in DNA repair capacity, and that the restitution

of DNA synthetic capacity is initially dependent on a cell's capacity
to excise thymine dimers.

Fornace et al. (1976) measured DNA single strand breaks in UV-irradiated
XP, XP-variant and normal fibroblasts by DNA alkaline elution. In normal
fibroblasts, breaks appeared rapidly after UV irradiation and resealed
slowly; half-recovery time was 8 hours. Breaks did not appear in XP cells,
suggesting that the defect in XP cells is related to an endonuclease re-
action. Cells of the variant form of XP characterized by normal DNA repair
synthesis exhibited normal production of breaks following UV irradiation,
but resealed more slowly than normal fibroblasts; half-recovery time was
over 12 hours. This difference was enhanced by caffeine. The authors sug-
gest that the results substantiate Lehmann's (1974) hypothesis that the ab-
normality in XP-variants may be due to an impairment in their ability to
bypass defects in the template strand during replication. This post-
replication or recombination repair defect in XP-variant fibroblasts would
be expressed when two pyrimidine dimers occurred near each other on opposite
strands. The discontinuities left opposite the dimers would be sealed at a
later time, if at all. Figure 6 illustrates the blocking of DNA synthesis
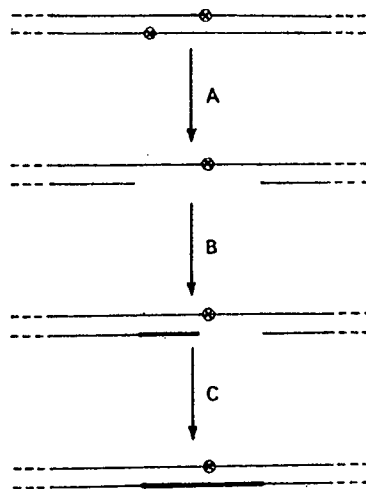in XP-variant cells.

Figure 6:

Proposed mechanism for retardation of strand rejoining during
ultraviolet repair in Xeroderma pigmentosum variant cells, based
on an assumed defect in the ability of these cells to cope with
template damage. The symbol ⊕ represents a pyrimidine dimer.
The heavy line segments represent DNA generated by repair synthesis.
(From Fornace et al., 1976)

Maher et al. (1976) demonstrated that the frequency of mutations in XP-variant fibroblasts was increased by placing the cells in growth medium containing 0.7 mM caffeine immediately after UV irradiation (0.3-3 J/m^2). Mutation frequency was increased four-fold by the addition of caffeine following UV irradiation at 1.2 J/m^2. Caffeine alone did not induce mutations in these cells.

Their results confirmed earlier work by Fox (1974), who found that treatment with caffeine (0.5 or 0.75 mM) following UVR at a dose of 5 J/m^2 or higher increased the mutation frequency of mouse lymphoma cell lines P388 and L5178YS and of Chinese hamster V-79 cells. No effect was observed in two lines of Yoshida murine sarcoma, suggesting that the effect of caffeine is specific to cell lines which undergo post-replication repair.

Hussain et al. (1976) found that the mutagenic effect of UV irradiation (surface dose: 0.25 J/m^2/sec) in bacteria was augmented by caffeine (500 µg/ml) post-treatment, further supporting the hypothesis that caffeine inhibits post-replication repair. The inhibition by caffeine of post-replication repair may convert mutational events into lethal events.

When Zajdela and Latarjet (1975) painted a solution of caffeine on one ear of Swiss mice before irradiation with UVR (10^6 J/m^2), they found that the caffeine-treated ears developed about half the number of skin tumors as the unpainted ears on the same animal. The results suggest that UV-induced carcinogenesis is initiated by a DNA repair mechanism which allows the cell to survive but leaves in place or even favors subsequent errors in DNA replication, resulting in greater possibility of malignant transformation.

Most rodent cells grown in culture have been found to poorly excise pyrimidine dimers from their DNA (Cleaver, 1974). However, Bowden et al. (1975) found that in the intact adult Charles River CD-1 mouse, epidermal cells excised 29 to 61% of the UV-induced pyrimidine dimers from their DNA within 24 hours after irradiation, demonstrating that nonsemiconservative (repair) DNA synthesis does in fact occur. The conflicting observations concerning the excision of UV-induced pyrimidine dimers in rodent cells might be resolved by the hypothesis that cell development and differentiation influence the level of post-UVR excision repair.

Albert (1976) reported that the cellular effects of UVR are strongly affected by the stage in the cell cycle in which the cells are exposed. The sensitivity to damage is greatest in the G_1 stage and progressively decreases with age. However, chromosomal damage peaks in the S period, and is largely of the chromatid variety. Holmberg (1976) analyzed chromosomal aberrations in the first mitotic division in UV irradiated (7.5 J/m^2) human lymphocytes in the G_1 stage. UVR was found to induce chromatid aberrations. No significant yield of dicentric chromosomes was observed. These results confirm the findings of Griggs and Bender (1973), who demonstrated that UV irradiation of V-79 Chinese hamster cells in the G_1 phase produced predominantly chromatid-type aberrations and rare chromosome deletion and dicentrics.

When Bender et al. (1973) studied chromosomal aberration production in V-79 Chinese hamster tissue culture cells by UVR administered during post-

DNA-synthetic G_2 phase of the cell cycle, they found only achromatid lesions and chromatid deletions. Isochromatid and exchange type aberrations were found to be induced in S cells. Figure 7 shows a schematic diagram of a model to account for the production of chromatid-type aberrations in cells irradiated by UV during the G_1 phase of the cell cycle.

Griggs and Bender (1973) demonstrated that UV irradiation of A8W243 *Xenopus laevis* toad cells in the G_1 phase produced only chromatid-type aberrations and no chromosome aberrations. Post-treatment with white light was able to eliminate most of the aberrations induced by UVR, indicating that repair of the photoreactivating type had taken place.

Photoreactivation is an enzymatic process in which pyrimidine dimers are monomerized in the presence of light of wavelength 300-600 nm so that
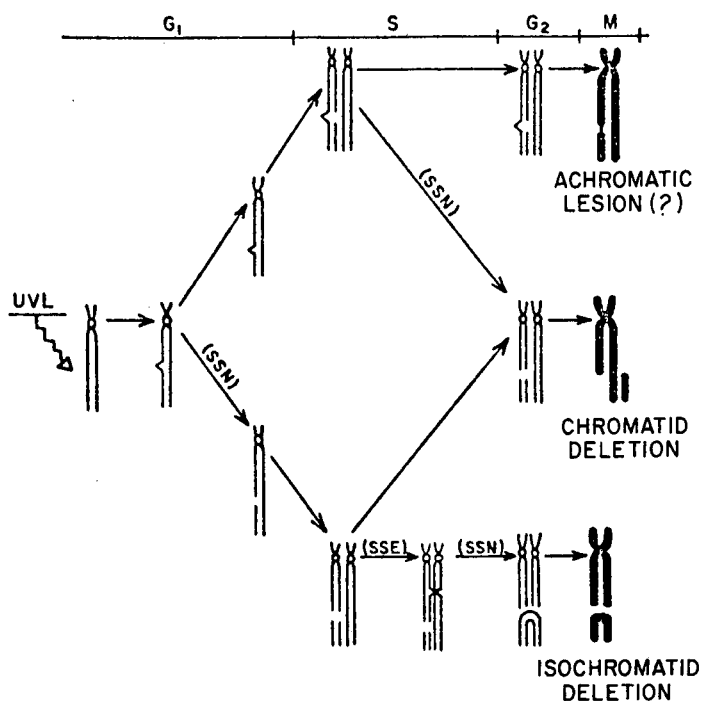

Figure 7:

Model to account for the production of chromatid-type aberrations from cyclobutane pyrimidine dimers in cells ultraviolet-irradiated during the G_1 phase of the cell cycle. Not all possible pathways are shown. SSN = action of a single strand nuclease. SSE = a recombinational or post-replication repair mechanism. (From Bender et al., 1973)

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the bases are restored to their pre-irradiation configuration without being excised (Robbins et al., 1974; Cleaver, 1974; Sutherland and Oliver 1976). Since photoreactivation is specific for the repair of pyrimidine dimers, and since no other photoproducts are affected (Hart and Setlow, 1974; Griggs and Bender, 1973; Setlow, 1975), demonstration that photoreactivation can prevent the induction of tumors by UVR would provide evidence that the presence of pyrimidine dimers in DNA can cause neoplastic transformations.

Hart and Setlow (1974) induced carcinoma in *Poecilia formosa*, a small fish, by exposing cells from a number of fish to UV irradiation in vitro, and injecting the cells back into isogeneic recipients. When the UV irradiated cells were exposed to photoreactivating illumination before injection, less than 10% of the recipients developed tumors, indicating that repair had taken place.

Harm and Rupert (1976) demonstrated that intense, millisecond pre-illumination of photoreactivating enzyme with near-UV (313 nm) or visible radiation (545 nm) prior to its use for photoenzymatic repair of UV-induced pyrimidine dimers in bacterial cells promotes DNA repair and enhances the stability of photoreactivating enzyme to thermal inactivation. *Haemophilus* transforming DNA was exposed to an energy fluence of 254 nm radiation of 0.8 $J/m^2/sec$. Photoreactivation was carried out in 313 to 435 nm region, peaking at 366 nm, at a fluence of 3 $J/m^2/sec$. Both the pre-illumination effect and the photo-enzymatic repair occur with maximum effectiveness around 366 nm, but the action spectrum for the pre-illumination effect extends much farther toward longer wavelengths.

The activation of photoreactivating enzyme reported by Harm and Rupert (1976) contrasts with evidence published by Tyrell et al. in 1973, indicating that photoreactivating enzyme is inactivated by 365 nm radiation. However, since Tyrell et al. used UV fluences roughly 100 times greater than those used by Harm and Rupert (1976), the results may not be incompatible.

Until recently, it was thought that photoreactivation took place only in bacteria, metazoa and the lower vertebrates. However, Sutherland and Oliver (1976) demonstrated that the photoreactivating enzyme is present in human fibroblasts and other mammalian cells and that it can repair UV-induced damage in human DNA. Since other investigators have been unable to observe photoreactivation of pyrimidine dimers in mammalian cells, Sutherland and Oliver (1976) tested three possible differences in experimental procedures. They concluded that cell culture conditions can change the level of photore-activating enzyme and thus of cellular dimer photoreactivation. Differences in illumination conditions and analysis methods did not affect the results. Earlier studies by Sutherland and co-workers had shown that photoreactivating enzyme was present at reasonably high levels in cultured fibroblasts from normal humans. Sutherland (1976) examined the specific activity of photo-reactivating enzyme in cells derived from XP patients. Results demonstrated that photoreactivating activity is reflected in the biological repair capacity of cells and that XP cells have a low level of photoreactivating enzyme. Table 10 shows comparative repair capacities of normal, XP and progeroid cells.

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Table 10

Repair Capacities of Normal, Xeroderma, and Progeroid Cells*

Cell Line	Description	Unscheduled DNA Synthesis	Photoreactivating enzyme activity (% of normal)
HESM	Normal embryonic	100	100
El San	8 yr. normal	100	112
Le San	33 yr. normal	100	107
XP12BE (Jay Tim)	7 yr. xeroderma A	<2	36
XP-1LO	32 yr. xeroderma A	<2	20
XP7BE (TeKo)	11 yr. xeroderma	25-55	8
XP4BE (WoMec)	Xeroderma	100	11
XP13BE (PeHay)	Xeroderma	100	9
1277 (KeHe)	Progeroid	—	88

* From Sutherland (1976)

Consideration of XP variants, who have all the clinical signs of XP and also have normal levels of excision repair but are deficient in both photoreactivation and postreplication repair, led Sutherland (1976) to postulate that the presence of one operative repair process does not guarantee immunity from UV-induced skin cancer. She proposed that total repair capacity is a better biological index of cellular ability to withstand damage to its DNA.

The cross-linking of DNA to enzymes and other proteins in bacterial and mammalian cells has been demonstrated to be a photochemical heteroaddition reaction to UVR (Helene, 1975). It was the first such reaction to be reported in vivo (Smith, 1975). In microorganisms, DNA-protein cross-linking plays an important role in cell survival.

Han et al. (1975) studied the general features of UV-induced DNA-protein cross-links in synchronized HeLa cells, and found that UV-induced DNA-

protein cross-linking exhibited age-dependent variations. Fluctuations in the yield of DNA cross-linked to protein were almost identical to changes in cell survival throughout the cell cycle, indicating that proteins are involved in the response to UVR.

Kornhauser (1976) reported an earlier study demonstrating that UVR could induce DNA-protein cross-linking in guinea pig epidermal DNA. Two hours after irradiation this lesion was no longer identifiable, suggesting that there was an active repair process operating in the viable cells of the epidermis that was capable of excising the DNA-protein cross-link.

Similarly, Smith (1975) reported that earlier work performed by him indicated that DNA-protein cross-links are amenable to post-replication repair. However, when Kornhauser (1976) reviewed literature on the UV-induced covalent linkage of DNA to proteins, he found no other reports of evidence for the cellular repair of DNA-protein heteroadducts. In their review of DNA-protein cross-links, Todd and Han (1975) also concluded that there exists very little published evidence that DNA to protein cross-links are repaired.

Han et al. (1975) and Todd and Han (1975) suggested that the formation of cross-links between DNA and enzymes or other proteins (e.g., histones) in its vicinity could prevent normal replication and DNA repair processes.

Since DNA-protein cross-links could possibly contribute to sunlight-induced skin diseases and disorders, further study in this area is needed to elucidate the chemical nature and biological consequences of this photoproduct (Kornhauser, 1976).

Although defective repair of UV-induced damage in DNA has been identified as the probable mechanism responsible for cell death, mutagenesis, and carcinogenesis resulting from exposure to UVR, other mechanisms have been investigated.

Kripke and Fisher (1976) studied the immunological responses of UV irradiated and unirradiated inbred mice to UV-induced tumor transplants, and found that UV-irradiated mice were more susceptible to the growth of autochthonous tumors and syngeneic UV-induced tumors than unirradiated mice, suggesting that UVR alters host reactivity as well as initiating neoplastic transformation. This abrogation of host resistance to UV-induced tumors was not brought about by direct inactivation of immunocompetent cells, indicating that chronic treatment with UVR causes a systemic alteration in inbred mice.

Kripke (1976) demonstrated that the suppression of resistance to UV-induced tumor growth is effected by UVR absorbed by the skin rather than through the retina of inbred mice. The finding that skin was the target organ of UVR implies that exposure to UVR may either produce chemical mediators or destroy biochemical regulators in the skin.

Black and co-workers (Black and Lo, 1971; Black and Douglas, 1972 and 1973; Lo and Black, 1973; Black, 1973; Chan and Black, 1974) demonstrated

that a carcinogenic cholesterol-derived oxidation product was formed in the skin of hairless mice and of humans upon repeated exposure to UVR, and suggested that cholesterol-5α,6α-epoxide (CAE) may play a role in UV-induced carcinogenesis.

However, when Black and Chan (1976) compared CAE levels in the skin of hairless mice receiving a regular or an antioxidant supplemented diet during repeated exposures to UVR, they found that although CAE levels were higher in animals maintained on the supplemental diet, those animals developed fewer and less severe UV-induced tumors than mice on the regular diet. This finding seems to rule out a causal role for CAE in the developmental sequence of UV-mediated carcinogenesis. Black and Chan (1976) suggested that if CAE is involved at all, it is probably as a pre-carcinogen.

The association of sun exposure with cutaneous neoplasia continues to stimulate research into the defenses of cells and tissues against light-induced damage. Epidemiological studies indicate that melanin pigment provides a major cutaneous defense against UVR. The photoprotective properties of melanin derive from its ability to filter and scatter biologically harmful radiation.

London et al. (1976) carried out a study to determine whether cellular melanin quantitatively alters the rate of formation of pyrimidine dimers in DNA of UV irradiated Cloudman mouse melanoma cells in culture. They found that the formation of dimers in both pigmented and non-pigmented cell lines can be represented as linear functions of the dose of UVR, and that the formation of dimers in both cell lines is different at all levels of irradiation investigated, the rate of formation of dimers in pigmented cells being lower than that in nonpigmented cells. The authors assume that only a portion of the UVR penetrates the shield of intracellular melanin pigment and reaches the nuclear area, where, absorbed by nucleic acids, the irradiation promotes thymine dimer formation. However, Cleaver (1974) reported that lack of melanin protection does not appear to play a quantitative role in photocarcinogenesis.

DOSE-RESPONSE RELATIONSHIPS

Although UVR has been implicated in carcinogenesis, exact quantitative relationships have not yet been established. To date, intensity dependent effects of UVR have been investigated only peripherally. Investigations have been carried out in microorganisms, in mammalian cells, in mouse skin, and in laboratory animals, principally mice. However, the experiments have been performed under controlled conditions which do not duplicate those found in nature, where radiation levels and exposure times vary considerably.

In microorganisms, the rate of UVR-induced mutagenesis has been linked to UV dose levels. When Balgary and Rauko (1976) studied the induction of tryptophan revertants in wild-type *Escherichia coli* B with UV doses of 18.9 J/m^2, 37.8 J/m^2 and 132.3 J/m^2, they found that the ratio between mutagenic and lethal lesions was higher at low doses than at high doses. Kubitschek and Venema (1976) investigated antibiotic resistant loci in *Bacillus subtilis* irradiated at 0.5, 2.5-4, and 5-6.5 J/m^2. At low doses, all

UV-induced mutants were resistant to streptomycin, neomycin and kanomycin, and 2/49 were rifampicin mutants. Higher doses gave an increase in the number of mutant antibiotic loci, a greater diversity of mutational patterns and increased frequencies of rifampicin and erythromycin mutants. Kubitschek and Venters (1974) also observed that forward mutations induced with UVR in *Escherichia coli* WP$_2$ Hcr followed a dose squared response. Bacteriophage T5-resistant mutations were induced by exposures to 254 nm wavelength UVR at an irradiance of 0.225 J/m^2/sec for periods of 2, 4, 6 or 8 seconds. The frequencies of T-5 resistant mutants increased with the square of the period of exposure to UVR.

UVR has also been linked to mutagenesis in human fibroblasts. Maher and McCormick (1976) found that exposure of two excision deficient XP strains and of normal human fibroblasts to low doses of UV irradiation resulted in a dose-dependent increase in 8-azaguanine-resistant mutations. Figure 8 shows the mutagenic effect of UV irradiation as a function of dose administered.

In UV-irradiated mammalian cells, the rate of survival and the ability to repair UV-induced damage to DNA appear to be dose-dependent. Wang (1974) exposed mouse 3T6 fibroblast cells to a UV flux of 40 W/m^2. After an exposure time of 90 minutes, 90% of the cells lost their ability to form clones, while 99% of the cells showed reduced viability after an exposure time of 130 minutes. Skin fibroblasts from patients with XP also show a
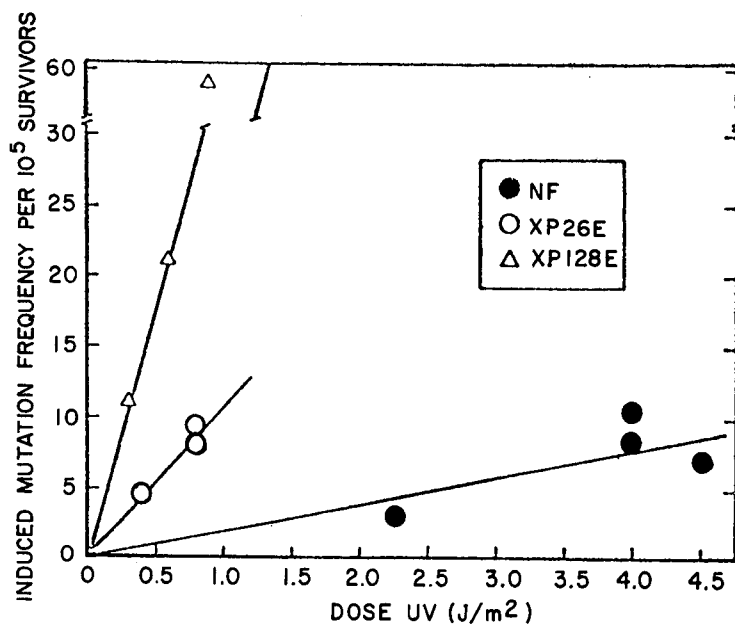
Figure 8:

Mutagenic effect of ultraviolet irradiation in three strains of human fibroblasts as a function of the dose of ultraviolet administered. Lines are calculated by the method of least squares. (From Maher and McCormick, 1976)

pronounced increase in susceptibility to the lethal effects of UV radia-
tion. Figure 9 compares the single cell survival of normal and XP
fibroblasts at various dose levels of UVR.

In this regard, Maher and McCormick (1976) studied the cloning ability of
XP and normal cells in culture and found that XP cells were more sensitive
to the effects of UVR than normal cells. Figure 10 shows that the survival
rate of all cell lines studied was inversely proportional to the UV dose.

When Edenberg (1976) studied DNA replication in UV irradiated HeLa cells,
he found that both the degree of inhibition of DNA repair and the delay
of recovery were related to the UV dose. After doses of less than 10 J/m^2,
the rate of DNA synthesis was initially depressed but showed recovery 1.5
hours after irradiation, while after higher doses, a constant low rate of
synthesis was seen for at least the initial 6 hours. Figure 11 shows
relative replication after various doses of UV radiation in the initial
1.5 hour interval after irradiation.

The repair of UV-induced damage of DNA appears to operate more efficiently
in vivo than in vitro. Albert (1976) reports that suppression of DNA
synthesis and mitotic inhibition have been observed in the skin of hair-
less mice and in human skin after a single exposure to a UV dose of 4.5 x
10^3 J/m^2. The following series of experiments were performed to demonstrate
that UV irradiation initiates nonsemiconservative DNA synthesis in mice.
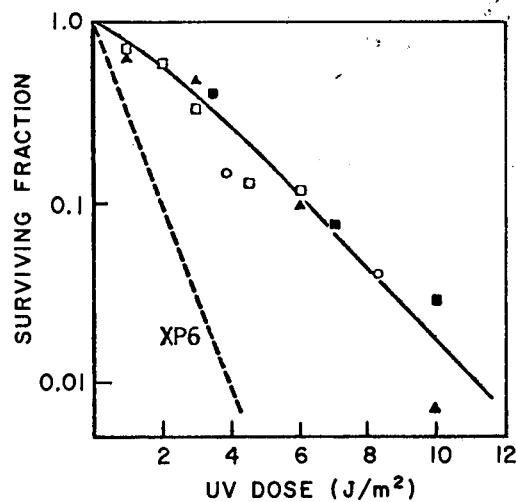
Figure 9:

Single cell survival curve for normal and xeroderma pigmentosum
fibroblasts. ■,▲ = normal fibroblasts. ❑,○ = XP-variants with
normal excision repair. Dashed line for XP6, a cell that has
reduced repair. (From Cleaver, 1974)

31
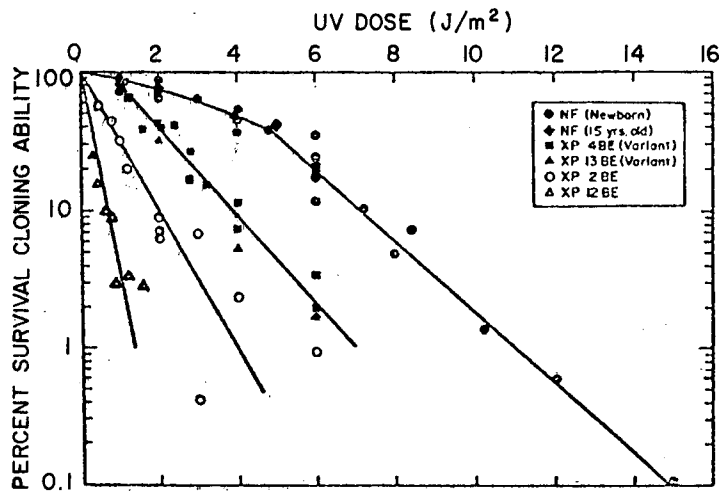
Figure 10:

Percent survival of the cloning ability, as a function of ultra-
violet irradiation, of strains of human skin fibroblasts with
different DNA repair capabilities. Cloning efficiencies ranged
from 15 to 35% for the normal cells, 10 to 20% for the XP2BE,
XP3BE, and XP 4BE cells, and 5 to 15% for XP12BE. The expo-
nential portion of these survival curves were drawn using the
least squares method. Each symbol represents the survival of the
cloning efficiency averaged from a series of 8 to 12 replicate
dishes and the data are drawn from a large number of experiments.
(From Maher and McCormick, 1976)

32
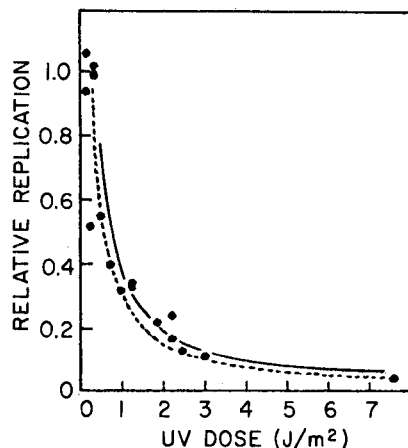
Figure 11:

Relative replication after various doses of ultraviolet radiation. The relative rate of replication in the initial 1.5 hour interval is plotted against the dose. The two curves represent the relative replication predicted from a model in which the replication forks within each replicon continue at their original rate until they encounter the first dimer (in each direction) and then stop. In that case, the relative replication equals the ratio of the lengths of the average interval between dimers into which origins fall to the lengths of the average replicon. The curves are for average replicon sizes of 20 µm (upper curve) and 25 µm (lower curve). The average replicon size which best fits the data (3.3 J/m^2 and above) is 22.3 µm. (From Edenberg, 1976)

Bowden et al. (1975) studied pyrimidine dimer production and excision in epidermal DNA in the skin of intact female Charles River CD-1 mice exposed to six different dose levels of UVR. A bank of four 15-W G 15T8 ITT-germicidal A lamps, emitting primarily in the 254 nm wavelength range, was used to irradiate the mice at an intensity of 28 $J/m^2/sec$. Dose levels studied ranged from 0 to 8,400 J/m^2. Table 11 shows that thymine dimer production in mouse epidermal cells was approximately linear with UV dose levels up to 5040 J/m^2, but that dimer yield at 8400 J/m^2 was approximately equal to that obtained at 5040 J/m^2, possibly indicating that higher dimer yields cannot be obtained in mouse skin.

Basal cell loss was estimated by studying the loss of methyl-tritiated thymidine-prelabeled DNA after five different dose levels ranging from 420 to 8400 J/m^2 of UVR irradiation (Table 12). While no apparent cell loss was observed at 420 J/m^2 within 24 hours after irradiation, there was approximately a 20% loss at the four higher dose levels. The rate of DNA repair in mouse epidermal cells was also studied at nine different dose levels ranging from 0 to 8400 J/m^2 (Table 13). The level of nonsemiconservative DNA synthesis increased with increasing doses up to 420 J/m^2 and subsequently decreased. Quantitative measurements of repair replication at 3 hour intervals up to 24 hours after irradiation of mouse skin with 840 J/m^2 of UV are shown in Table 14.

Since Findlay's early work in 1928, numerous experiments have demonstrated that repeated exposures to high intensity UVR produce cancer in mouse skin. Recently, Hsu et al. (1975) reported the induction of squamous and spindle cell carcinomas, as well as papillomas, in hairless mutant mice following a single exposure to a UV dose of $3-24 \times 10^4$ J/m^2. Tumorigenic effects at various dose levels of UVR observed by Hsu et al. (1975), Urbach et al. (1974), Zigman et al. (1976), Kripke (1974), Stenback (1975), Forbes (1973), and Freeman (1975) are shown in Table 15.

Blum, who performed the first quantitative photocarcinogenesis experiments in the nineteen forties, subjected strain A albino mice to UV doses ranging from 0.32 to 8.6×10^4 J/m^2 at regularly scheduled intervals of time until cancers appeared. Dose size and time schedule were held constant for each experiment, but varied from one experiment to another. Blum found that for each dosage schedule, the logarithm of the median time to tumor formation varied inversely with the dose and reached a point beyond which further increments in dose had no effect. Increasing the dose or shortening the intervals between exposures accelerated tumor formation but did not alter the shape of the incidence curve, a finding subsequently confirmed by Urbach et al. (1976).

Figure 12 shows the incidence of skin cancer in four earlier experiments conducted by Blum. However, when Blum (1975) plotted the incidence of skin cancer in mice against the logarithm of the number of doses (Figure 13), he concluded that each successive UV dose adds a proportionate increment to an accumulating process. Therefore, not only the size of the dose but also the time schedule of the doses are important factors in photocarcinogenesis in mice.

Table 11

Thymine-Containing Dimer Production and Excision in Mouse Skin
Epidermis After Exposure of Mice to UV*

UV Irradiation (J/m^2)	Time after irradiation (hr)	Dimers/thymine** (%)	Dimers*** excised (%)
0	0	0.005 ± 0.005****	
420	0	0.076 ± 0.023	
420	24	0.046 ± 0.016	39
840	0	0.130 ± 0.010	
840	24	0.092 ± 0.013	29
1,680	0	0.196 ± 0.016	
1,680	24	0.134 ± 0.02	32
5,040	0	0.566 ± 0.059	
5,040	24	0.218 ± 0.014	61
8,400	0	0.560 ± 0.24	
8,400	24	0.320 ± 0.036	43

*From Bowden et al. (1975)
**The thymine-containing dimer production is expressed as the ratio (in terms of percentage) of radioactivity associated with thymine-containing dimers to the radioactivity associated with thymine.

***Thymine-containing dimer excision is expressed as the percentage of dimers present at 0 hr that had been excised 24 hr after irradiation.

****Each value is the average of 2 independent experiments ± the range, except that 3 experiments were done at the 420 J/sq m dose level, and these data are expressed as the average ± S.D.

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Table 12

The Effect of Various Doses of UV on the Loss of Prelabeled
Epidermal DNA *

UV Irradiation (J/m^2)	Control DNA (dpm/μg DNA)	Irradiated DNA (dpm/μg DNA)	Irradiated DNA/ Control DNA (%)	p value
420	149 ± 34[a]	172 ± 17 **	108	0.2
480	117 ± 14	93 ± 12	79	0.4***
1,680	100 ± 2	80 ± 5	80	0.0005***
5,040	121 ± 12	92 ± 22	76	0.11***
8,400	124 ± 4	114 ± 11	81	0.01***

* From Bowden et al. (1975)
** Mean ± S.D. of from 3 to 5 values, each determined with a different group of mice.

*** At these dose levels, the p values suggest that irradiation with UV caused a significant loss of prelabeled epidermal DNA.

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Table 13

Quantitative Measurement of Repair Replication after Dose Levels
of UV irradiation in Epidermis*

UV Irradiation (J/m^2)	Specific activities of nonsemi-conservative replicated DNA ** (dpm/µg DNA)
0	8.9, 9.6
56	9.7, 11.4
140	16.5, 18.3
280	16.9, 19.7
420	28.6, 26.4
840	18.7, 22.9
1,680	18.6, 22.6
5,040	15.1, 18.6
8,400	15.9, 23.2

* From Bowden et al. (1975)

** The data are from 2 separate experiments. In each experiment, 2
CsCl gradients were run at each level of irradiation, and the
variation of the values for specific activity from the mean did
not exceed 15%.

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Table 14

Quantitative Measurement of Repair Replication at Various Times
After UV Irradiation (840 J/m^2 in Mouse Skin Epidermis*

Time interval (hr) after 840 J/m^2 of irradiation	Specific activities of nonsemiconservative replicated DNA **(dpm/μg DNA)
None	8.9, 9.6
0-3	25.2, 27.5
3-6	16.4, 14.8
6-9	13.6, 6.4
9-12	16.4, 16.4
12-15	16.7, 15.9
15-18	10.9, 10.6
18-21	11.4, 7.6
21-24	10.1, 7.6

* From Bowden et al. (1975)

** The data are from 2 separate experiments. In each experiment 2
CsCl gradients were run for each time interval, and the variation
of the values for specific activity from the mean did not exceed
15%.

Table 15

Some Effects Observed at Various Dose Levels *

System/Effect	Light Source	Wavelength	Flux	Dose	Duration
(1) C3Hf/Sm mice spindle cell tumors observed (latent period 31-60 wk); squamous cell carcinomas observed (latent period 47-78 wk)	Hanovia quartz-mercury arc lamp	280-320 nm	nr**	3×10^2 J/m^2/sec	60,20, or 6 sec (3 x/wk)
(2) A/J mice spindle cell tumors observed (latent period 42-67 wk)	"	"		"	30 sec (3 x/wk)
(3) female NMR strain rats benign tumors observed in 8/40 animals; malignant tumors observed in 8/40 animals	40 W fluorescent Westinghouse sunlamps	nr	nr	1.8×10^2 J/m^2	3 hr (1 or 2 x/wk) for 60 wk
(4) female guinea pigs malignant tumors observed in 2/25 animals	"	"	"	"	"
(5) Syrian golden hamsters benign tumors observed in 14/40 animals	"	"	"	"	"
(6) Swiss mice benign tumors observed in 3/40 animals; malignant tumors observed in 20/40 animals	"	"	"	"	"

* Data from references: (1), (2): Kripke (1974); (3(, (4), (5), (6): Stenback (1975b)
* * not reported

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Table 15 cont'd

Some Effects Observed at Various Dose Levels*

System/Effect	Light Source	Wavelength	Flux	Dose	Duration
(7) hairless mice first cancer observed at 25 wks; tumor prevalence at 31 wk 0.14; at 36 wk, 0.14	Fluorescent sunlamp FS40T12	UV-B + UV-A	nr	1.8×10^2 J/m^2 1.3×10^2 J/m^2	20 min/day, 5 x/wk for up to 36 wks
(8) hairless mice first cancer observed at 17 wks; tumor prevalence at 31 wk 1.00	1000 W Xenon solar simulator	UV-B + UV-A	nr	1.8×10^2 J/m^2 1.2×10^3 J/m^2	"
(9) albino mice no tumors observed	high intensity diffraction-grating monochromator	290 nm	nr	1.4×10^2 J/m^2	3 x/wk for up to 465 days
first tumors observed after 323 days; 15/30 animals developed squamous cell carcinomas by 458 days		300 nm	nr	2.0×10^2 J/m^2	"
no tumors observed		310 nm	nr	2.0×10^2 J/m^2	"
first tumors observed after about 330 days; of 8 tumors in 16 survivors at 465 days, 5 were squamous cell carcinomas, 2 were fibrosarcomas and 1 was an angiosarcoma		310 nm	nr	2.5×10^3 J/m^2	"
2/5 survivors developed squamous cell carcinoma at 417 and 464 days		320 nm	nr	1.6×10^4 J/m^2	"

* Data from references: (7) & (8) Forbes (1973); (9) Freeman (1975)

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Table 15 cont'd

Some Effects Observed at Various Dose Levels*

System/Effect	Light Source	Wavelength	Flux	Dose	Duration
(10) hairless mice first carcinomas observed after 20 wk	F4012 fluorescent black-light lamps	UV-A	1×10^5 W/m^2	nr	continuous exposure for over 20 weeks
(11) inbred albino A/J mice 6/61 papillomas, 6/61 squamous cell carcinomas, 3/61 fibrosarcomas, observed at 50-70 wk	40 W black light tubes BLB	365 nm	$1\text{-}6 \times 10^4$ W/m^2 depending on age of lamps	nr	12 hr/day 60-90 wks
(12) hairless mutant mice HRS/J strain earliest tumor (papilloma) observed at 50 days after 280 days; 2/79 tumors observed were squamous cell carcinomas in mice receiving 12 or 24 $\times 10^4$ J/m^2	FS20/40T12 fluorescent lamps	56% 280-320 nm peaking at 313 nm 28% 320-400 nm 16% visible/IR	9-20 W/m^2	3×10^4 J/m^2 24×10^4 J/m^2	single exposure 30-210 min

*Data from references: (10) data cited by Urbach et al.(1974); (11) Zigman et al. (1976); (12) Hsu et al. (1975)

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Table 15 cont'd

Some Effects Observed at Various Dose Levels*

System/Effect	Light Source	Wavelength	Flux	Dose	Duration
(13) hairless mutant mice HRS/J strain 3 tumors observed at 3×10^4 and at 6×10^4 J/m^2; 38 tumors observed at 12×10^4 J/m^2. Most tumors appeared between 15-28 wks after exposure, with greatest number present at 25-30 wks. After 280 days, 14 tumors had regressed; of 19 tumors present 17 were papillomas and 2 were spindle cell carcinomas.	FS20/40T12 fluorescent lamps	56% 280-320 nm peaking at 313 nm 28% 320-400 nm 16% visible/IR	11.1 W/m^2	3×10^4 J/m^2 6×10^4 J/m^2 12×10^4 J/m^2	single exposure 30 min 60 min 120 min

*Data from references: (13) Hsu et al. (1975)
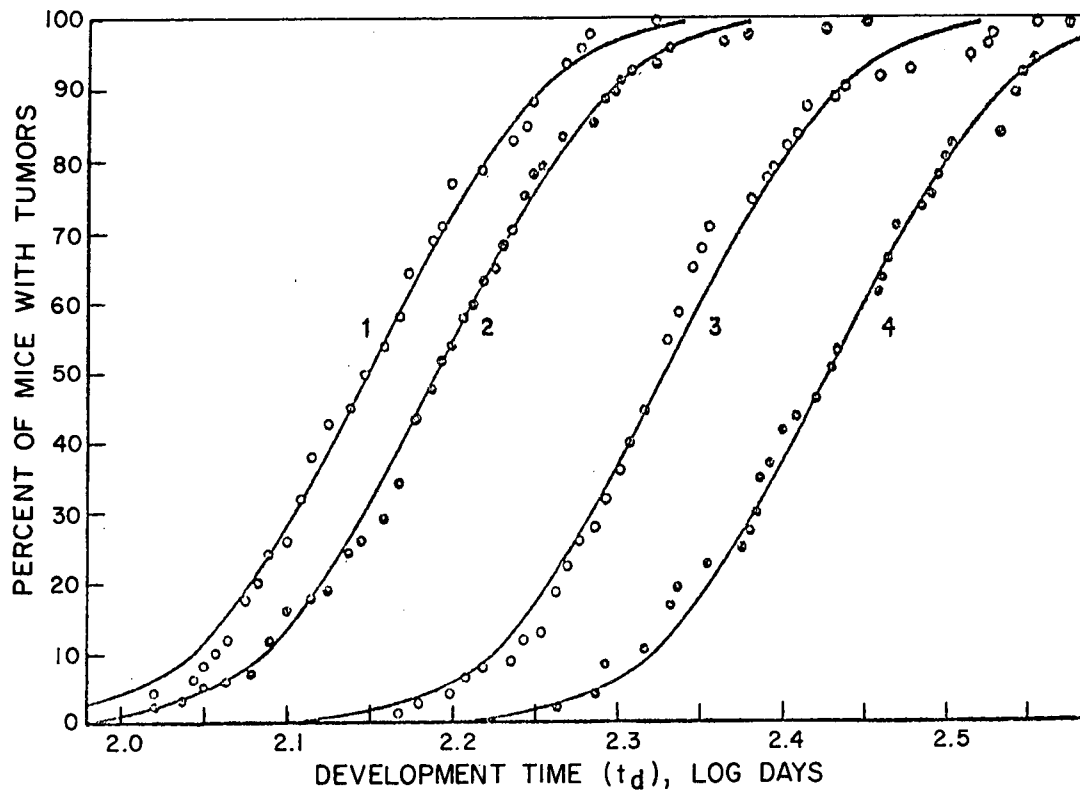
Curve in figure	Number of mice	Single dose J/cm^2	Interval between doses (days)	Dose rate $J/cm^2/sec$
1	47	2.0	1.0	4.3
2	98	2.6	1.4	4.3
3	41	1.8	1.4	3.3
4	44	1.8	1.4	0.18

Figure 12:

Data for four experiments carried out under conditions listed above, plotted in terms of tumor development time. (From Emmett, 1973)

Urbach et al. (1976) have subsequently undertaken a series of experiments to investigate the relationships between flux, dose-fractionation and total dose and animal skin photocarcinogenesis. They exposed groups of SKh-1 hairless mice to equal doses of UVR delivered in time periods of unequal duration (5, 50 or 500 minutes, 5 times weekly). Animals receiving the
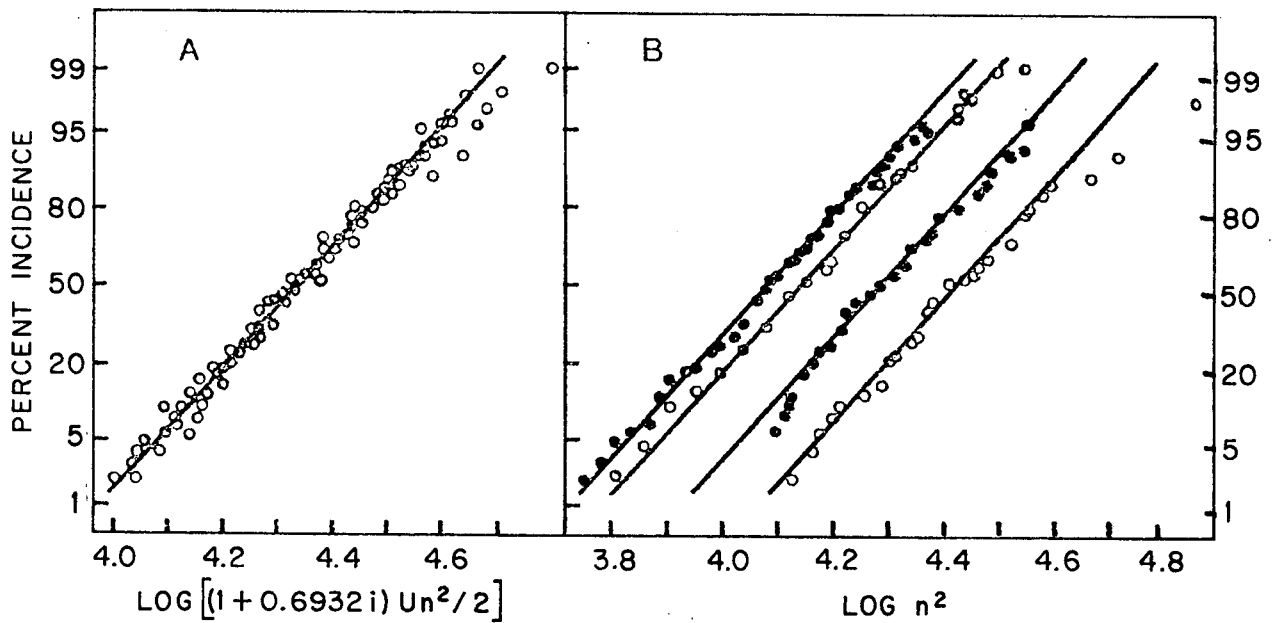
Figure 13:

The incidence of skin cancer in mice plotted against the log of the number of doses. Log [(1 + 0.6932i)Un^2/2] is a function relating the measured UVR dose to its photochemical effectiveness. (From Blum, 1976)

total dose within 5 minutes developed fewer tumors than those receiving the same dose in 50 or 500 minutes, indicating that protraction of UV doses increases the radiation's carcinogenic effects.

In another time-related experiment, Urbach et al. (1976) exposed two groups of mice to daily 600 J/m^2 doses of UVR for periods of 36 weeks and of 10 weeks. Tumors first appeared in both groups at 13 weeks after the first exposure. At 18 weeks, tumor prevalence (0.5), yield (1.0), size, and morphology in both groups were virtually identical. However, at 27 weeks, tumor prevalence was higher in the mice still being subjected to UV irradiation than in the mice which were no longer exposed (1.0 versus 0.7), as were tumor yields (6.5 versus 3.0). Continued exposure also resulted in the development of larger and more aggressive tumors.

Although the carcinogenic response of mice to UVR is clearly linked to dose levels, quantitative extrapolation of animal data to man is not possible. However, evidence derived from epidemiological studies tends to substantiate the observation that the cumulative action of repeated doses of UVR is effective in the production of skin cancer in human populations as well as in mice. Macdonald (1975), Urbach et al. (1974), Scotto et al. (1974), Magnus (1976), Scotto et al. (1976), and Blum (1975) have reported that increased incidence of skin cancer correlates with increased age.

Skin cancer incidence also has been found to correlate inversely with latitude of residence (Scotto et al., 1974; Elwood et al., 1974; Fears et al., 1976; Emmett, 1973; Macdonald, 1975; Magnus, 1976). Gordon and Silverstone (1975) observed that skin cancer incidence appears to double with every 10° in decreasing latitude. Table 16 shows global distribution of non-melanoma skin cancer by latitude and demonstrates that in white-skinned populations, skin cancer incidence increases with decreasing latitude. Figure 14 shows age-specific incidence rates of non-melanoma skin cancer in four countries.

When Mo and Green (1975) calculated UV dose estimates for various locations throughout the globe, they found that annual dose can be represented as a function of latitude. This finding was corroborated by Scotto et al. (1976), who measured levels of UVR in 10 locations in the United States (Figure 15). Latitude and annual UV count correlated positively, justifying the use of latitude as a surrogate for annual UV dose (Table 17). Skin cancer incidence of each cell type and sex group in four areas surveyed was also related to dose.

Finally, Scotto et al. (1976) suggest that cumulative exposure to UVR is the significant factor in human photocarcinogenesis and propose a dose-response model relating skin cancer incidence to cumulative exposure. Green et al. (1976), in turn, have correlated annual UV dose estimates with age-specific and age-adjusted non-melanoma skin cancer incidence data in white populations in English speaking countries. They have also examined five mathematical dose-response models. The first, a reciprocity model, assumes that non-melanoma skin cancer rates are dependent on exposure (a product of age and annual dose). The other models each violate reciprocity and of these, the "age-exposure" and "double cause" models appear to be most compatible with the available epidemiological and experimental data.

Table 16

Global Distribution of Skin Cancer Incidence Other Than Melanoma
(Male Data With Correspondence Female to Male Ratios (F/M))*

Average Incidence of Skin Cancer per 100,000 (both sexes)	ZONAL LATITUDES **				
	A	B	C	D	E
0.0-1.9			Japan	S.A. Cape Bantus S.A. Cape Colored Natal Africans Natal Indians Bulawayo Africans	Bombay Nigeria
			F/M = 0.80	F/M = 1.27	F/M = 1.49
5.0-19.9	Sweden**	Poland Rumania Denmark	Yugoslavia	Texas (Latin)	Jamaica
	F/M = 0.48	F/M = 0.84†	F/M = 0.56	F/M = 1.01	F/M = 0.94
20.0-29.9	Finland	United Kingdom German Dem. Rep. Hungary	New York State††		
	F/M = 0.88	F/M = 0.72§	F/M = 0.66		
30.0-49.9		Canada	Nevada		Colombia Puerto Rico
		F/M = 0.67	F/M = 0.64		F/M = 0.95
50.0-99.9			Victoria (Australia) Tasmania (Australia) F/M = 0.49		
100 and over				S.A. Cape (whites)‖ Texas (non-Latin)¶ Queensland (whites)‡ F/M = 0.59	

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Table 16 (continued)

Global Distribution of Skin Cancer Incidence Other Than Melanoma
Male Data With Correspondence Female to Male Ratios

LEGEND:

*From Gordon and Silverstone (1976)

**Zonal latitudes are: A, above 60°; B, 45°-60°; C, 35°-45°; D, 20°-35°; E, 0°-20°.

***Zoning based on male rates only.

†Poland = 0.84; Rumania = 1.09; Denmark = 0.59.

††Excluding New York City.

§U.K. = 0.58; G.D.R. = 0.70; Hungary = 0.88.

‖Males, 133.0; females, 72.2.

¶Males, 168.2; females, 106.1.

‡Males, 265.1; females, 155.8.

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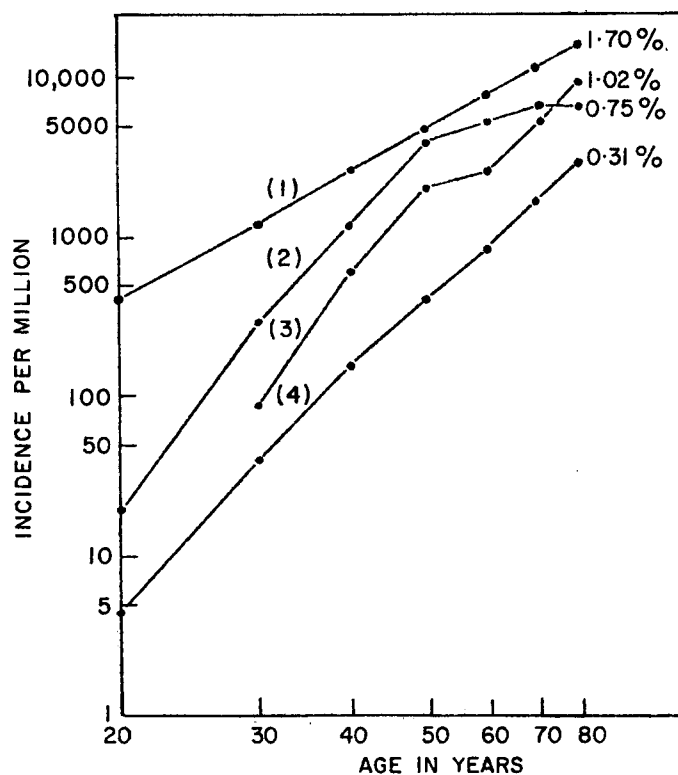
Figure 14:

Age-specific incidence rates/million for skin cancer, excluding melanoma, in four countries (males). 1 = Queensland, Australia, coastal regions; 2 = El Paso, Texas (Non-Latins); 3 = Cape Province, South Africa (Whites); 4 = South-west England.
(From Gordon and Silverstone, 1976)
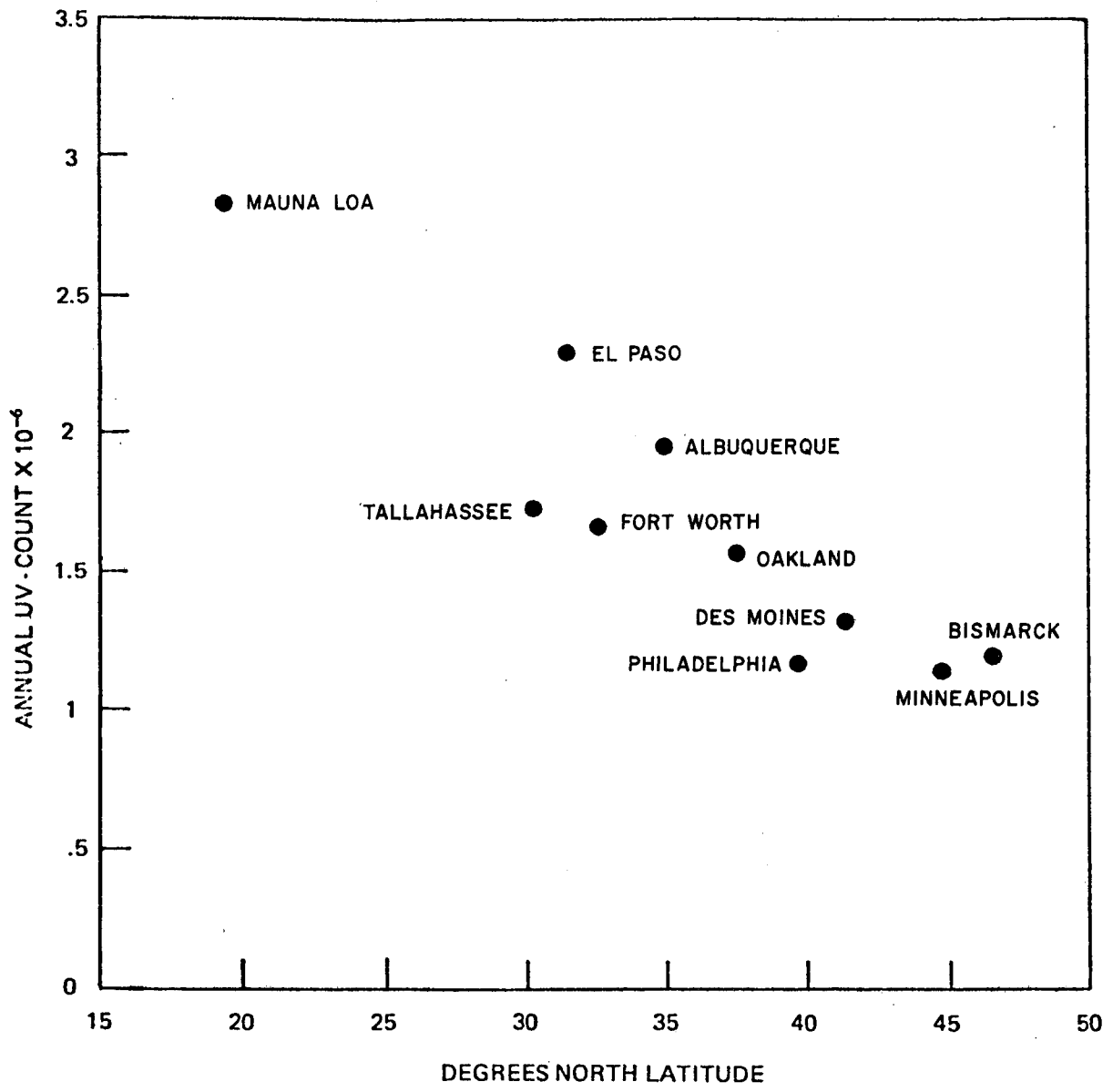
Figure 15:

Annual ultraviolet count by latitude.
(From Scotto et al., 1976)

Table 17

Correlations Among Environmental Variables for 10
Stations (Below Diagonal Line) and for the 9 Continental Stations
(Above Diagonal Line)*

	UV COUNT	LATITUDE	ALTITUDE	SKY COVER
UV COUNT	1.00	-.83	.64	-.91
LATITUDE	-.92	1.00	-.20	.68
ALTITUDE	.85	-.72	1.00	-.57
SKY COVER	n.a.	n.a.	n.a.	1.00

* From Scotto et al. (1976)

The age-exposure model assumes that even apart from the cumulative effect of UV doses, skin becomes more sensitive to UVR with age. The double cause model considers other carcinogenic events such as spontaneous mutations and the presence of chemical carcinogens.

WAVELENGTH DEPENDENCE

The precise action spectrum for photocarcinogenesis, or relationship between the incident UV wavelength and the intensity of the response, has not yet been accurately determined. Available experimental evidence suggests that in the absence of photosensitizing substances such as 8-methoxypsoralen, UVR of wavelengths ranging from 290 to 320 nm is an effective carcinogen. Such radiation penetrates the skin and is absorbed in the epidermis and upper dermis where it damages DNA and causes a variety of acute and chronic biological effects (Gianelli, 1976). Wavelengths shorter than 290 nm are attenuated in the ozone layer and do not reach the surface of the earth to any appreciable extent. However, animal skin cancer has been induced in the laboratory with sources of shorter wavelength, as well as with sources emitting radiation of wavelengths longer than 320 nm (Blum, 1974; Freeman, 1976). Figure 16 shows designations used to describe different portions of the UV spectrum.

It has generally been assumed that the wavelengths responsible for inducing skin cancer in humans are similar to those producing erythema and sunburn, i.e., 290-320 nm (Emmett, 1973; Schulze, 1974, 1976; Urbach et al., 1974; Albert, 1976). However, Setlow (1974) has proposed that the appropriate action spectrum is one that coincides with the action spectrum for affecting DNA. Figure 17 shows an average action spectrum for the effects of UVR on a number of simple DNA containing systems, including inactivation of bacteria and bacterial viruses, mutagenesis in bacteria, formation of cyclobutane pyrimidine dimers in DNA, and the production of sites susceptible to the in vitro action of repair endonuclease. Figure 18 shows that wavelengths below 305 nm in sunlight effect DNA more strongly than those above.
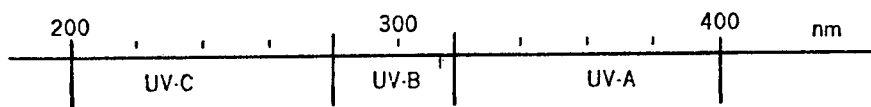
Figure 16:

Ultraviolet spectrum. (From Urbach et al., 1974)

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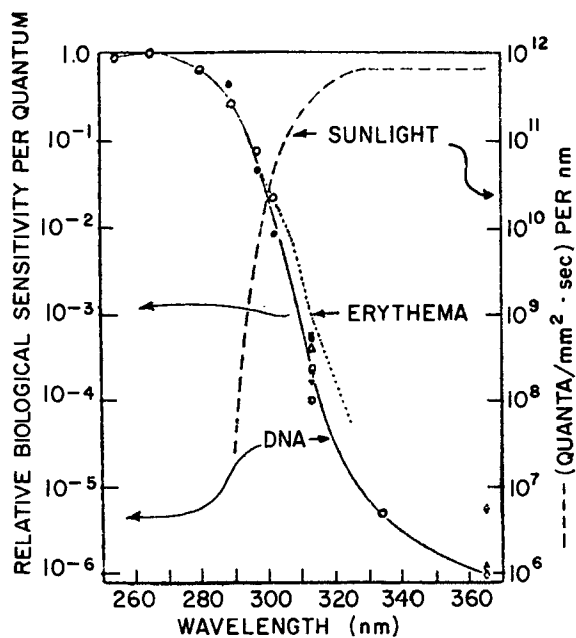
Figure 17:

The solid curve is an average action spectrum for affecting DNA.
The broken curve represents the sun's spectrum at the earth's
surface for Gainesville, Florida (12 noon, 8 September 1972).
The dotted curve is a recent erythemal action spectrum.
(From Setlow, 1974)
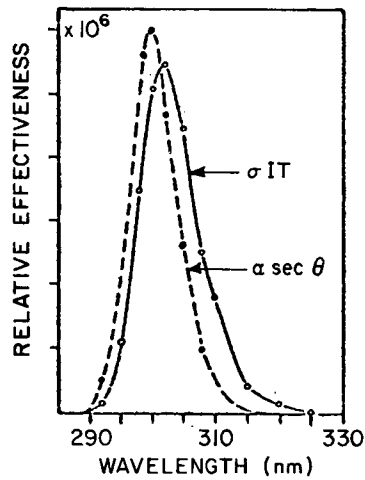
Figure 18:

The solid curve represents the probability of sunlight affecting DNA below a layer of skin as a function of wavelength (2.3 mm O_3, zenith angle 25°). The broken wave shows the change in effectiveness with changing ozone content. The change in effectiveness relative to the probable effectiveness at 2.3 mm O_3 is 0.88 mm^{-1} O_3. (From Setlow, 1974)

Tan et al. (1970) have studied the action spectrum of UV light-induced damage to nuclear DNA in vivo and compared it with the erythema action spectrum for human skin produced by UV light from the grating monochromator. Figure 19 shows that erythema production did not vary significantly between 254 nm and 295 nm, while at 310 nm or longer, the relative effectiveness of erythema production fell markedly.

When Tan et al. (1970) irradiated hairless mice at different wavelengths with energies which were comparable in terms of human minimal erythema dose (MED), the following results were obtained (Table 18). From 254 nm to 300 nm, energy equivalents of 10 MED delivered at different intervals induced photochemically altered nuclear DNA in the epidermal cells of all the mice studied. At 305 nm, 10 MED (2.8×10^3 J/m^2) produced less extensive lesions in nuclear DNA. At 310 nm, the equivalent of 10 MED (1.8×10^4 J/m^2), produced no detectable photochemically altered DNA. At wavelengths of 320 nm and 330 nm, doses of 1.8×10^4 J/m^2 were also ineffective in producing photochemical DNA lesions. Further experiments with energy equivalent to 40 MED indicated that effectiveness falls off gradually after 310 nm. Tan et al. (1970) conclude that there appears to be a close parallel between the curve of the erythema action spectrum and the action spectrum of photochemically induced DNA lesions in cell nuclei.

In a series of experiments designed to test the hypothesis that the carcinogenic effectiveness of UV radiation is proportional to its erythemal effectiveness, Freeman (1975) exposed groups of albino mice to narrow ($\pm$ 5 nm) bands of high-intensity UVR from 290 nm to 320 nm in wavelength. Mice were irradiated three times a week at different wavelengths and different dose levels until 50% of the animals surviving long enough to develop tumors had done so. The irradiation schedule was selected to simulate the chronic recurrent exposure of humans to sunlight. When mice were irradiated with a dose of 200 J/m^2 per session at 300 nm and at 310 nm, no tumors or visible damage appeared in the group receiving 310 nm. In the mice exposed to 300 nm, the first tumor appeared after 323 days, and half the animals had developed squamous cell carcinomas by 458 days. When mice were exposed to 310 nm at a dose of 2500 J/m^2, half the animals developed squamous cell carcinomas, fibrosarcomas, and an angiosarcoma by 465 days (Figure 20). No tumors or visible damage developed in mice exposed tm 290 nm radiation (140 J/m^2). Two of five survivors exposed to 320 nm radiation developed squamous cell carcinomas. These results are summarized in Table 19.

Freeman (1975) suggested that the occurrence of malignant tumors in mice exposed to monochromatic UV light at 300, 310 and 320 nm in quantities proportional to its erythemal effectiveness supports the hypothesis that the carcinogenic effectiveness of UVR is proportional to its erythemal effectiveness at those wavelengths.

In 1934, Roffo had observed that the carcinogenic effect of UV radiation was blocked by window glass, suggesting that wavelengths longer than 320 nm did not produce skin cancer. However, Forbes (1974) has reported skin cancer in hairless mice following chronic continuous irradiation with erythemogenic doses of UV-A (>320 nm). Carcinomas were first observed in hairless mice after 20 weeks of continuous (24 hours/day) exposure to UV-A at 10^5 W/m^2. Although the conditions of the experiment are not comparable to the human situation, the demonstration that long UV wavelengths can be carcinogenic at any level is significant.
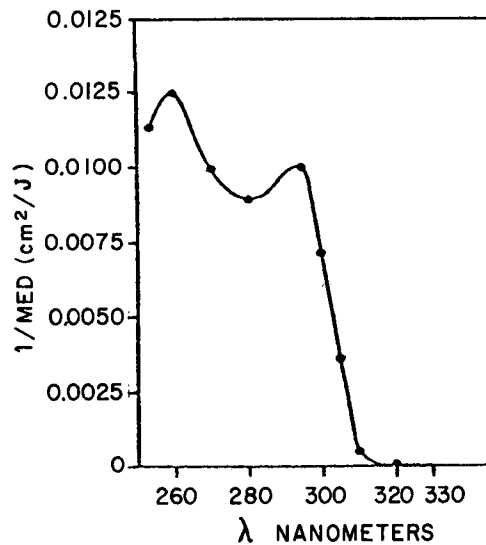
Figure 19:

Curve for erythema spectrum. The ordinate is the reciprocal of the
energy required to produce minimal erythema on untanned human
abdominal skin. The scale on the ordinate thus corresponds to the
effectiveness of different wavelengths in producing erythema. This
erythema action spectrum was used as the basis to determine UV
wavelengths that would induce the photochemical DNA lesion in cell
nuclei. (From Freeman, 1975)

Table 18

Irradiation of Hairless Mice with UVR*

Wave-length nm	Energy** (J/m²)	Equivalent Number of MED's	Animals with DNA lesions/ Animals tested
254	880	10	4/4
260	800	10	2/2
260	1,500	19	2/2
270	1,000	10	2/2
270	2,020	20	2/2
280	1,100	10	2/2
295	1,000	10	5/5
300	1,400	10	4/4
305	2,800	10	4/4
310	18,000	10	0/3
320	18,000	—†	0/1
330	18,000	—†	0/1
295	4,000	40	3/3
310	72,000	40	2/2
320	72,000	—†	1/1
330	72,000	—†	0/1

  * From Tan et al. (1970)

 ** Energy was measured over a 10 nm half-power bandwidth and 90% was within ±5 nm of the dial setting.

  † At these higher wavelengths, the amount of energy equivalent to minimal erythema dose was not determined.

Table 19

Carcinogenesis by Narrow (± 5 nm) Bands of UVR*

Wavelength (nm)	Weekly dose (J/m^2)	TD50[+]		Total dose: MED**	Number of survivors	Number with tumors
		Days	Total dose (J/m^2)			
290	420	—	—	—	30	0
300	600	458	34,000	243	30	15
310	600	—	—	—	30	0
310	7	465	455,000	250	16	8
320	49,500	417 and 464	—	—	5	2

*From Freeman (1975)
**Minimal erythemal dose. [+]TD50 = the time required for tumor development in 50% of those animals
suriving long enough to develop tumors.

In a similar vein, Zigman et al. (1976) reported the induction of papillomas, squamous cell carcinomas and sarcomas in A/J albino hairless mice after 60-90 weeks exposure to black light fluorescent lamps for 12 hours daily. However, unlike the previous experiment, the UV-B (280-320 nm) component was not filtered out and constituted about 2% of the dose delivered to the animals. The intensity of UV-A radiation was about $7-8 \times 10^4$ W/m^2 and of UV-B was about $2-3 \times 10^3$ W/m^2. Although the radiant energy delivered by the lamps was predominately (98%) in the UV-A region, the authors state that the resulting skin tumors can be ascribed only to the mixture of UV-A and UV-B wavelengths. Furthermore, they point out that tumorigenesis may be related more to the total accumulated dose of UVR over the long term of the experiment than to the intensity of exposure.

Willis et al. (1972) studied the effect of long wave (>320 nm) solar simulating UVR in 12 Caucasian adults. Responses to UV-A alone (250 W/m^2), and UV-A plus sunburn radiation (400 W/m^2), were evaluated by routine histologic

Figure 20:

Skin tumors in albino mice exposed to monochromatic ultraviolet light.
From Freeman (1975)

and autoradiographic techniques. Exposure to UV-A alone caused no skin change, while UV-A plus sunburn radiation intensified the erythema response. H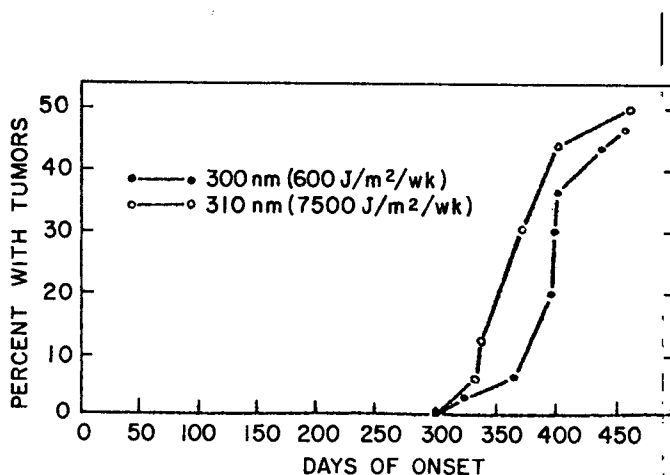owever, although skin exposed to UV-A alone was clinically and histologically unchanged, DNA synthesis was slightly accelerated within 24 hours. Protein synthesis was not affected. The results indicate that UV-A should not be considered harmless in the production of sunburn and its sequelae (solar degradation and skin cancer).

The possibility of interactive or additive effects between long and mid-UVR has also been investigated by Ying et al. (1974). Varying doses of UV-A and UV-B were delivered to the backs of fair-skinned Caucasians and the minimal perceptible erythema dose in each of those wavelength regions was determined. Subsequently, the subjects received various overlapping suberythemal doses of UV-A and UV-B to the same site. The erythema response of each doubly exposed site was quantitatively comparable to the sum of the two constituent singly irradiated sites, regardless of the wavelength regions included or the order in which the UV-A and UV-B radiation was administered.

Table 20 shows the UV light sources used by Ying et al. The authors note that the erythema response to both UV-A and UV-B appears to be dose-dependent. UV-B erythema was present with doses equal to or greater than 760 J/m^2. Long-wave UV induced erythema when the UV-A dose was equal to or greater than 192×10^3 J/m^2. When the effects of a large range of UV-A energies on UV-B erythema were investigated, it was found that UV-A doses below 10^5 J/m^2 had no effect on the erythema response to UV-B radiation. When UV-A doses greater than 10^5 J/m^2 were used, doubly exposed sites showed greater erythema than those exposed only to UV-B. The authors conclude that the erythemogenic properties of high dose UV-A are additive to subclinical or visible erythema induced by UV-B.

Finally, UVR in the UV-A wavelength region has been found to affect UV-B induced mouse skin photocarcinogenesis as well as human skin erythema. Forbes (1973) exposed hairless mice to UVR from each of two light sources with equivalent UV-B but differing in UV-A content. The light sources, a fluorescent lamp and a Xenon solar simulator, delivered a daily dose of 180 J/m^2 UV-B, and 130 J/m^2 and 1200 J/m^2 UV-A respectively. The mice exposed to the greater dose of UV-A developed more tumors than those exposed to the same quantity of UV-B and less UV-A. The first tumor in the former group of mice appeared at 17 weeks; in the latter group at 25 weeks. By 31 weeks, tumor incidence was 1.00 in the first group and 0.14 in the second. Although the mechanism of interaction is not yet known, Forbes (1973) suggested that both UV-A and UV-B play a significant role in photocarcinogenesis.

However, more recent experiments conducted by Forbes have shown that protraction of UVR doses has a marked effect on mouse skin carcinogenesis. When the same daily dose of UVR from a Xenon arc solar simulator was given in periods of 5, 50, and 500 minutes, animals receiving the protracted dose (500 minutes/day) developed more tumors at an earlier time than the other animals. Forbes believes that his earlier results (Forbes, 1973) may be due to protraction rather than to UV-A-UV-B interaction, since the UV-A plus UV-B radiation from the Xenon arc was delivered over a much longer time period than the UV-B alone. Forbes has recently repeated the 1973 experiment with an arrangement of light

Table 20

Ultraviolet Light Sources *

Source	UV-B Middle wave (280-320 nm)		UV-A Long wave (320-400 nm)	
	Filter	Intensity $(\mu W/cm^2)$	Filter	Intensity $(\mu W/cm^2)$
150-watt xenon arc lamp	Schott WG-295 and International Light NB-300	4,700	Schott WG-345	24,000
	International Light NB-297	620		
High-pressure 325-watt quartz mercury vapor lamp (Hanovia)	Acetate	500	Mylar	1,300
Solar radiation	None	75	Mylar	1,800
Blacklight fluorescent lamps	–	–	Mylar	2,300

*From Ying et al. (1974)

sources allowing the UV-B dose to be delivered at the same dose rate as the UV-A plus UV-B dose. No difference in the tumor producing effectiveness of both light sources was noted (personal communication).

The observation that dose rate of UVR delivery markedly affects experimental skin carcinogenesis is of great importance, since some of the phenomena ascribed to wavelength interactions may be due to extraneous conditions imposed on experiments by lamp design and by other as yet unexplored factors.

SYNERGISTIC EFFECT OF EXPOSURE TO OTHER AGENTS

Exposure to various chemical agents has been observed to affect human and animal skin responses to UVR. The potentiating effect of exogenous chemicals such as coal tar was first described by Findlay in 1928. Since that time, the influence of chemical agents on animal skin photocarcinogenesis has been tested extensively. The effects of known chemical carcinogens as well as those compounds which are phototoxic but non-carcinogenic per se have been investigated, often with apparently conflicting results. No epidemiologic data is available on the influence of carcinogenic or phototoxic substances on human skin photocarcinogenesis, and it is not known how occupational exposure to such chemicals as coal tar, anthracene, etc. contributes to the occurrence of skin cancer in humans.

One agent which has been studied repeatedly in this regard is methoxalen, or 8-methoxypsoralen (8-MOP). One of a group of photosensitizing furocoumarin compounds (psoralens), 8-MOP has been widely used in conjunction with UVR in the treatment of certain human skin diseases. In the presence of long wavelength (365 nm) UVR, this compound causes phototoxic damage to the cell nucleus through the formation of C-4 photoadducts with the 5,6 double bond of the pyrimidine base of DNA (Emmett, 1973).

In an attempt to clarify the nature of 8-MOP mediated phototoxic injury, Epstein and Fukuyama (1965) examined the effects of 8-MOP (1% solution in acetone) and long wavelength (315-400 nm) UVR in albino hairless mouse skin in vivo. They found that semiconservative premitotic DNA synthesis in the germinative layer of the epidermis was inhibited shortly after exposure. Recovery by 24 hours was followed by a progressive acceleration of DNA synthesis over a seven day period. The 8-MOP photosensitized injury had no apparent early effect on RNA and protein synthesis, but at 48 hours, the outer layers of epidermal cells no longer produced RNA or protein and appeared dead. The synthesis of these macromolecules was resumed by 72 hours after exposure. The authors conclude that responses to the 8-MOP mediated phototoxic injury differ qualitatively and perhaps quantitatively from the phototoxic reactions induced by shorter wavelength (<320 nm) UVR.

Carter et al. (1976) observed an increased frequency of sister chromatic exchanges in cultured human lymphocytes exposed to 8-MOP and 365 nm UV light. They suggest that the exchanges can be correlated with cross-link excision and thus may represent cellular repair of 8-MOP-UV-A-induced DNA damage.

Extensive chromosome damage was reported by Ashwood-Smith and Grant (1976) in Chinese hamster cells in culture exposed to psoralen (3.44 µg/ml of

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culture medium) and graded doses of 320-360 nm UVR. Because somatic chromosome damage of the magnitude observed can result in later malignancy, the authors suggest that caution be exercised in the use of psoralen in the treatment of psoriasis.

Forbes and Urbach (1975 b, 1975 d) and Forbes et al. (1976) found that daily topical pretreatment of albino hairless mice and hairless mutant mice with 8-MOP (40 μl of 0.1% solution) followed by exposure to UVR delivered by a Xenon arc solar simulator markedly enhanced photocarcinogenesis. However, when Forbes et al. (1976) studied the effects of pretreatment with the phototoxic agent anthracene on hairless mouse skin carcinogenesis, they found that tumor production was not significantly different from the control group, indicating that phototoxicity alone cannot be used to predict enhancement of photocarcinogenesis.

Gilchrest et al. (1976) studied the effects of 8-MOP photochemotherapy in nine patients with mycosis fungoides, an uncommon malignancy of the lymphoreticular system. All patients received 30-50 mg 8-MOP orally (approximately 0.6 mg/kg) followed by exposure to UVR for periods ranging from 8 to 28 months. Although earlier studies had demonstrated the enhancing effect of orally and intraperitoneally administered 8-MOP in murine photocarcinogenesis, Gilchrest et al. (1976) found no evidence that photochemotherapy with methoxalen and UV-A results in the production of human skin tumors. Moreover, there exists evidence that, in therapeutic doses, the pigment-enhancing properties of psoralen and UV-A treatment are actually protective against cutaneous neoplasia (Carter et al., 1976).

The extensive use of fluorescent whitening agents (FWA), or optical brighteners, in industry and in the home has prompted interest in their potential toxicity. Falk and Bingham (1973) reported that three FWAs tested in their laboratories could augment photocarcinogenesis in C3H mice exposed to germicidal (254 nm) UVR. However, when Forbes and Urbach (1975 a, 1975 b, 1975 c, 1975 d) tested five FWAs (Figure 21), including one of the FWAs investigated by Falk and Bingham (1973), they found no evidence of either phototoxicity or enhancement of photocarcinogenicity in hairless mutant mice exposed to UV-C, UV-A, UV-A and UV-B, or the UV, visible, and infrared component of simulated sunlight. In a series of four experiments using different light sources delivering radiation of the above mentioned wavelengths, Forbes and Urbach (1975 d) found that while 8-MOP enhanced photocarcinogenesis, no such enhancement was seen in animals receiving even greater amounts of FWAs.

Some chemicals, e.g. many polycyclic hydrocarbons, are both phototoxic and carcinogenic. Early studies on the modifying effect of UVR on skin carcinogenesis induced by chemical carcinogens have reported apparently conflicting results; in some cases, an inhibitory effect was observed, whereas, in other cases, a potentiating effect was seen.

When Stenback (1975 a, 1975 b) studied the effect of UV light on chemically-induced skin carcinogenesis, he observed both enhancement and retardation. UV irradiation of Swiss mice before topical application of 7,12-dimethylbenz(a)anthracene (DMBA) resulted in an increased tumor yield, while post-treatment irradiation decreased tumor induction.

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	Formula

sodium 2-(4-styryl-3-
sulfophenyl)-2H-naptho-
[1,2-d]triazole
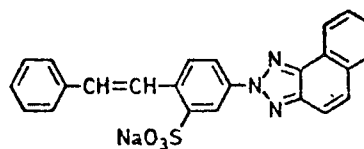
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disodium 4,4'-bis[(4-
anilino-6-morpholino-
1,3,5-triazin-2-yl)amino]-
stilbene-2,2'-disulfonate
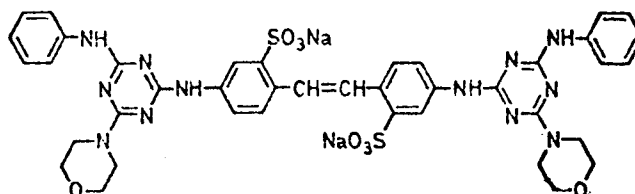
2

disodium 4,4'-bis-[(4-
anilino-6-[N-methyl-N-
2-hydroxyethyl]amino-
1,3,5-triazin-2-yl)amino]-
stilbene-2,2'-disulfonate
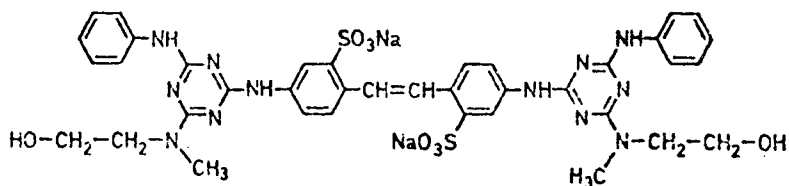
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disodium 4,4'-bis(2-
sulfostyryl)-biphenyl
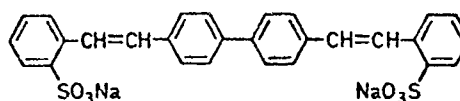
4

disodium 4,4'bis[(4,6-
dianilino-1,3,5-triazin-
2-yl)amino]stilbene-2,2'-
disulfonate
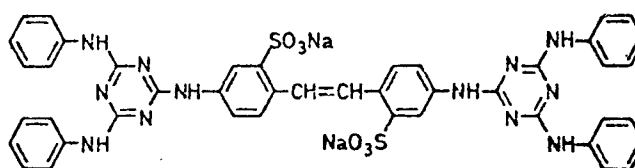
5

Figure 21:

Fluorescent whitening agents. After Forbes & Urbach (1975 d)

Davies and co-workers (Davies and Dodge, 1972; Davies, Dodge and Austin, 1972; Davies, Dodge and DeShields, 1972) observed that DMBA-induced tumor yield is affected by exposure to light sources containing different wavelengths and that the effectiveness of these sources is proportional to their ability to photodecompose DMBA. Moreover, rhino mice irradiated immediately after treatment with DMBA exhibited no response to either the chemical or the light. If irradiation was delayed between 1 and 4 hours post-treatment, a phototoxic response was observed and the rate of tumor appearance was accelerated.

Urbach et al. (1976) have carried out a series of DMBA carcinogenesis experiments using red, blue, and white light sources. Tumor yield was considerably higher in rhino mutant mice exposed to red light. However, brief preirradiation of DMBA with a Xenon arc lamp significantly reduced tumor development, presumably because DMBA degrades into non-carcinogenic photoproducts when exposed to light.

In an attempt to determine when DMBA induces neoplastic transformation, Urbach et al. (1976) studied the effect of in vivo irradiation at various time intervals after DMBA application. Irradiation with a Xenon arc solar simulator immediately following application of DMBA abolished all immediate effects of DMBA. If irradiation was delayed for 24 hours, it had little effect. Irradiation 4 hours after DMBA treatment resulted in a reduction in the severity of the DMBA reaction and in the total tumor yield. At times ranging from 30 minutes to 2 hours post-treatment, irradiation caused a moderate to severe phototoxic response, and a greater tumor yield than that observed in animals irradiated at either 0 or 4 hours after carcinogen treatment. The tumor yield was, however, considerably lower than in unirradiated control animals. The authors suggest that light may affect DMBA carcinogenesis in two opposing ways: by photodecompostion of the carcinogen into non-carcinogenic products, and by stimulating a phototoxic reaction which appears to be coincident with increased tumor yield.

The increased incidence of skin cancers in organ transplant patients suggests a possible interaction between the immune status of the host and UV radiation. Maize (1977) reports that 39% of renal transplant patients recorded in the Denver Transplant Tumor registry developed skin cancer, primarily on sun-exposed skin, and that the overwhelming majority of these cancers were squamous cell rather than basal cell carcinomas. The risk of developing skin cancer correlated with the length of immunosuppression. It is suggested that immunosuppressive drugs may act as co-carcinogens with UVR in the induction of skin cancer.

In an attempt to evaluate factors affecting photocarcinogenesis, Forbes (1975) tested an immunosuppressive drug in mice exposed to UV-B radiation over a 5-month period. Compared with control animals, mice receiving intraperitoneal injections of rabbit antimouse antilymphocyte serum (ALS) developed tumors at an earlier time and in larger numbers, indicating that ALS enhances photocarcinogenesis. Nathanson et al. (1973) also found that ALS resulted in earlier tumor induction in UV irradiated Skh hairless mice. However, when 6-mercaptopurine (6-MP), which is cytotoxic as well as immunosuppressive, was tested under the same conditions, tumor appearance was delayed.

Tests performed by Koranda et al. (1975) on the relationship between UV carcinogenesis and two commonly used immunosuppressive agents also produced divergent results. Azathioprine (50 mg/kg of feed) and prednisone (20 mg/kg of feed) were added to the diet of hairless mice concurrently irradiated with sunlamps daily for 220 days. While azathioprine potentiated the carcinogenic effect of UVR, prednisone seemed to exert a protective effect.

Furthermore, in contrast to the experiments cited above, where immunologic reactivity of the test animals was diminished or abrogated during the process of photocarcinogenesis, the studies of Kripke and Fisher (1976) demonstrated another possible pathway for immunologic alteration of UV-induced tumor bearing hosts. Their experiments showed that UV irradiation rendered mice susceptible to challenge with highly antigenic syngeneic UV-induced tumors rejected by normal animals, suggesting that UVR, in addition to its carcinogenic action, may induce a systemic alteration which changes the outcome of this particular host-tumor interaction. This UV-induced systemic alteration may also affect the host-tumor relationship during viral or chemical carcinogenesis as well as during photocarcinogenesis.

The interaction between UVR and chemical agents is complex and warrants further investigation. Only a few environmental chemicals, e.g. coal tar, 8-MOP, DMBA, and anthracene, have been studied, and the results are far from being definitive. The synergistic effects of UVR and agents to which man is habitually exposed such as drugs and pesticides should be examined systematically. Another area which should also be explored further is the relationship between phototoxicity and enhancement of photocarcinogenesis. If such a relationship were better understood, it could be used to identify and protect man from potentially dangerous substances in the environment.

Humans are often exposed simultaneously to UVR and heat, but there have been very few investigations of the possible interaction between UVR and other physical agents such as infrared radiation. Although temperature does not affect photochemical reactions per se, it may affect the biochemical reactions secondary to the primary photochemical reaction, and Urbach et al. (1974) point out that clinical experience indicates that heat accelerates human skin photocarcinogenesis.

The effects of heat on murine skin photocarcinogenesis have been investigated by Bain et al. (1943), Freeman and Knox (1964), and by Owens (1977). When Bain et al. (1943) studied the influence of temperature on UV-B carcinogenesis in ABC mice, they found that tumors appeared earlier when mice were irradiated in an environment heated to 35-38°C than at room temperature (23°C). There was, however, little difference in the rate of carcinogenesis at 3-5°C and at 23°C. Freeman and Knox (1964) observed that albino mice, exposed to chronic UV irradiation at constant high environmental temperatures (32.2°C) developed more tumors at a faster rate than mice kept at room temperature (24°C) and suggested that heat enhances UV carcinogenesis. More recently, Owens (1977) studied the effect of heat, humidity and wind on mouse skin responses to UVR. Mice were irradiated for 400 days with suberythemal UV light at 32.2°C and at room temperature. Significantly greater numbers of mice developed tumors while maintained at higher temperatures. Owens (1977) also found that wind and humidity enhanced murine tumorigenesis.

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Although the experimental evidence is sparse, it does suggest that physical agents augment UV-mediated injury. Henry (1946), for instance, reports an increased incidence of skin cancer in glass workers, steel mill workers, smiths, firemen, and other individuals occupationally exposed to heat. However, it is possible that this is due not to IR radiation alone but to associated exposure to ultraviolet radiation, soot and tar. Exposure to heat has also been associated with an increased incidence of squamous cell carcinoma of the lower extremities in Irish women (Peterkin, 1955). These latter women spend much time sitting in front of peat fires and as a result, develop erythema *ab igne,* a condition which is presumably related to chronic exposure to very hot fires and sometimes complicated by cancer. Again, however, peat fires also emit ultraviolet radiation and chemical carcinogens. The abovementioned carcinomas may thus result from chronic exposure to ultraviolet radiation and chemicals rather than IR itself. Burns et al. (1976), on the other hand, have studied the interaction between ionizing radiation and UVR. They report no evidence of synergism in 28-day-old rats irradiated with 690, 1,380, 2,060, or 3,450 rads of electrons, followed by erythemal UVR (4.2×10^3 or 2.1×10^4 J/m^2/week x 20). Except for a delay in electron-induced tumorigenesis during the 20 weeks of UVR exposure, the carcinogenic effects of these two agents appeared to be strictly additive and independent of either. Further work is needed to elucidate the mechanisms involved in the apparent synergistic effects of physical agents on UV-induced carcinogenesis.

PREDICTION OF EXCESS CANCERS EXPECTED AT TYPICAL DOSE LEVELS ENCOUNTERED IN THE WORK ENVIRONMENT OR AT CURRENTLY RECOMMENDED MAXIMUM PERMISSIBLE DOSE LEVELS

Epidemiologic studies have provided extensive evidence that prolonged exposure to solar radiation is linked to the development of skin cancer in man. Observations on the incidence, prevalence, and anatomic distribution of skin cancer have led to the characterization of the person who is most prone to skin cancer. This individual is fair skinned, with light hair and eyes, tans poorly, sunburns and freckles readily and is often of Celtic origin (Urbach et al., 1974). To avoid unnecessary exposure of susceptible individuals to UVR, it becomes interesting to attempt to further define the population at greatest risk of developing skin cancer.

In this regard, Tannenbaum et al. (1976) compared the erythema and tanning responses of 19 Caucasian patients with cutaneous carcinoma and those of a normal control group to an artificial light source emitting 297 nm UVR. A prolonged erythema, lasting 2 to 3 weeks after a single exposure to six to eight times the minimal erythema dose of artificial UVR was present in 58% of the fair skinned cancer patients versus 36% of the control group. The presence of prolonged erythema correlated with a history of skin cancer but did not correlate with the other established high-risk factors for cutaneous carcinoma. Although the population studied by Tannenbaum et al. (1976) is very small, the results suggest that further work is needed to elucidate the mechanism of prolonged erythema. Whether indeed it is a predictive marker identifying individuals at greater risk of developing UVR induced skin cancer should be determined. These individuals could then avoid work situations in which they would be exposed to UVR or take appropriate protective measures.

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The problem underlying the question of prediction of excess cancer expected at typical dose levels encountered in the work environment or at currently recommended maximum permissible exposure limits is compounded by the observation that the vast majority of all basal cell and squamous cell carcinomas of the skin, namely the common skin cancers, are due to exposure to sunlight UVR.

Skin carcinogenesis by UVR is generally assumed to be the result of genetic damage in DNA molecules. Thus, the skin carcinogenesis action spectrum and the DNA absorption spectrum may correspond. The erythema spectrum compares well with the DNA absorption spectrum in the spectral region from 295 to 330 nm which appears to cause nearly all the response. The action spectrum for skin carcinogenesis in mice also covers the same spectral range as the human erythema action spectrum. The weight of evidence is consistent with the concept that UV-induced photodamage to skin is the main causative factor in skin cancer and that there is no threshold effect. A relationship should therefore exist between skin cancer incidence and accumulative dose using a sensitivity function.

Accumulative dosage or exposure to solar UV radiation is a function of stratospheric ozone levels, atmospheric conditions (such as cloudiness), latitude, and life style (including time and type of outdoor activity). Of these factors, the thickness of the stratospheric ozone layer is a major determinant of the amount and spectral distribution of biologically effective UVR reaching the earth.

Determination of present incidence rates of skin cancer and their relationship to the amount of UVR reaching the ground is extremely problematic because epidemiologic data in man are difficult to obtain, and reliable epidemiologic data exist for very few locations only, none of which are far enough apart in latitude to provide good cancer-latitude-UVR gradients. Furthermore, quantitative evaluation of the relationship between skin cancer and solar UVR requires accurate knowledge of ozone conditions which is currently not available. Possible anthropogenic depletion of stratospheric ozone levels caused by NOx effluents of supersonic transport aircraft and chlorofluorocarbons used as aerosol propellants or refrigerants has led to an attempt to extrapolate change in UVR secondary to changes in the thickness of the ozone layer and to correlate them with the projected incidence of skin cancer. At this time, measurements of solar UVR have been performed with some accuracy and reliability in 10 places in the United States (Scotto et al., 1976).

All existing models which relate changes in UVR dose to the incidence of skin cancer in man are based on certain assumptions:

1. There is a quantitative relationship between the thickness of the ozone layer and UVR-induced erythemogenesis for untanned white skin.

2. The average increase in the erythemogenic effectiveness of UVR per unit decrease in ozone thickness is approximately two. Therefore, a 5% reduction in ozone thickness would result in a 10% increase in sunburning solar UVR (<320 nm) reaching the earth.

3. The observed increase in skin cancer with decreasing latitude
    is due to several interacting factors, including ozone thick-
    ness, the variety of differences in local atmospheric condi-
    tions, genetic background of the population, type, length
    and kind of outdoor exposure and other not yet specified condi-
    tions.

Since incidence data for skin cancer by latitude are inadequate, it follows
that estimates of the relationship of UVR to skin cancer at the present time
are also inadequate.

A series of different models have been proposed for the relationship of
changes in UVR secondary to stratospheric ozone reduction and an eventual
increase at steady state of skin cancer in the population of the United States.
Such models include those of Setlow (1976), Green and his associates, (Green
and Mo, 1975; Green, 1976), Cutchis (1975), and Fears et al. (1976). The
most recent and probably the best model is one proposed by Rundel and Nachtwey
of the Lyndon B. Johnson Space Center (personal communication).

These authors have developed a dose response model for non-melanoma skin
cancer incidence in Caucasians which is biologically reasonable and consistent
with available epidemiologic data. The model postulates that the probability
of first incidence of skin cancer is distributed log normally as a function
of total accumulated lifetime doses of biologically effective UVR, and that
for any given location, the accumulated lifetime UV dose to an individual
is proportional to his age. This is consistent with Blum's (1975) finding
that the induction of skin cancer in mice by repeated exposure to UVR is
dependent on the dose per fraction and on the square of the total number of
fractions delivered before detection of skin cancer. Whether it is caused
by a reduction of stratospheric ozone or to exposure in the work place, the
effect of an increase in biologically active UVR on skin cancer incidence
can be calculated directly from the extent to which each individual's life-
time accumulated dose is correspondingly increased. The result of such a
pertubation, on the average, would be the appearance of skin cancer at an
earlier age. Since skin cancer is predominantly a disease of the elderly,
the shift to younger ages, when integrated over the entire population, would
result in an increase of the overall number of skin cancers. It should be
noted, however, that many of these additional cases would occur in elderly
people shortly before their death from other causes.

Rundel and Nachtwey estimate that for the United States as a whole, a 1%
permanent decrease in the average stratospheric ozone thickness would produce
about a 2% increase in the biologically effective UV dose, and would ultimately
lead to an increase of 8% in skin cancer incidence. This estimate is predi-
cated on unchanged lifestyle, genetic susceptibility, and geographic distribu-
tion of the population. Such an increase in cases would occur gradually over
the course of a human lifespan, or approximately 75 years.

Within the framework of the postulated dose-response model, the uncertainty
in the above results is estimated at approximately ± 25%. There are also
uncertainties in the model postulates which cannot at present be quantita-
tively evaluated: (a) the degree to which UVR is the predominant cause of
skin cancer, (b) time-dose relationships, and (c) the influence of genetic

susceptibility of subsequent cases. The overall prediction uncertainty may, therefore, be substantially greater than 25%. This uncertainty can, however, be significantly reduced in the future by carefully designed epidemiologic surveys and experimental studies.

These models and this type of calculation deal entirely with solar UVR and with changes in that radiation secondary to changes in the ozone layer. Clearly, markedly increased natural exposure due to work in an outdoor environment might have a similar effect.

At this time little data exists on the UV load in the work place. For practical purposes, exposure to UVR in the 300-320 nm range under working conditions is limited primarily to situations involving the use of high temperature devices such as heliarc welding equipment, carbon arc lamps or lasers. With the possible exception of the steel industry, namely individuals working near molten metal, industrial exposure to high intensity UVR is not significant. Limited data relative to the amount of UVR emitted in indoor occupational situations are available from the work of Lyon et al. (1977) on electric welding and cutting arcs. Based on these data, Sliney estimates that the welding arc delivers 1 minimum erythema dose (MED) of UVR to an individual at a distance of 1 meter from the arc in 50 seconds (personal communication).

Since the average daily outdoor MED in the Philadelphia area between the hours of 10 A.M. and 2 P.M. is 6 MED, a welder is exposed to the equivalent of the daily Philadelphia MED within 5 minutes. If welders did not take appropriate precautions, exposure of this magnitude could lead to a significant increase in skin cancer. However, in general, welders are adequately protected by clothing, gloves, and face shields which are opaque to UVR, and the amount of radiation reaching such individuals may not, in fact, affect skin cancer incidence. It is by no means clear whether the same is true of individuals working near molten metal, electric ovens, or other UV emitting situations since measurements do not exist at this time. Adequate measurements of UV-B radiation in a variety of indoor working situations where exposure may occur must be performed. Once such data are available, existing models for the relationship of solar UVR to skin cancer incidence can be extrapolated to obtain a calculation of any possible risk of skin cancer induced by artificial UVR.

With regard to currently recommended maximum permissible occupational exposure to UVR, the criteria and standards developed by NIOSH (1972) are considerably lower than an equivalent 1 or 2 hours' exposure to summer sunlight out-of-doors. Table 21 shows permissible UV doses and relative spectral effectiveness of some selected monochromatic wavelengths. It is, therefore, unlikely that exposure to the currently accepted maximum permissible limits of UVR would lead to any increase in skin cancer incidence, as long as there is no concomitant exposure to very large, casual, non-work-related amounts of solar UVR.

RECOMMENDATIONS FOR FURTHER STUDIES

1. Recognition of potentially hazardous effects of UV-B on man:

UVR of wavelengths between 200-320 nm should be generally recognized

Table 21

Total Permissible 8-Hour Doses and
Relative Spectral Effectiveness of Some
Selected Monochromatic Wavelengths *

Wavelength (nm)	Permissible 8-hour dose (J/m^2)	Relative spectral effectiveness ($S\lambda$)
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	100000	0.003

* From NIOSH (1972)

as a toxic agent that is potentially hazardous to the workforce.

2. <u>Measurement of UVR reaching subjects at risk:</u>

Devices to accurately measure UVR in narrow bandwidths in the field
(spectroradiometers) need to be developed as well as integrating UV
dosimeters on agreed upon action (or safety) spectra. Such instruments
should be rugged, reliable, automatic, and reasonably inexpensive.
Developmental work on the above has been sponsored by NIOSH.

Measurements are needed to establish baseline UVR levels in nature
and industry, to establish the range of natural or present variations,
to monitor persistent changes due to various causes, and to control
exposure and enforce future regulations.

3. <u>Development and use of personal ultraviolet radiation monitors:</u>

Population studies with personal monitors of UV-B radiation (such as
the KPR (Kodak Photo-Resist) type already studied in Switzerland) are
needed to determine the fraction of daily UV dose delivered to the ground
received by persons at risk for skin cancer. The amounts of the daily UVR
dose actually received by human skin must vary greatly with occupation,
behavior, and local climatic conditions. Present knowledge of this factor
is minimal, and the lack of this knowledge seriously interferes with the
interpretation of existing data on the relationship of UVR to the develop-
ment of skin cancer and chronic skin and eye damage.

4. <u>Improvement of high intensity ultraviolet radiation sources with
narrow (monochromatic) and wide (solar simulator) spectra:</u>

One major problem in the applicator of UVR field measurement data to
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 that of skin erythema, the fine structure of the car-
cinogenesis action spectrum is not known. The primary reason for this
lack of information is the lack of high intensity, narrow band UV
sources capable of irradiating relatively large areas (e.g., even the
surface of <u>one</u> mouse). The development of high output tunable contin-
uous UV lasers, are of importance for such crucial studies. Better
high intensity, large area solar simulators, which have been designed
for space applications but presently are too expensive to use for
chronic (1-2 year) animal experiments are also urgently required.

5. <u>Gathering of epidemiologic data:</u>

Since incidence data are extremely difficult to obtain accurately,
prevalence data should be obtained at first. Areas of study should be
separated by at least 300 miles north-south over a latitude span reach-
ing beyond the most populated areas. Data should include age to first
tumor, sex, occupation, skin phenotype, and estimate of solar UV-B dose
obtained by personal dosimeters. It is of utmost importance that all
these studies be performed to the <u>same</u> protocol, so that valid compar-

isons can be made. Promising areas for such studies, in addition to the United States, are Australia (particularly Queensland), Scandinavia, and South Africa.

6. Gathering of industrial data:

Similar incidence data should be obtained in industries (e.g., welding, glass blowing, metal working, printing, etc.) where the probable (or measured) exposure to UVR is high.

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CHAPTER TWO

VISIBLE RADIATION

The visible portion of the electromagnetic spectrum (i.e., that portion which is specifically perceived by the human eye) ranges from 380 nm to 750 nm. Light may be reflected, transmitted, or absorbed by biological tissues, depending upon the wavelength and the organ involved. Although it is known that visible radiation can cause chromosomal damage (Bradley and Sharkey, 1977; Gantt et al., 1977), the available data regarding DNA damage is preliminary, and there is little information concerning mechanisms, action spectra, and dose-response relationships. There is no present evidence that exposure to visible radiation induces cancer in humans or in animals. Moreover, photoreactivation in the presence of radiation of wavelengths from 300 nm to 600 nm has been shown to repair ultraviolet (UV) induced damage to DNA, and thus to decrease or eliminate the possibility of neoplastic transformation.

Radiation in the near UV or UV-A range (320-380 nm) is one thousand to one hundred thousand times less effective in killing unpigmented microorganisms than UV-B and UV-C (<320 nm) radiation, and is a thousand times less effective in eliciting a delayed erythema response (sunburn) in normal human skin (Eisenstark, 1971). Visible radiation is even more ineffective than near UV in causing these effects.

The most efficient reactions elicited in humans by UV-A and by visible light occur in the presence of photosensitizers, or under abnormal conditions, such as those involved in immune system hypersensitivity, in which the response to a small number of photochemical events can be extreme. These reactions are called phototoxic or photoallergic responses.

Over the past few decades, a large number of drugs (e.g., chlorpromazine, griseofulvin, declamycin), topical antibacterials such as salicylanilides, cosmetic and perfume ingredients (e.g., psoralens), and chemicals inadvertently introduced systemically or topically (e.g., chlorophenols, hexachlorobenzene) have been identified as phototoxic or photoallergic agents. Colored drugs and food additives are possible photosensitizers for organs other than the skin because visible (especially red) radiation penetrates deeply into the body.

CHEMICAL AND CELLULAR EFFECTS OF VISIBLE RADIATION

The observation of DNA repair in various irradiated mutant strains of *E. coli* suggests that visible radiation in the 460 nm region can induce a variety of lesions which are traceable to DNA damage (Eisenstark, 1971). Although many such events are secondary to the formation of photoproducts in the incubation medium during irradiation, it appears that at least some of these events

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are direct effects of visible radiation on DNA, resulting in single strand breaks or alkali labile bonds. Webb and Brown (1976) have observed that these reactions are oxygen dependent, are partially repairable by excision and recombination mechanisms, and can cause growth inhibition.

Speck and co-workers (Speck and Rosenkranz, 1975; Speck et al., 1975) have shown that light (450 nm) induces base substitution mutations in *Salmonella typhimurium* and that illumination by blue light of HeLa cells in vitro and in vivo causes photodegradation of DNA in the presence of low levels of riboflavin.

Furthermore, Bradley and Sharkey (1977) have recently reported that irradiation with light induced mutagenicity as well as lethality and DNA single strand breaks in V-79 Chinese hamster lung cells. Gantt et al. (1977) have observed DNA crosslink formation in mouse cell cultures exposed to light. This light effect was not noted in human fibroblasts. It is not known at this time whether light does not form crosslinks in human cells or whether crosslinks are formed but repaired more efficiently.

In an attempt to investigate the possible direct carcinogenic effect of visible radiation on skin, Ehlers and Florian (1973) irradiated mice with 694.3 nm ruby lasers. Although much skin damage was observed, the authors were unable to induce either precancerous or cancerous skin lesions with ruby laser radiation.

INTERACTION OF VISIBLE RADIATION AND CHEMICALS

Light and certain chemical compounds can interact to man's detriment when the light causes the chemical to change into one that is more harmful. A prime example of this interaction is photochemical smog. However, exposure to light can also cause photodegradation into a harmless chemical.

Urbach et al. (1976) have described work done on photomodified chemical carcinogenesis which shows that, depending on the wavelengths of UV or visible radiation, phenanthrene carcinogens can be photodegraded into a less carcinogenic compound, can cause phototoxicity which may augment carcinogenesis, or can cause such severe local phototoxic reactions that epithelial cells are destroyed. Thus enhancement or inhibition of skin carcinogenesis may occur, depending on the carcinogen, and the radiation wavelengths and doses used.

Joseph-Bravo et al. (1976) studied the interaction of riboflavin, aflatoxin and solar simulating light in Charles River CD rats. The acute toxicity of aflatoxin to the liver was enhanced by simultaneous light or riboflavin treatment. However, chronic irradiation caused a significant decrease in aflatoxin induced liver cancer, possibly by photodecomposition of aflatoxin in the presence of riboflavin and light into a less carcinogenic metabolite.

Finally, photochemotherapy using visible radiation and photoactive chemicals has been investigated. Dougherty and co-workers (Dougherty, 1974; Dougherty et al., 1976) report the inactivation of mouse mammary carcinoma cells by hematoporphyrin derivative and red light, and retardation in growth of mouse mammary carcinoma by exposure of the tumor to light (>488 nm) after

preferential incorporation of fluorescein. Diamond, Granelli,and associates (Diamond et al., 1972; Granelli et al., 1975) found that the administration of hematoporphyrin followed by exposure to white light destroyed glioma cells in culture and gliomas growing subcutaneously in rats.

RECOMMENDATIONS FOR FURTHER STUDIES

1. The information regarding DNA damage by visible radiation is very preliminary. Detailed studies of such effects, particularly an attempt to delineate an action spectrum for such effects, are badly needed.

2. There is evidence that many chemicals which are widely dispersed through the environment are photochemically altered by UV-A and visible radiation. Studies are needed of the photochemistry of a wide variety of compounds and of the carcinogenic, and/or mutagenic, effects of the photoproducts.

3. The possible photobiologic (augmenting or inhibiting) effect of light on photoproducts defined above should be investigated.

4. There is evidence that photochemistry of normal biologic constituents occurs in intact organisms (e.g., bilirubin degradation in infants). The effect of such photochemical action and possible interaction with other drugs or chemicals (e.g., aflatoxin) in vivo under the influence of light, as well as the action spectra of such effects, should be studied.

5. Indirect effects of light have also been noted. The periodic fluctuations of visible and near-UV radiation which occur with the regular light-dark cycles in nature, and the lengthening and shortening of light periods due to seasonal changes are both known to critically affect biological phenomena. The phenomenon of photo-periodism was originally studied in flowering seasonal plants. However, many functions in animals and man are also affected by changes in the light-dark period (Wolfson, 1964; Sisson, 1977). The majority of such light-dark effects are based on circadian (day-length) cycles, and are controlled by the pineal system, which can be affected either directly by the transmission of light to the pineal gland or indirectly via effects on the optic nerve pathway. The prime target is the reproductive (estrus) cycle. Effects on human growth hormone have also been reported. No specific effects on carcinogenesis are known, and little is known about the action spectra or mechanisms of the known photo-periodic effects. These also need to be studied.

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CHAPTER THREE

INFRARED RADIATION

Infrared radiation (IR) comprises that band of the electromagnetic spectrum between 760 nm and 1 mm. It is absorbed by many substances and its principal biological effect is due to hyperthermia which can be lethal to cells but is not normally mutagenic. Although there is no evidence that IR per se can cause cancer, it may be implicated in carcinogenesis induced primarily by other agents.

Henry (1946) for instance, reports an increased incidence of skin cancer in glass workers, steel mill workers, smiths, firemen and other individuals occupationally exposed to heat. However, it is possible that this is due not to IR radiation alone but to associated exposure to ultraviolet radiation, soot, and tar.

Exposure to heat has also been associated with an increased incidence of squamous cell carcinoma of the lower extremities in Irish women (Peterkin, 1955). These latter women spend much time sitting in front of peat fires and as a result, develop erythema *ab igne*, a condition which is presumably related to chronic exposure to very hot fires and in the present case, sometimes complicated by cancer. Again, however, peat fires also emit ultraviolet radiation and chemical carcinogens. The above mentioned carcinomas may thus result from chronic exposure to ultraviolet radiation and chemicals rather than IR.

In a related vein, Lawrence (1952) has observed the rare occurrence of squamous cell carcinoma in old burn scars (Marjolin ulcers). Whether there is a causal relationship between the two is not yet known. Preliminary results by Owens (1977) also indicate that mice irradiated with UV-B develop more skin tumors at a faster rate when they are kept in a heated environment (38-39°C) than at normal room temperature. However, more quantitative study is required before any firm conclusions may be adduced.

Similar conclusions may be made regarding possible synergistic effects between IR and chemical carcinogens. In addition to the above data, Hahn et al. (1976) have shown that hyperthermia (43°C) increases mammalian cell membrane permeability and enhances the effects of adriamycin and other cytotoxic agents. Danilenko et al. (1974) have shown that the presumably thermal effects of 37,000 MHz microwave radiation have a synergistic effect with chemical mutagens such as N-nitroso-N-methylurea and N-methyl-N-nitro-N-guanidine. These results suggest that hyperthermia -- and by implication, exposure to IR -- might also potentiate the effects of chemical carcinogens. Thus, although the Kangri cancer in India is thought to result from the custom of wearing a charcoal brazier next to the skin to produce warmth (Mulay, 1963), this cancer

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more likely results from chemicals in the accompanying fumes than from heat.

Beyond this, little evidence, either direct or indirect, has been found to link exposure to IR radiation and carcinogenesis. However, due to the serious consequences of underestimating the risk of cancer, further investigation should be performed.

RECOMMENDATIONS FOR FURTHER STUDIES

Given the paucity of data regarding the ability of IR to enhance already carcinogenic or potentially carcinogenic situations, only three recommendations are possible at present:

1. The only currently known carcinogenic augmenting effect of IR relates to skin photocarcinogenesis by UV-B. Elucidation of the corresponding dose-response function would provide positive confirmation of this effect.

2. Epidemiologic studies of the incidence of cancer at all sites in workers chronically exposed to heat stress should be performed.

3. Rigorous quantitative studies of the interaction of heat and chemical carcinogens are needed to explore the possible synergism between the two.

In all, much more quantitative study is required to ascertain the margin of safety currently afforded those persons occupationally exposed to IR.

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APPENDIX A. MEASUREMENT UNITS

MKS units of measurement are employed throughout the present volume. Radiant energy is expressed in joules (J), and radiant exposure (dose) given in J/m^2. Irradiance (exposure dose rate) is measured in watts/m^2 (W/m^2). Conversion factors for other commonly used units of measurement are listed below:

RADIANT ENERGY

	joule	mJ	erg	W·sec	μW·sec
1 joule =	1	10^3	10^7	1	10^6
1 mJ =	10^{-3}	1	10^4	10^{-3}	10^3
1 erg =	10^{-7}	10^{-4}	1	10^{-7}	0.1
1 W·sec =	1	10^3	10^7	1	10^6
1 μW·sec =	10^{-6}	10^{-3}	10	10^{-6}	1

RADIANT EXPOSURE

$$
\begin{aligned}
1\ J/m^2 &= &= 10^{-4}\ J/cm^2 &= 10^{-6}\ J/mm^2 \\
&= 10^3\ mJ/m^2 &= 0.1\ mJ/cm^2 &= 10^{-3}\ mJ/mm^2 \\
&= 10^7\ ergs/m^2 &= 10^3\ ergs/cm^2 &= 10\ ergs/mm^2 \\
&= 1\ Wsec/m^2 &= 10^{-4}\ Wsec/cm^2 &= 10^{-6}\ Wsec/mm^2 \\
&= 1\ \mu Wsec/m^2 &= 10^2\ \mu Wsec/cm^2 &= 1\ \mu Wsec/mm^2
\end{aligned}
$$

IRRADIANCE

$$
\begin{aligned}
1\ W/m^2 &= &= 10^{-4}\ W/cm^2 &= 10^{-6}\ W/mm^2 \\
&= 10^6\ \mu W/m^2 &= 10^2\ \mu W/cm^2 &= 1\ \mu W/mm^2 \\
&= 1\ J/m^2\ sec &= 10^{-4}\ J/cm^2 \cdot sec &= 10^{-6}\ J/mm^2 \cdot sec \\
&= 10^3\ mJ/m^2 \cdot sec &= 0.1\ mJ/cm^2 \cdot sec &= 10^{-3}\ mJ/mm^2 \cdot sec \\
&= 10^7\ erg/m^2 sec &= 10^3\ erg/cm^2 sec &= 10\ erg/mm^2 \cdot sec
\end{aligned}
$$

APPENDIX B.   GLOSSARY OF TERMS

Action Spectrum –   The range of wavelengths in which biological effectiveness can be defined.

Biological Effectiveness –   The measure of the effectiveness of radiation at different wavelengths (within a defined range or action spectrum) in carrying out a specific reproducible photobiological process.

Irradiance –   The unit of radiant power per unit area (watt/m^2) is the irradiance.

MED –   Minimal erythema dose.

Radiant Exposure (Dose) –   The unit of radiant energy per unit area (joules/m^2).

Relative Biological Effectiveness –   The experimentally determined ratio of an absorbed dose of radiation to an absorbed dose of a reference radiation required to produce an identical biological effect in a particular organism or tissue.

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