POSSIBLE HEALTH EFFECTS OF INCREASED EXPOSURE TO ULTRAVIOLET RADIATION

Elizabeth M. Sloss, Thanne P. Rose

July 1985

N-2330-EPA

Prepared for

The U.S. Environmental Protection Agency
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Among the possible effects of stratospheric ozone depletion, perhaps the most important concerns are the implications of such depletion for the health of human beings. Because a reduction in stratospheric ozone would increase the amount of ultraviolet radiation reaching the earth's surface, human diseases that might be influenced by increased exposure to ultraviolet radiation (UV) are important to consider. This Note discusses the characteristics of several types of skin cancer and other diseases believed to be related to sunlight. The information in the Note is based on a survey of the literature related to these diseases. The primary aim is, by translating into layman's language information available in the scientific literature, to educate the reader regarding the natural history and consequences of UV-related diseases. This information lays the groundwork for further research on the economic costs of these diseases in estimating the impact of stratospheric ozone depletion.

The Note was prepared as part of Rand research, supported by the U.S. Environmental Protection Agency, to examine possible risks associated with the potential depletion of stratospheric ozone. The projected use, emissions, and banks of potential ozone-depleting substances have also been investigated as part of this research.
ACKNOWLEDGMENTS

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I. INTRODUCTION AND BACKGROUND

Among the possible consequences of stratospheric ozone depletion, perhaps the most important consequences are the health implications for human beings. Increased exposure to ultraviolet (UV) radiation may cause or promote the development of skin cancers. That and other diseases that may be affected by sunlight constitute a policy concern for environmental policymakers. However, very little information about these diseases is accessible to policymakers, policy analysts, or the general public. How serious are these diseases? Do they occur frequently or infrequently? What is their relationship to sunlight? How can we recognize these diseases and how do they progress? And what methods are available for treatment?

This Note addresses these questions, with a detailed discussion of several types of skin cancers and a brief description of other diseases believed to be related to sunlight. Our primary goal is to translate into layman's language information already available in the scientific literature; most of the Note, then, is not based on original research. Rather, it attempts to educate the reader on what is known about the natural history and consequences of UV-related disease, especially skin cancers. It also discusses treatment methods in some detail, and provides flow charts of possible patient contacts with the medical care system. As a result, this analysis should prove useful for structuring further research on the economic costs of these diseases in estimating the impact of potential stratospheric ozone depletion.

Ozone, one component of the earth's stratosphere, shields the surface of the earth from short-wavelength ultraviolet solar radiation by absorbing it. Because solar radiation from this part of the ultraviolet spectrum can be harmful to plant and animal life, the stability of the so-called ozone layer has become an issue of great concern. The concentration of ozone in the stratosphere is thought to remain constant under natural conditions, as a result of continuous chemical reactions that form and decompose the ozone molecule. In the early 1970's, concern arose regarding the possible effects of human
activities on the balance between formation and decomposition of ozone. It was hypothesized that release of certain chemicals into the atmosphere might shift the equilibrium and result in a decrease in the ozone concentration in the stratosphere. A reduction in stratospheric ozone would increase the amount of ultraviolet radiation reaching the surface of the earth. In the last few years, however, there has been conflicting evidence indicating that the ozone concentration may be either decreasing or increasing. A complete discussion of the issues related to predicting the future of the ozone layer can be found in the National Academy of Sciences report series on this topic, the most recent of which was published in 1984 (NRC, 1984).

If the ozone concentration in the stratosphere decreases, the amount of solar radiation in the ultraviolet-B (UV-B) spectrum reaching the surface of the earth will increase. The effects of increased exposure to UV-B have been studied in humans and other animals, marine life, and plants. Although all plants and animals are dependent upon solar radiation as a source of energy, some effects of solar radiation are harmful to humans and other living organisms. Exposure to ultraviolet radiation has been associated with numerous skin diseases in man and other animals, and can impair the development and growth of certain plants and marine life.

Policymakers considering the implications of changes in stratospheric ozone must be informed about the possible biologic effects. Although currently there is no conclusive evidence that ozone will decrease, the possible effects on human health are important in any decisionmaking process related to regulation of chemicals that may affect the ozone concentration. Many animal and human studies strongly support the hypothesis that exposure to solar UV-B can cause nonmelanoma skin cancer. Projections of the expected increase in cases of nonmelanoma skin cancer have been made for different increases in UV-B exposure (Fears and Scotto, 1983; Rundel and Nachtweg, 1983). Section II of this Note presents a detailed discussion of the progression, risk factors, and treatment of nonmelanoma skin cancer. Another more deadly form of skin cancer, malignant melanoma, is also thought to be related to sunlight. Although the evidence supporting the hypothesis that UV-B causes melanoma is much weaker than for nonmelanoma skin cancer,
scientists continue to hypothesize that melanoma is probably related in some way to ultraviolet radiation exposure. Melanoma skin cancers are the subject of Section III of this Note. Section IV briefly discusses a variety of other skin diseases with the goal of providing information regarding the nature of the diseases and their relationship to ultraviolet radiation. Finally, a glossary of terms is provided at the end of the text to assist the reader in understanding this Note.
II. NONMELANOMA SKIN CANCER

Nonmelanoma skin cancer is the most common cancer in humans. Between 400,000 and 500,000 cases of nonmelanoma skin cancer are diagnosed in the United States each year (Scotto et al., 1983). Most cases of nonmelanoma skin cancer are treated and cured. According to Scotto et al. (1983), one percent of those with nonmelanoma skin cancer develop metastases (the spread of the cancer from the original site to other body organs) and subsequently die from the disease. The two types of nonmelanoma skin cancer, basal cell carcinoma and squamous cell carcinoma, are distinguishable from one another by their clinical appearance and pattern of growth at the microscopic level.

The incidence rates by age and sex for white populations in selected areas of the United States, 1977-1978, are shown in Table 1 for nonmelanoma skin cancer. The two most notable patterns in these rates are the marked increase in incidence with increasing age and the higher rates among males. The rate of skin cancer among white males 75 to 84 years of age is more than ten times the rate among white males 35 to 44 years of age and more than twice the rate among white females 75 to 84 years of age. The incidence rates for basal cell carcinoma are generally between 4 and 5 times those for squamous cell carcinoma among white populations.

The death rates due to skin cancer other than melanoma during 1979 are shown in Table 2 for the white population of the United States. The average annual mortality rates by age and sex for 1950-1969 are also shown for comparison. The increase in mortality with age is more dramatic than incidence; however, the magnitudes of the mortality rates are less than 1 percent of the incidence rates. The mortality rates for males are at least twice as high as the female mortality rates in the upper age groups. The 1979 mortality rates are considerably lower than those for 1950-1969. This difference may reflect an actual decrease in

1Some of these deaths may be attributable to causes other than squamous cell carcinoma or basal cell carcinoma, because deaths resulting from other rare skin diseases are coded into the same category as deaths due to nonmelanoma skin cancer.
Table 1
ANNUAL INCIDENCE RATES OF NONMELANOMA SKIN CANCER AMONG SELECTED U.S. WHITE POPULATIONS DURING 1977-1978, BY AGE, SEX, AND TYPE (PER 100,000 PERSONS)

<table>
<thead>
<tr>
<th>Age(years)</th>
<th>Basal Cell Males</th>
<th>Basal Cell Females</th>
<th>Squamous Cell Males</th>
<th>Squamous Cell Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>0.6</td>
<td>0.6</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>15-24</td>
<td>3.6</td>
<td>6.5</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>25-34</td>
<td>33.9</td>
<td>34.9</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>35-44</td>
<td>138.7</td>
<td>120.8</td>
<td>18.7</td>
<td>9.4</td>
</tr>
<tr>
<td>45-54</td>
<td>370.8</td>
<td>259.8</td>
<td>77.0</td>
<td>26.7</td>
</tr>
<tr>
<td>55-64</td>
<td>671.5</td>
<td>397.4</td>
<td>170.6</td>
<td>56.8</td>
</tr>
<tr>
<td>65-74</td>
<td>1084.2</td>
<td>586.7</td>
<td>300.4</td>
<td>102.6</td>
</tr>
<tr>
<td>75-84</td>
<td>1475.4</td>
<td>765.6</td>
<td>517.4</td>
<td>183.8</td>
</tr>
<tr>
<td>85 and over</td>
<td>1528.2</td>
<td>780.7</td>
<td>577.1</td>
<td>278.1</td>
</tr>
</tbody>
</table>

SOURCE: Scotto et al., 1983.
NOTE: Rates are based on data for Seattle (King County only), Minneapolis-St. Paul SMSA, Detroit SMSA, the state of Utah, San Francisco-Oakland SMSA, Atlanta SMSA, the metro area of New Orleans, and the state of New Mexico.

Mortality due to earlier diagnosis and treatment; in addition, part of this difference may reflect a change in diagnostic practices or coding rules between the two time periods (Elwood and Lee, 1974).²

As noted above, there are two major types of nonmelanoma skin cancers, squamous cell carcinoma and basal cell carcinoma. The progression of the disease differs in these two types of skin cancers. Using simple flow diagrams to structure the analysis, the following sections discuss the progression and treatment of these diseases.

²If some proportion of individuals dying from melanoma were misclassified as dying from nonmelanoma skin cancer, the death rate due to the latter cause would be artificially inflated. Misclassification might occur at the time of diagnosis of the illness by the attending physician or coroner, or at the point at which the death is assigned to a precoded cause-of-death category by a nosologist or coding clerk.
Table 2
ANNUAL DEATH RATES DUE TO SKIN CANCER OTHER THAN MELANOMA AMONG U.S. WHITES DURING 1979 AND 1950-1969, BY AGE AND SEX (PER 100,000 PERSONS)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5-9</td>
<td>---</td>
<td>0.0</td>
<td>---</td>
<td>0.0</td>
</tr>
<tr>
<td>10-14</td>
<td>---</td>
<td>0.0</td>
<td>---</td>
<td>0.0</td>
</tr>
<tr>
<td>15-19</td>
<td>---</td>
<td>0.0</td>
<td>---</td>
<td>0.0</td>
</tr>
<tr>
<td>20-24</td>
<td>---</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>25-29</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>30-34</td>
<td>---</td>
<td>0.1</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>35-39</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>40-44</td>
<td>0.2</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>45-49</td>
<td>0.5</td>
<td>0.7</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>50-54</td>
<td>1.0</td>
<td>1.3</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>55-59</td>
<td>1.5</td>
<td>2.3</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>60-64</td>
<td>2.0</td>
<td>3.5</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>65-69</td>
<td>3.3</td>
<td>5.0</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>70-74</td>
<td>5.3</td>
<td>8.2</td>
<td>1.5</td>
<td>3.4</td>
</tr>
<tr>
<td>75-79</td>
<td>7.7</td>
<td>17.5</td>
<td>2.9</td>
<td>8.1</td>
</tr>
<tr>
<td>80-84</td>
<td>11.9</td>
<td>17.5</td>
<td>3.6</td>
<td>8.1</td>
</tr>
<tr>
<td>85 and over</td>
<td>21.7</td>
<td>46.8</td>
<td>9.4</td>
<td>28.4</td>
</tr>
</tbody>
</table>


NOTES: Rates in the table include all deaths coded as Other Malignant Neoplasms of Skin (category number 173) under the Ninth Revision International Classification of Diseases.
Dashes indicate that no deaths due to nonmelanoma skin cancer occurred in this age group during 1979.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma is considered a more serious disease than basal cell carcinoma primarily because it is more likely to spread to other body organs and possibly result in death. About 20 percent of newly diagnosed cases of nonmelanoma skin cancer are squamous cell carcinoma (Scotto et al., 1983); this means there are between 80,000 and 100,000 new cases of squamous cell carcinoma diagnosed in the United
States each year. Most squamous cell carcinoma occurs on parts of the body most frequently exposed to sunlight. About 75 percent of cases in males, and 60 percent of cases in females, are located on the skin of the face, head, and neck. Most of the remaining squamous cell carcinomas occur on the arms and hands (18 percent of cases in males and 26 percent of cases in females) (Scotto et al., 1983).

The different stages in the development of squamous cell carcinoma and the treatment-seeking behavior of the patient are described here and illustrated in Figure 1. This figure provides a detailed flow chart of the progression of squamous cell carcinoma and its treatment.

Some cases of squamous cell carcinoma are preceded by a precancerous skin condition called actinic keratosis. (The term actinic simply means the condition is caused by the sun.) Actinic keratosis may not be recognized by the patient as unusual or abnormal, especially since it develops gradually over a long period of time. If the patient notices it, he may decide to consult a physician. The physician may treat the condition in order to prevent the possibility of progression to squamous cell carcinoma in situ. Otherwise, the physician may choose not to treat the disease, but rather to check on the condition periodically for evidence of progression. Actinic keratosis is treated by cryosurgery, topical chemotherapy, or excision when squamous cell carcinoma is suspected. If the patient does not recognize the condition or chooses not to consult a physician, the actinic keratosis remains untreated. The untreated condition may progress to the next stage as squamous cell carcinoma in situ.

To clarify the discussion of different types and stages of the skin cancer, Figure 2 provides a simple illustration of human skin. the outermost layer of skin (towards the top of the figure) is known as the epidermis and the inner layer is called the dermis. Between the epidermal and dermal layers lie pigment-producing cells called melanocytes. Melanocytes are responsible for manufacturing and distributing the pigment melanin. This activity determines the fairness (or color) of an individual's skin. More important, melanocytes provide the mechanism through which human skin is protected from sunlight. Different types and stages of skin cancer are distinguished by the pattern of growth in the layers of skin shown in Figure 2. Like many
Fig. 1 -- Progression of disease and clinical contacts related to squamous cell carcinoma
Fig. 1 -- (Continued)
forms of cancer, squamous cell carcinoma develops gradually in most
cases over a period of many years. When the disease is confined to the
epidermis, it is known as squamous cell carcinoma \textit{in situ}. Once the
malignant cells have invaded the dermis beneath the epidermal layer, the
tumor is an \textit{invasive squamous cell carcinoma}.

As Figure 1 indicates, squamous cell carcinoma \textit{in situ} may appear
on normal skin as well as on sun-damaged skin. As with actinic
keratoses, the patient may visit a physician; however, unlike actinic
keratoses, squamous cell carcinoma must be treated. The condition may
be treated with any one of five therapies: cryosurgery, excision,
electrosurgery, radiation therapy, or Mohs' chemosurgery. If the
patient never consults a physician about the growth, the \textit{in situ}
squamous cell carcinoma will remain confined to the epidermis, or it
will progress to the invasive stage of squamous cell carcinoma.

At the time of diagnosis, the squamous cell carcinoma may have
already progressed past the \textit{in situ} stage to the invasive stage. As
with the previous stages of this disease, the patient may consult a
physician. If presented with a squamous cell carcinoma, the physician
will invariably treat it. Some physicians will choose to biopsy the
lesion before treatment to allow better judgment about the method of
treatment. The tumor characteristics can only be determined from a
histologic specimen obtained through biopsy. Even if the tumor is
treated, it may recur at exactly the same place and have to be treated
again. In the case of treatment and recurrence, or no treatment, a
small proportion of squamous cell carcinomas metastasize, i.e., the
malignant cells detach themselves from the tumor, travel to another part
of the body, and a second malignancy arises there. The disease is life-
threatening once metastasis occurs. Treatment of metastatic disease may
require surgery, chemotherapy, and/or radiation therapy.
Fig. 2 -- A cross-section of human skin
Clinical Manifestations

Actinic keratosis is a skin condition characterized by changes in cells of the outer layer of skin (epidermis) caused by chronic exposure to the sun. An actinic keratosis first appears as a small, scaly patch of skin, yellow or brown in color. In most cases, more than one actinic keratosis is present on an individual with the condition. They occur most often on the backs of hands, forearms, and face, and are usually accompanied by sun-induced degeneration of the surrounding skin (Sanderson et al., 1979).

If actinic keratosis transforms into squamous cell carcinoma, the latency period for the transition to skin cancer is usually at least ten years. The transition may be shorter in patients undergoing immunosuppressive therapy as part of treatment for other diseases. The cancerous skin tumor arising from an actinic keratosis is almost always a slow-growing tumor with little likelihood of spreading to other body organs. Graham and Helwig (1966) report that among 570 patients with actinic keratosis, about 12 percent progressed into in situ or invasive squamous cell carcinoma. Others report that a small proportion of actinic keratoses become malignant and some keratoses may disappear spontaneously (Sanderson et al., 1979).

The first sign of a squamous cell carcinoma is a small, firm, reddish bump, with indistinct edges. The surface may be smooth or rough, and when present on damaged skin, usually exhibits scaling. As the cancer grows, the tumor remains firm, increasing in both diameter and elevation. Breakdown of the tissue may occur in the center of the tumor. The ulcerated surface may bleed easily or may be crusted, with hard, elevated edges (Stoll, 1979).

The natural history of squamous cell carcinoma varies greatly, ranging from a slowly growing, locally contained tumor to a rapidly growing, widely invasive tumor likely to spread to other organs. In general, invasive squamous cell carcinoma arising from carcinoma in situ or actinic keratosis is less likely to spread than that arising from apparently normal skin (Stoll, 1979).
The incidence of metastasis reported in the literature varies greatly for squamous cell carcinoma, from none to more than 50 percent depending upon the source and type of cases included in the study (Stoll, 1979). The likelihood of metastasis seems to be related to the cause, location, and structural characteristics of the tumor. As mentioned above, squamous cell carcinomas arising from skin showing signs of sun damage are thought to spread to other organs infrequently, while those arising on skin with radiation damage, or in scars, ulcers, or sinuses have been reported to be more likely to spread. In addition, squamous cell carcinoma on certain parts of the body is also more likely to spread; these high-risk sites include the lip, penis, vulva, and anus (Stoll, 1979).

Pathology

In addition to changes that can be observed with the naked eye, there are many changes that occur at the microscopic level in actinic keratosis and squamous cell carcinoma. The edges of the actinic keratosis are well defined at the cellular level, with the abnormal cells quite different in appearance from normal skin cells. The abnormal cells grow entirely within the epidermal layer of skin. A thickening of the epidermal layer of the skin occurs as a result of abnormal increased division of skin cells. The abnormal cells mature to some degree to form a scale of varying thickness on the surface of the skin. The basal cells within the actinic keratosis exhibit unusual structures varying in size and shape (Sanderson et al., 1979); dividing cells are frequent.

The cells in squamous cell carcinoma in-situ lack normal cellular organization and are abnormal in appearance with considerable variation in size and shape throughout the epidermis. Their cell nuclei are larger and stain more deeply than those in normal cells (Stoll, 1979). Invasive squamous cell carcinoma consists of malignant epidermal cells invading the dermis. The invading cells may be organized as long, slender arms or broad masses. The malignant cells do not have a uniform appearance; this lack of uniformity is referred to as the degree of differentiation. A tumor with a high proportion of undifferentiated
(abnormal) cells is considered "aggressive." This characteristic of a
tumor is commonly classified as either well, moderately, or poorly
differentiated with poorly differentiated being the most aggressive.
Invasive squamous cell that is poorly differentiated shows an increasing
proportion of abnormal cells, with enlarged nuclei, abnormal cell
division, and poor cohesion between cells (Stoll, 1979), resulting in
the loss of function which is characteristic of normal skin.

BASAL CELL CARCINOMA

About 80 percent of nonmelanoma skin cancer cases are basal cell
carcinoma (Scotto et al., 1983), meaning between 320,000 and 400,000
cases of basal cell carcinoma are newly diagnosed in the United States
each year. Basal cell carcinoma occurs largely on body sites frequently
exposed to sunlight. A higher percentage of basal cell carcinoma occurs
on the face, head, or neck than with squamous cell carcinoma; over 81
percent of basal cell carcinomas in males, and over 84 percent in
females are located in these sites. Most of the other basal cell tumors
occur on the trunk portion of the body (12 percent in males and 9
percent in females) (Scotto et al., 1983).

The possible interactions between the patient and the physician
during the diagnosis and treatment of basal cell carcinoma are depicted
in Figure 3. The general flow of the diagram is similar to Figure 1 for
squamous cell carcinoma. The appearance of a basal cell carcinoma may
prompt a patient to seek the assistance of a physician. In most cases,
the tumor will be treated, with or without a preliminary biopsy. A
tissue sample is always submitted for histologic examination. If the
tumor recurs, it will have to be retreated. If the basal cell tumor is
not treated initially or following recurrence, the malignancy may spread
to other organs, i.e., metastasize. When the metastasis is detected, a
more systemic mode of treatment is employed, possibly requiring surgery,
chemotherapy, and/or radiation therapy. Metastatic basal cell
carcinoma, although rare, may result in death.
Fig. 3 -- Progression of disease and clinical contacts related to basal cell carcinoma
Clinical Manifestations

Most basal cell carcinomas fall into three main categories based on clinical features. The first and most common basal cell tumor is the noduloulcerative type. This form of tumor is characteristically a well-defined nodule or thickened flat area on the skin. The skin covering the tumor may scale and crust. The tumor may turn into an open sore late in its development, often healing and re-opening several times before becoming permanently unable to heal. As the tumor increases in size, its surface usually becomes more irregular. The tumor may be skin-colored or pink or red, sometimes exhibiting an irregular distribution of brown or black pigment. The edges of a basal cell carcinoma often exhibit spidery red lines and the tumor may appear translucent or pearly. The majority of nodular basal cell tumors arise on the head and neck, particularly on the upper central part of the face (Sanderson et al., 1979).

A second and less common basal cell carcinoma is the superficial type. The surface of the tumor is flat, covered with scaly skin, and bounded by a slightly elevated string-like border which is irregular in shape. The skin may be crusted or eroded, and often is pigmented. This form of basal cell carcinoma occurs most often on the trunk (Sanderson et al., 1979).

The third and least common of these three forms of basal cell carcinoma is the morpheaform tumor. This tumor appears as a thickening of the skin with indefinite borders. The smooth surface may be slightly elevated or slightly depressed relative to normal skin, and is characteristically yellowish in color. Ulceration of the tumor surface is uncommon. This tumor arises almost exclusively on the face (Sanderson et al., 1979).

Two other less common types of basal cell carcinoma encountered in the clinic and literature are the fibroepithelioma and pigmented varieties. The fibroepithelioma of Pinkus looks like a pink, nonpigmented, seborrheic keratosis and arises most often on the skin of the lower back and abdomen (Popkin and DeFeo, 1976). Pigmented basal cell carcinomas are uncommon and may be mistaken for a malignant melanoma, but do not differ markedly in their degree of malignancy from other forms of basal cell carcinomas (Van Scott, 1979).
Pathology

Basal cell carcinomas occur as a result of a defect resulting in the inability of the skin cell to mature. As part of normal skin metabolism, the cells of the epidermal layer of the skin arise from the layer of basal cells within the epidermis. Normally, cells of the epidermis are gradually displaced upward by the new cells created by division of the basal cells. As the epidermal cells migrate from the bottom of the epidermis toward the skin's surface, they mature in a process known as keratinization. Once they reach the surface, they are eventually shed. The tumor defect interrupts this maturation, resulting in an accumulation of basal cells that form a tumor (Van Scott, 1979).

The first sign of a basal cell tumor at the microscopic level is an invasion of the dermal layer of skin by basal cells. The basal cells grow into the dermis showing various degrees of differentiation. The basal cell carcinoma microscopically appears as aggregates of tumor cells retracted from a well-organized support structure called the stroma. Experimental removal of the epithelial portion of the tumor without the stroma has been shown to result in the lack of growth of the tumor cells. This dependence on the stroma provides at least a partial explanation for the infrequent spread of basal cell carcinomas to other organs (Sanderson et al., 1979).

RISK FACTORS FOR NONMELANOMA SKIN CANCER

Several personal characteristics predispose persons to develop skin cancer. Light-skinned individuals, i.e., those with little pigmentation, are at a much higher risk than persons with darker skin color (Scotto and Fraumeni, 1982). Age and sex are also good indicators of a person's risk of developing skin cancer. Nonmelanoma skin cancer incidence rates increase steadily with increasing age; males develop skin cancer at a rate approximately twice that of females (Scotto and Fraumeni, 1982). Certain health conditions also increase the risk of skin cancer. Skin damaged from the sun, chemicals, or ionizing radiation is more susceptible to squamous cell carcinoma. Several genetic conditions also greatly increase individual susceptibility of skin cancer. Among these are the nevoid basal cell carcinoma syndrome,
xeroderma pigmentosum, and albinism. Persons on immunosuppressive therapy also appear to experience a higher incidence of squamous cell carcinoma. A more complete discussion of risk factors is given in Scotto and Fraumeni (1982).

The evidence supporting ultraviolet radiation as a cause of nonmelanoma skin cancer is based on several observations. First, skin cancers tend to arise on the skin surfaces exposed to the sun (Scotto et al., 1983). Second, occupational groups exposed to sunlight exhibit high rates of skin cancer (Beral and Robinson, 1981). Third, skin cancer rates increase with decreasing distance from the equator (Fears and Scotto, 1983; Elwood et al., 1974). Fourth, dark pigmentation of the skin protects against sun damage and lower incidence rates of skin cancer have been observed among dark-skinned people (Scotto et al., 1983). Fifth, persons exhibiting photosensitivity due to certain genetic diseases are highly susceptible to skin cancers on sun-exposed skin (Stenback, 1982). Sixth, experiments on animals have been successful in inducing nonmelanoma skin cancers following repeated UV exposure, especially in the UV-B wavelengths (Forbes et al., 1981; Strickland et al., 1979).

Three hypotheses have been suggested to explain at least part of the carcinogenic (cancer-causing) effect of sunlight on human skin. These include the:

- DNA hypothesis
- Immunologic suppression hypothesis
- Prostaglandins hypothesis

The first hypothesis is based on experimental studies which show structural changes in DNA following exposure to ultraviolet radiation. These alterations in cellular DNA may result in a change in the structure and function of the skin cell, and ultimately may cause the growth of a tumor (Parrish et al., 1979). Although skin cells are capable of repairing some damage to DNA (Setlow and Carrier, 1964; Rupp and Howard-Flanders, 1968; Sutherland et al., 1974), it has been suggested that the skin cells of persons at high risk of skin cancer may have repair mechanisms that are defective in some way (Robbins, 1978).
The second hypothesis concerns the effect of ultraviolet radiation on the immunologic resistance of the host to tumor formation. Exposure of animals to ultraviolet radiation results in profound changes in their immune response to skin tumors caused by ultraviolet light. UV-induced tumors transplanted into experimental animals are rejected routinely by the recipient animals; the tumors thrive, however, in animals that have been exposed to UV (Kripke and Fisher, 1978). One explanation of this observation is that exposure to ultraviolet radiation may stimulate the formation of cells which prevent the rejection of UV-induced tumors by mammalian species (Fisher, 1978). A recent article (DeFabo and Noonan, 1983) has suggested that a compound in mammalian skin, acting as a photoreceptor, may mediate the suppression of the protective immune response following exposure to UV, indicating that the compound may be important in the induction of UV-induced skin cancers.

The third hypothesis suggests that substances in human skin called prostaglandins may protect against nonmelanoma skin cancer. Exposure of human skin to ultraviolet light reportedly increases the production of smooth muscle contracting agents (Greaves and Sondergaard, 1970) called prostaglandins (Greaves, 1978). Increased levels of prostaglandin may decrease the growth rate of human skin cells (Greaves, 1978). Because cells are more susceptible to mutagenic effects while they are actively dividing, decreasing the rate of cellular division may result in decreased susceptibility of the skin cells to the mutagenic effect of UV radiation. For this reason, it has been suggested that prostaglandins may protect against the mutagenic effect of ultraviolet radiation on skin cells (Greaves, 1978). Much experimental work is needed, however, before the theoretical basis of this proposed mechanism for photocarcinogenesis is substantiated.

Several environmental factors besides ultraviolet radiation have been linked to an increased risk of skin cancer. The first among these is ionizing radiation. The causal relationship between skin cancer and ionizing radiation is supported by epidemiologic evidence (Martin et al., 1970) as well as data from experimental animal studies (National Research Council, 1980). Exposure to certain chemicals has also been linked to nonmelanoma skin cancer; these include the polycyclic aromatic
hydrocarbons (Everall and Dowd, 1978), oral intake of arsenic (IARC, 1980), and 8-methoxy-psoralen-photochemotherapy (known as PUVA therapy) used in the treatment of psoriasis (Stern et al., 1979). Reports have also been published regarding the increased occurrence of squamous cell carcinoma on damaged skin. Ulcers, burns, scars, chronically infected skin, and wounds have been found to predispose to the development of squamous cell carcinoma (Malik et al., 1974; Fleming et al., 1975; Camain et al., 1972).

TREATMENT OF NONMELANOMA SKIN CANCER

If stratospheric ozone depletion increases the exposure of human beings to ultraviolet radiation, one consequence might be an increase in the resources required to treat nonmelanoma skin cancer. The economic costs of this treatment could be significant and represent a potential benefit of policy actions aimed at preventing ozone depletion. This section identifies possible treatment strategies for nonmelanoma skin cancers and for actinic keratosis. Based on the treatment systems described below, future research might estimate the direct costs of any UV-induced increases in nonmelanoma skin cancer incidence.

Figures 4 through 8 summarize the therapeutic strategies a physician might choose to treat nonmelanoma skin cancer. In effect, these figures expand parts of the flow diagrams in Figures 1 and 3 to allow a more detailed look at the type of treatment.

As noted above, five methods are commonly used in the treatment of squamous cell and basal cell carcinoma. These treatments include: electrosurgery, excision, radiation therapy, Mohs' chemosurgery, and cryosurgery. Two important general considerations in the choice of a treatment method are the general type and size of the tumor. Figures 4 through 8 indicate how these characteristics alter treatment decisions. The author of the article on which these figures are based (Albright, 1982) describes these diagrams as "guidelines to aid physicians involved in skin cancer therapy in their efforts to try to select the best method of treatment for each specific skin cancer." He emphasizes, however, that they are "only relative guidelines," to be used in conjunction with other information, most notably the location of the skin cancer and the age of the patient. For a more complete discussion, the reader is referred to the article by Albright (1982).
Figures 4 and 5 summarize likely treatment methods for squamous cell carcinoma, distinguishing between well-differentiated and pseudoglandular tumors, and tumors that are moderately or poorly differentiated. As mentioned above, the degree of differentiation of a tumor is thought to be related to its "degree of malignancy," with poorly differentiated tumors considered the "most" malignant. Poorly differentiated tumors are, therefore, treated in a manner that gives the most assurance that all tumor cells are completely removed. For each type of squamous cell carcinoma, Figures 4 and 5 indicate that the treatment of choice differs according to the size of the tumor: less than 6 mm, 7 to 13 mm, or over 13 mm.

Similarly, Figures 6 through 8 illustrate treatment of three types of basal cell carcinoma: nodular, nodulocystic, and keratotic tumors (described above as noduloulcerative); superficial tumors; and fibronodular, morpheaform, and sclerosing tumors. The pattern of growth of these three categories of basal cell carcinoma make some treatments more effective than others, the objective of any treatment being the prevention of recurrence or spread with the minimum amount of disfiguration. Note that the indicated treatments for basal cell carcinoma generally differ from squamous cell carcinoma, but still depend upon the tumor size: small (less than 6 mm), medium, or large (larger than 13 mm).

The five treatments described below differ in the method used to remove the tumor and the skills they require. Most treatment of nonmelanoma skin cancer is performed in the physician's office or an outpatient clinic setting (Albright, 1982). Large tumors requiring skin grafts after removal may, however, require hospitalization.

Electrosurgery consists of curettage and electrodessication. The curettage step of the procedure consists of removal of the cancerous tissue using a small, sharp, spoon-shaped instrument called a curet. Normal skin tissue is resistant to removal by a curet while the tumor tissue is usually soft and easily removed. The second step consists of electrodessication (burning of tissue with a high frequency electric current) of the tumorous tissue (Albright, 1982). A second and/or third electrodessication and curettage is often performed (Levene et al.,
Fig. 4 -- Squamous cell carcinoma: Suggested treatment for well-differentiated and pseudoglandular tumors of various sizes
(Adapted from Albright, 1982)
Fig. 5 -- Squamous cell carcinoma: Suggested treatment for moderately to poorly differentiated tumors of various sizes
(Adapted from Albright, 1982)
Fig. 6 -- Basal cell carcinoma: Suggested treatment for nodular, nodulocystic and keratotic tumors of various sizes
(Adapted from Albright, 1982)
Fig. 7 -- Basal cell carcinoma: Suggested treatment for superficial tumors of various sizes
(Adapted from Albright, 1982)
Fig. 8 -- Basal cell carcinoma: Suggested treatment for fibronodular, morpheaform, and sclerosing tumors of various sizes
(Adapted from Albright, 1982)
1982). The tissue surrounding the skin cancer is usually anesthetized locally before the procedure (Levene et al., 1982). Contraindications for electrosurgery include any skin cancers over 13 mm in diameter or extending into the dermis or fat; skin cancers with poorly defined margins; poorly differentiated squamous cell carcinoma; recurring skin cancers; and any skin cancers on the lower eyelids, scalp, upper lip, on the side of the nose, and immediately in front of the ears (Albright, 1982).

Any size or shape of skin cancer can be excised from, i.e., cut out of, the surrounding normal skin. The surgical excision may be wedge-shaped, circular, or elliptical and may require a skin flap or skin graft depending upon the size and location of the excision. These surgeries are performed with a local or general anesthetic, depending upon the size and location of the tumor. The objective of the excision is to remove the tumor, allowing for a margin free of tumor which will lead to cure. If the margin of the tumor is indefinite, frozen sections may be inspected to determine the extent of the tumor at the time of excision (Levene et al., 1982). Removal by excision is contraindicated if the wound is sizeable and is located in an area with little available tissue for closure, such as the nose, ears, forehead, temples, back of hand, and fingers (Albright, 1982).

Radiation therapy is a highly effective method of treating basal cell and squamous cell carcinomas. The volume of tissue irradiated during treatment is kept to a minimum through protection of the skin and other vital organs surrounding the skin cancer. The x-ray energy is limited and only penetrates to the level necessary for the size and depth of the tumor. The dose and number of radiation exposures are determined by the diameter and thickness of the tumor (Levene et al., 1982). Contraindications for use of radiation therapy include small skin cancers on the trunk, arms, legs, hands, and feet; patients under the age of 50 years; and skin cancer on sun-damaged skin (Albright, 1982).

The Mohs' chemosurgery technique is a microscopically controlled excision of skin cancer after the application of a fixative to the tumor site. The fixative is a chemical that helps the tissue to maintain its
form and structure in preparation for the microscopic examination. Successive horizontal layers are shaved off microscopically from the site of the skin cancer, with examination of the removed tissue to determine where, within the lesion, further excisions are required. This procedure is repeated until the examined specimens reveal no remaining tumor. Although this treatment can be used on any type of skin cancer with a high cure rate (Levine et al., 1982), it requires specialized equipment and training, neither of which are currently widely available. Consequently, Mohs' chemosurgery is not usually used in cases of skin cancer where other modes of treatment would serve equally well (Albright, 1982). The tumor characteristics that make Mohs' chemosurgery the treatment of choice are a widely invasive tumor with poorly defined margins, or a tumor recurring after previous treatment (Levene et al., 1982). Because superficial basal cell carcinomas can be easily and completely removed using other techniques, Mohs' chemosurgery is not considered appropriate and, therefore, does not appear in Figure 7.

Treatment of skin cancer by cryosurgery consists of destroying the cancer tissue with extreme cold, usually in the form of a liquid nitrogen spray. The liquid nitrogen is sprayed at the center of the tumor until the tissue is frozen to a radius 2 to 5 mm beyond the edge of the tumor (Levene et al., 1982). The lesion is allowed to thaw slowly to maximize the effectiveness of the treatment in killing the tumor tissue. The thawing lasts from one-and-a-half to more than two minutes depending upon the part of the body. Usually, two freeze-thaw cycles are performed in order to assure complete destruction of the tumor. The frozen tissue begins to swell immediately and usually turns to a purple/red/brown color in 24 hours. The dead tissue is shed, leaving behind a rough raw surface. This area should be treated with an antibacterial preparation and washed regularly to avoid secondary infection. The wound heals within 3-4 weeks on the face, but takes longer on other parts of the body (Levene et al., 1982). Possible contraindications for cryosurgery include skin cancers with poorly defined borders; poorly differentiated squamous cell carcinoma; recurring skin cancers; and all types of skin cancers on the borders of the lips, and on the eyebrows, scalp, legs, and feet (Albright, 1982).
Thus, cryosurgery is a good treatment for well-differentiated squamous cell carcinoma (Figure 4) and other well-defined skin cancers, but is rarely used for poorly differentiated squamous cell (Figure 5) or fibronodular, morpheaform, and sclerosing basal cell carcinomas (Figure 8).

Finally, we note that actinic keratoses can also be treated with cryosurgery, electrosurgery, or application of a topical solution of 5-fluorouracil. The treatment of actinic keratosis with a topical solution of 5-fluorouracil (5-FU) has been quite effective in controlling the condition. The 5-FU medication is applied once or twice daily on the affected area of skin for 2 or 3 weeks. After the first week, the skin reddens and may begin to peel. The 5-FU preparation causes the keratoses to erode, while normal skin is unaffected (Levene et al., 1982). The 5-FU treatment is not recommended for all types of basal cell and squamous cell carcinoma; superficial basal cell carcinoma and squamous cell carcinoma in situ, however, may be treated with topical 5-FU.
III. MELANOMA

Although melanoma skin cancer is much less common than nonmelanoma skin cancer, melanoma is much more likely to result in death. The American Cancer Society estimates that more than 17,000 cases of malignant melanoma were diagnosed during 1983 in the United States (Silverberg and Lubera, 1983). Age- and sex-specific annual incidence rates for melanoma are shown in Table 3 for several white populations in the United States; these rates are based on incident cases diagnosed from 1973 through 1977. The incidence rates increase consistently with age, but the increase is not nearly as dramatic as with the nonmelanoma skin cancer incidence rates. Incidence is slightly higher among females than males for those under 40 years of age, but is consistently higher among males for those 40 years and over. In sharp contrast to nonmelanoma skin cancer, the mortality rates due to melanoma shown in Table 4 are almost as high as the incidence rates. The death rates increase with age for both males and females and are higher among males than females in every age group. The mortality rates due to melanoma for 1979 are considerably higher than those for 1950-1969; this difference may be attributable to an actual increase in mortality due to an increase in incidence or a decrease in survival of incident cases.

PROGRESSION OF MELANOMA SKIN CANCER

Figure 9 illustrates the progression of malignant melanoma and the decisions made by the patient and the physician during the course of treatment. At the time of diagnosis, melanoma patients are classified as having Stage I, Stage II, or Stage III disease. Stage I disease is defined as melanoma that is completely contained within the epidermal or dermal layers of skin. Stage II disease is defined as melanoma that has spread to lymph nodes close to the site of the original growth on the skin. Stage III disease is defined as melanoma that has spread to lymph nodes or body organs far away from the site of the skin growth. Stages I, II, and III of melanoma can be treated by the methods described below.
Table 3

ANNUAL INCIDENCE RATES OF MELANOMA OF THE SKIN
AMONG SELECTED U.S. WHITE POPULATIONS DURING 1973-1977,
BY AGE AND SEX (PER 100,000 PERSONS)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>---</td>
<td>0.1</td>
</tr>
<tr>
<td>5-9</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>10-14</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>15-19</td>
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<td>1.2</td>
</tr>
<tr>
<td>20-24</td>
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<td>3.6</td>
</tr>
<tr>
<td>25-29</td>
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<td>6.9</td>
</tr>
<tr>
<td>30-34</td>
<td>6.5</td>
<td>7.7</td>
</tr>
<tr>
<td>35-39</td>
<td>8.0</td>
<td>9.3</td>
</tr>
<tr>
<td>40-44</td>
<td>10.0</td>
<td>9.6</td>
</tr>
<tr>
<td>45-49</td>
<td>13.4</td>
<td>11.0</td>
</tr>
<tr>
<td>50-54</td>
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<tr>
<td>60-64</td>
<td>14.6</td>
<td>11.0</td>
</tr>
<tr>
<td>65-69</td>
<td>17.0</td>
<td>12.7</td>
</tr>
<tr>
<td>70-74</td>
<td>17.7</td>
<td>10.0</td>
</tr>
<tr>
<td>75-79</td>
<td>22.0</td>
<td>13.9</td>
</tr>
<tr>
<td>80-84</td>
<td>19.2</td>
<td>17.3</td>
</tr>
<tr>
<td>85 and over</td>
<td>20.9</td>
<td>20.7</td>
</tr>
</tbody>
</table>

NOTES: Rates are based on data from the SEER reporting areas of Connecticut, Detroit, Iowa, Atlanta, New Orleans, New Mexico, Utah, Seattle-Puget Sound, San Francisco-Oakland, and Hawaii.
Dashes indicate no cases of melanoma occurred in this age group during 1973-1977.
Table 4

ANNUAL DEATH RATES DUE TO MELANOMA OF THE SKIN
AMONG U.S. WHITES DURING 1979 AND 1950-1969,
BY AGE AND SEX (PER 100,000 PERSONS)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males 1979</th>
<th>Males 1950-1969</th>
<th>Females 1979</th>
<th>Females 1950-1959</th>
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<tr>
<td>0-4</td>
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<td>5-9</td>
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<td>0.0</td>
<td>---</td>
<td>0.0</td>
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<tr>
<td>10-14</td>
<td>---</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15-19</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>20-24</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
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<td>30-34</td>
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<td>35-39</td>
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<td>40-44</td>
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<td>45-49</td>
<td>4.8</td>
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<td>2.9</td>
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<td>15.7</td>
<td>8.9</td>
<td>9.4</td>
<td>6.7</td>
</tr>
</tbody>
</table>


NOTES: Rates include all deaths coded as Melanoma of Skin (Category number 172) under the Ninth Revision International Classification of Diseases.

Dashes indicate that no deaths due to melanoma occurred in this age group during 1979.
Fig. 9 -- Progression of disease and clinical contacts related to melanoma
Fig. 9 — Continued
A potential melanoma patient typically shows up at a family doctor or dermatologist after having noticed some changes in growth or color of a pigmented lesion on a part of the body. These color changes may be in a mole or in the vicinity of one. If the change is not dramatic enough to alarm the person, he or she may not go to the doctor. If it is malignant and goes untreated, the person has a decreased probability of living five years beyond that point in time.

Otherwise, Figure 9 indicates that the physician looks at the skin changes and performs an incisional or excisional biopsy. The biopsied tissue is reviewed by a pathologist and a diagnosis is made. If it is malignant, any of three definitive diagnoses are possible: the tumor may be either lentigo maligna melanoma, nodular melanoma, or superficial spreading malignant melanoma; otherwise, the condition is classified as one of several rare types of malignant melanoma (type not otherwise specified).

Superficial spreading melanoma, the most common melanoma and most rapidly increasing in incidence rates, appears circular with an irregular margin. It is commonly seen on the legs of women and the trunks of men. The median age of diagnosis of a superficial spreading melanoma is less than for the other types of melanoma. Nodular melanoma is round, very dark and berry-like. It has a similar site distribution for men and women to that of superficial spreading melanoma. Lentigo maligna is noninvasive; however, when it grows vertically down into the deeper tissues it is referred to as lentigo malignant melanoma. It typically occurs on exposed body sites of older people (Scott and Straf, 1977). When all types of melanomas are combined, the percent distribution by body site is different for men and women. For men, 60 percent of all melanomas are located in the trunk, head and neck; in contrast, for women, 60 percent of all melanomas are located on the arms and legs (Lee, 1983).

Regardless of which type of malignant melanoma, the management is the same: surgical removal with appropriate margin clearance, generally on an outpatient basis. If the biopsy is not malignant, then there is no further physician contact, unless the patient has a family history of melanoma, or the patient has the dysplastic nevus syndrome, both of which require frequent follow-up.
If the site of the Stage I melanoma is on the trunk, upper limbs or head and neck, the local lymph nodes may be biopsied also. If the nodes are not biopsied, the patient remains under the physician's observation. There is some probability of this patient living five years beyond this point in time.

If the lymph nodes are positive, then the nodes are surgically removed, and chemical and immunological therapies are administered. If metastasis does not occur, then the patient has some probability of living five years beyond this point in time (Stage II). If metastasis does occur, then aggressive therapies are employed. The patient has some probability of living one year beyond this point in time (Stage III).

**Clinical Manifestations and Pathology**

The diagnosis of malignant melanoma is based on the individual's clinical presentation as well as histologic review of biopsy material taken from the suspicious mole. Occasionally, however, the diagnosis of "malignant melanoma" can be difficult to make because many lesions straddle the histologic criteria for benign or borderline malignant (in situ) and malignant (Stage I primary) melanoma. For this reason, the physician must use all available information about the individual's clinical history and the pathological findings in assigning a diagnosis. Clinical history includes such risk factors as the individual's age, sex, skin type (tanning history), exposure history, family history, presence of a pre-existing pigmented lesion (mole), skin damage from sunlight (freckling), bleeding or drainage from the lesion, a change in the size of the lesion, the body location of the lesion, rate of growth of the lesion, and other signs and symptoms. Pathological information includes such characteristics as how the melanocytes (pigment-producing cells) in the tissue sample are arranged, the presence of rapidly dividing cells, the presence of irregularly shaped groups of cells and nuclei, and the status of the skin layers above and below the lesion (Cochran, 1983).
Melanoma of the skin is usually characterized by a slow but noticeable enlargement of a collection of cells greater than 0.5 cm that form an irregular outline on the skin. The suspicious area can be a variety of colors ranging from brown or black to a red-blue-white color. At first, the growth pattern is usually horizontal. After a period of time (months to years), the growth bores down vertically into the deeper tissues of the skin. This vertical growth contributes to the deadly nature of malignant melanoma.

The major distinction between in situ lesions (or a borderline malignancy) and Stage I (or a primary malignancy) is primarily how far down into the layers of skin the abnormal cells are observed. In situ or level I melanoma involves only changes in the cells within the epidermis. Invasive melanoma (level II) involves disruption of cells within and below the epidermis. If invasive melanomas are not completely removed by surgical excision they will recur and spread. This can result in more advanced disease, Stage II (regional melanoma) and Stage III (metastasis).

Stage II melanoma is defined as spread of the melanoma cancer cells to the lymph nodes in the vicinity of the original site. In stage II, the clinician tries to ascertain the extent of involvement of the regional lymph nodes, whether the nodes are massive or fixed, whether all nodes in the area are involved, and if the lymph nodes elsewhere on the body are involved also. Stage III melanoma consists of the spread of melanoma cancer cells to lymph nodes or body organs far removed from the original site. In Stage III, the clinician tries to establish if distant lymph nodes are involved, if any structure other than skin is involved and if so, what locations (lungs, bone, liver, brain, eye, etc.). In this stage, melanocytes, the cells that produce pigment in the skin, are transformed into tumor cells that travel to other parts of the body and begin crowding the cells of vital organs, disrupting their ability to function normally. Eventually through crowding out the normal organ cells, the organ is compromised structurally and fails to function. This may lead to the patient's death.
Table 5 summarizes in greater detail the survival aspects of melanoma patients, showing survival rates for males and females by age at diagnosis. Factors influencing the length of survival among melanoma patients are of two major types: those relating to the patient and those relating to the primary tumor. The most important patient factors are age and gender. An age at diagnosis of less than 45 years is best in terms of survival for females who have the survival advantage for Stage I and II melanoma (Mastrangelo et al., 1982). This advantage is probably related to the observation that males and females differ dramatically in distribution of melanoma on parts of the body. Based on a large compilation of data from international tumor registries, males have over two-thirds of Stage I melanomas on the head, neck, and trunk, sites with poorer prognosis. Women have over half of Stage I melanomas on the arms and legs, sites with better prognosis (Lee, 1983). It is widely accepted that the most important factor relating to the primary tumor is tumor thickness, an actual measure of the vertical dimension of the tumor (Breslow, 1970). The number of positive (containing tumor) lymph nodes also affects prognosis. The deeper the melanoma and the more positive regional lymph nodes there are, the greater the risk for metastatic spread.
Table 5
FIVE-YEAR SURVIVAL RATES FOR WHITE PATIENTS WITH MELANOMA OF THE SKIN, BY SEX AND AGE

<table>
<thead>
<tr>
<th>Age at Time of Diagnosis (years)</th>
<th>No. of cases</th>
<th>Relative 5-Year Survival Rate (per 100)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35</td>
<td>1,598</td>
<td>Male 76, Female 86</td>
</tr>
<tr>
<td>35 - 44</td>
<td>1,171</td>
<td>Male 73, Female 85</td>
</tr>
<tr>
<td>45 - 54</td>
<td>1,523</td>
<td>Male 71, Female 83</td>
</tr>
<tr>
<td>55 - 64</td>
<td>1,374</td>
<td>Male 71, Female 83</td>
</tr>
<tr>
<td>65 - 74</td>
<td>895</td>
<td>Male 66, Female 69</td>
</tr>
<tr>
<td>75 or older</td>
<td>717</td>
<td>Male 52, Female 62</td>
</tr>
</tbody>
</table>

\(^a\)The relative survival rate is defined as the ratio of the observed survival rate (the proportion surviving for the period of time in question among those diagnosed with melanoma) to the expected survival rate for persons in the general population similar to the patient group with respect to age, race, sex, and calendar year of observation.

NOTE: Rates are based on data from all reporting areas of the Surveillance, Epidemiology, and End Results (SEER) Program (Ries et al., 1983).
Melanocytes and the Tanning Mechanism

The normal functioning of skin cells, including those that produce pigment, has been studied extensively in laboratory experiments conducted on cells of guinea pigs, mice and, when possible, human volunteers. Because guinea pigs and mice have skin pigmentation similar to that of humans, they have been used to study the effects of ultraviolet radiation. The skin's tendency to tan, burn and age has been studied at specific durations and doses of UV. Laboratory experiments are useful because factors other than UV can be controlled while the level of UV exposure can be manipulated and measured. This is not the case, of course, with observational human studies.

Different wavelengths of the ultraviolet spectrum cause different biologic activities in cells. At the present time, the shortest wavelengths in the ultraviolet spectrum (UV-C) have not been studied much because most UV-C is entirely absorbed by the ozone layer before it reaches the earth (Honigsmann, 1981). The middle range of the ultraviolet spectrum (UV-B) is quite often referred to as the "sunburn spectrum." Considerable research has focused on this part of the spectrum as well as the longer wavelengths (UV-A). On human skin, UV-C only penetrates the uppermost layers, UV-B penetrates down to the junction of the epidermis and dermis where most melanocytes reside, and UV-A penetrates into the dermis (Honigsmann, 1981).

When ultraviolet light is absorbed by human skin, two normal responses may occur, immediate and delayed tanning. Immediate tanning can occur but does not always occur if the person's melanocytes at that body site have any preformed melanin from previous exposure to sunlight (Willis et al., 1973). UV-A and visible wavelengths can stimulate this process (Jimbow et al., 1973). The darkening of the skin is short-lived and fades after a period of time. At the cellular level, melanocytes begin to divide following UV exposure, increasing in number at the site of exposure (Roda1 and Szabo, 1978). If the sunlight is particularly intense, however, just the opposite occurs: metabolic processes are arrested (Epstein et al., 1970). The normal cell cycle of the melanocyte is interrupted. DNA, the cell's genetic material, may be directly damaged by the UV and unusual chemical bonds known as
pyrimidine and thymine dimers are formed. Protein synthesis and enzyme activities important to the cell's function are also altered (Baden and Pearlman, 1964). This damage to the genetic material stimulates the melanocyte to start repairing the DNA by snipping out the damaged region and replacing it. This process is called "dark repair" (Epstein et al., 1969).

Concurrently, a protective response is initiated that clears the products of all damage from the skin cells by way of the blood vessels in the skin. The initial response consists of edema (swelling) and erythema (redness). The redness associated with sunburn is due to the vessels becoming dilated within the dermis which allows for clearance of the by-products of the cell damage (Parrish, 1978). These responses are collectively referred to as inflammation and the process occurs over a period of a few days. Inflammation of the skin can be caused by both UV-A and UV-B (Willis and Cylus, 1977). If inflammation is induced repeatedly, the skin responds by thickening.

Following the changes of immediate tanning, the process of delayed tanning is initiated. The melanosomes, small packages of melanin pigment, come together and travel toward the periphery of the melanocyte (Jimbow et al., 1973). Melanin is passed from the melanocytes to the other skin cells that are incapable of producing melanin (the keratinocytes). The transfer of pigment can be performed only by the melanocytes of the upper layers of skin (the epidermis) (Moellman et al., 1973). Melanin has chemical properties which enable it to absorb high-energy wavelengths that would normally damage tissues. Since the ability to produce high levels of melanin is genetically determined (Parrish, 1978), certain subgroups of people, such as fair-skinned individuals, are highly susceptible to the damaging effects of sunlight to both the melanocytes and the non-pigmented skin cells.

Long-term exposure to sunlight stimulates melanocytes to continue producing melanin at higher levels than melanocytes located in parts of the body that are rarely exposed to sunlight. As a person ages, the number of melanocytes per square unit of tissue decreases (Gilchrest et al., 1979); thus, in an older person, the remaining melanocytes must provide melanin for an even greater number of non-pigment-producing cells in order for a person to get a tan. Over a long period of time,
sunlight eventually damages the branches of the melanocytes causing the process of pigment transfer to be less effective.

Early clinical studies on human volunteers have shown that dark-skinned individuals have very different types of melanocytes. This is of interest because they have the lowest rates of melanoma. The darker the pigment, the less clustering there is of melanosomes and the larger the melanosomes are (Szabo et al., 1969). However, persons with dark skin do not have any greater numbers of melanocytes per square unit of their skin (Szabo et al., 1969).

RISK FACTORS FOR MELANOMA

A variety of risk factors that may affect the development of melanoma have been studied extensively for clues to the cause of this disease. Exposure to sunlight (or ultraviolet radiation) has been considered as a possible cause in many studies (Gellin et al., 1969; Teppo et al., 1978; Magnus, 1981; Klepp and Magnus, 1979; Lee, 1982; Anaise et al., 1978). Although no conclusive evidence has emerged on the role of UV in melanoma development, there is some consistency in the findings of these studies providing direction for further research. Other suspected risk factors have included pregnancy (George, 1960; Shiu, 1976), oral contraceptive use (Beral et al., 1977; Adam et al., 1981; Bain et al., 1982), fluorescent lighting (Beral et al., 1982; Rigel et al., 1983), occupation (Lee and Strickland, 1980), chemicals (Szabo et al., 1969) and gamma radiation from high energy nuclear physics (Austin et al., 1981). Recently, the dysplastic nevus syndrome has been formally described as a risk factor for malignant melanoma in the clinical literature (David and Spielvogel, 1983; Greene et al., 1985).

Experimental Evidence on the Role of Ultraviolet Radiation

Melanocytes play an important role in protecting human skin from damage caused by sunlight. Consequently, many observations have been made in the laboratory on the response of normal melanocytes and their neighboring non-pigmented cells to UV exposure (Honigsmann, 1981; Gilchrest et al., 1979; Willis et al., 1973; Rosdahl and Szabo, 1978; Jimbow et al., 1973). Mechanisms of damage by UV to the DNA of
melanocytes have been hypothesized. Because the technique for growing
normal human melanocytes in vitro has only been developed recently,
however, these hypotheses have not been tested thoroughly. Clinical and
epidemiologic studies of melanoma have also been conducted in an attempt
to explain the relationship between sun exposure and the incidence of
melanoma in humans.

In melanoma skin cancer, melanocytes somehow transform to a
malignant state. The components inside of the cell look abnormal and
the life cycle of the cell speeds up. In the upper dermis, there is
normally about a 1:10 ratio of melanocytes to non-pigmented cells.
However, following the transformation to malignancy, melanocytes
comprise a higher proportion of skin cells at the malignant site.
Microscopic examination can reveal what phase a normal melanocyte is in
during its life cycle. However, with melanocytes that are undergoing
abnormal changes, the phases are not distinct. The malignant
melanocytes change in shape, size, and position within the skin.

A study of human melanoma cells has demonstrated a high resistance
to UV, i.e., there is no DNA destruction. However, the melanin
production continues as in normal melanocytes. If the melanin
accumulates to a very high level, the melanoma cells die (Chalmers and
Levin, 1976).

Although observations in the laboratory have provided information
on the types of damage to the melanin-epidermal unit and have proposed
mechanisms of repair, laboratory scientists have not explained how the
melanocyte transforms into a malignant cell. With the recent success in
culturing normal melanocytes in vitro, perhaps this will be possible in
the near future (Gilchrest et al., 1984).

Epidemiologic Evidence on the Role of UV

A variety of epidemiologic studies have been conducted to study the
relationship between sunlight and melanoma. Some of the earlier studies
provided mortality rates by geographical location (or latitude) (cities
or counties). This type of descriptive study was conducted in North
America, England, the Scandinavian countries, Finland, and Australia
(Lee, 1982). Because a trend of increasing mortality from melanoma with
decreasing distance from the equator was observed, the inference was
made that sunlight was at least partially responsible. However, there are exceptions to this latitude gradient trend, causing much speculation about what other factors may be important. Such general factors as economic prosperity, vacations to Mediterranean countries, gradients of pigmentation in certain countries, and preventive practices of wearing more clothing have been mentioned as possible explanations. Within the U.S., melanoma mortality has not been consistently correlated with the ultraviolet levels received by geographical region (Lee, 1982).

In the 1970's, several case control studies were conducted on sunlight and melanoma (Gellin et al., 1969; Beardmore, 1972; Sober et al., 1979; Klepp and Magnus, 1979). These studies did not attempt to measure sun exposure directly but used skin response to sunlight (burning, tanning, or freckling) as a surrogate measure for duration and intensity of sun exposure. Important risk factors were skin fairness, number of sunburns in childhood, intolerance of sun, and freckling. Many studies of melanoma and other exposures conducted since these earlier findings have incorporated these risk factors, acknowledging that they are important and must be controlled for in any analyses. Although sunlight is considered a potentially important risk factor for melanoma, melanoma can appear on body sites rarely exposed to sunlight (Lee, 1982). In summary, while UV may play an important role in the development of melanoma skin cancer, the exact nature of the role remains a mystery. Moreover, the UV role in melanoma development appears different from its role in nonmelanoma skin cancer development. More research is needed to understand the UV-melanoma relationship.

**Chemical Exposures**

Hormones such as progesterone and estrogen and other chemicals have also been studied as a possible cause of melanoma. However, animals used in this research have pigment systems different enough from humans that they do not always yield useful information. Results also differ depending on which animal model is used. As early as the 1960's, laboratory research demonstrated that melanomas were responsive to estrogens (Fisher et al., 1976) and that large doses of hormones could influence the amount of melanin pigment produced in animals (Snell and Bischitz, 1960). Subsequent epidemiologic studies on hormones did not
yield consistent results about the risk of melanoma associated with hormone exposures (Beral et al., 1977; Bain et al., 1982; Adam et al., 1981). Industrial chemicals such as substituted phenols give rise to free radicals which can act to depigment active melanocytes (Bleehen, 1981). Epidemiologic studies focusing on other hypotheses have incidentally identified certain subgroups of the population that may be at higher risk of developing melanoma. However, the numbers of people in these studies are often small so conclusions are statistically weak. In general, the melanocyte responds to chemical exposure by increasing or decreasing pigment production when doses of chemicals are moderate. However, with increasing doses of chemicals, toxicity results in damage to the melanocyte's structural components.

TREATMENT OF MELANOMA

The medical procedures used in treating melanoma depend on the stage of disease at the time the physician first sees the patient. If the patient presents with a Stage I melanoma, it is surgically removed. The surgical removal is usually conservative, i.e., a large margin of disease-free skin around the melanoma is removed also. A margin of 2-5 cm in all directions is not unusual. This is thought to be a good therapeutic approach for keeping the melanoma localized or to prevent a recurrence in nearby skin. A skin graft may be required. Some sites such as the face are treated less conservatively (2-3 cm margin) for cosmetic reasons or if the primary lesion is not thick. Regional lymph nodes may also be prophylactically removed if they are palpable. Regional lymph node dissections may be done based on tumor thickness (Goldsmith, 1979).

Although the focus is still on surgical removal of the lesion, experimental variations in the management of a Stage I melanoma are currently being tested. These variations involve injecting biologic or chemical agents such as BCG (a bacteria) or DTIC (a chemical) into the lesion a few weeks before performing surgery (Peter et al., 1978).

As mentioned previously, the lesion may have characteristics that increase the likelihood of the cancer spreading to other organs, namely tumor thickness and many positive lymph nodes in the region near the
melanoma. Metastasis in melanoma has several patterns, unlike other cancers. Melanoma cells can travel and lodge in bone, lung, liver, gastrointestinal tract, or central nervous system tissue. Furthermore, metastasis may occur to more than one of these sites.
IV. OTHER DISEASES OF HUMAN SKIN INVOLVING SUNLIGHT

The NAS report entitled Causes and Effects of Changes in Stratospheric Ozone: Update 1983, contains a list of more than thirty skin diseases "involving" sunlight. Most of these diseases are discussed in this section, with the objective of providing information regarding their importance as possible health effects of increased UV-B radiation. Each disease was classified into one of two groups: those diseases most likely affected by increased UV-B exposure and those diseases most likely not affected by increased UV-B exposure. The classification is based on the following criteria: (1) the cause of the disease (ETIOLOGY), (2) the effects of ultraviolet radiation on the course of the disease (UV EFFECTS), (3) the part of the UV spectrum that causes the biologic effect (ACTION SPECTRUM), and (4) the frequency with which the disease occurs (FREQUENCY).

Information on the cause of the disease is important because any disease that is caused by exposure to sunlight cannot be ignored as a possible health effect of increased UV-B. The second criterion, the nature of the UV effects, allows discrimination between beneficial and detrimental effects of UV, as well as between mild and severe effects of UV on the course of the disease. The wavelengths of the UV spectrum responsible for the biologic effects (action spectrum) are important because a change in the ozone concentration would result in a change primarily in the level of UV-B and UV-C reaching the earth's surface; a disease affected only by the UV-A spectrum may not be as important in a consideration of the effects of ozone depletion. Finally, knowledge of the frequency of the disease, i.e., how many people are affected, allows prioritization in terms of public health and economic importance.

The information on each disease is based on the dermatologic literature and an interview with a dermatologist at the University of California at Los Angeles. Table 6 contains those diseases most likely to be affected by increased UV-B exposure. Table 7 lists those diseases most likely not to be affected by increased UV-B exposure. The diseases are listed alphabetically in each table. The rationale behind the
placement of the diseases into the two tables is discussed below. There is some uncertainty associated with the dichotomous classification represented in Tables 6 and 7. Uncertainty surrounding this information reflects the state of knowledge at the present time. The glossary provides a brief definition of each of the diseases listed in Tables 6 and 7; these definitions were adapted from Dorland's Medical Dictionary (1981) and the Merck Manual (Berkow, 1982).

DISEASES MOST LIKELY AFFECTED ADVERSELY BY INCREASED UV-B EXPOSURE

The diseases listed in Table 6 can be classified into three categories: those in which the disease can be said to be partially caused by UV-B radiation (Category 1.1); those in which the primary cause of the disease is genetic, but exposure to UV-B radiation results in complications of the disease (Category 1.2); and those in which the condition may be aggravated by UV-B radiation (Category 1.3). Category 1.1 includes actinic keratosis, actinic reticuloid, disseminated superficial actinic porokeratosis, photoallergic and phototoxic reactions, solar urticaria, and polymorphous light eruptions. The most important of these is actinic keratosis because of its frequency and malignant potential. As discussed in Section II, actinic keratosis may be a precursor lesion to squamous cell carcinoma. Category 1.2 includes xeroderma pigmentosum, Bloom's syndrome, and albinism. Each of these conditions is an inherited disorder that interferes with normal skin metabolism. The importance of these conditions is that they result in an increased risk of UV-B-related skin diseases, such as melanoma and nonmelanoma skin cancer. Category 1.3 includes herpes simplex, cutaneous lupus erythematosus (discoid and subacute forms), systemic lupus erythematosus, dermatomyositis, and pemphigus foliaceus. Herpes simplex infections may be reactivated by bodily trauma, including exposure to sunlight, and the reactivation usually results in herpes labialis (fever blisters and cold sores). The importance of herpes labialis is the frequency of the problem, not the severity. Lupus erythematosus is important because of its severity not its frequency; it can cause disfiguring skin changes and/or serious systemic disease. As another measure of frequency and seriousness, Table 8 provides the number of deaths due to each disease that occurred in the United States during 1979.
<table>
<thead>
<tr>
<th>Category**</th>
<th>Disease</th>
<th>Etiology</th>
<th>UV Effects</th>
<th>Action Spectrum</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Actinic keratosis</td>
<td>Sun, genetic, skin color (M:2117)*</td>
<td>Premalignant skin lesion (M:2117)</td>
<td>Sunlight (F:355)</td>
<td>very common (M:2117)</td>
</tr>
<tr>
<td>1.1</td>
<td>Actinic reticuloid</td>
<td>Unknown (F:965)</td>
<td>Precipitation of skin reaction (F:965)</td>
<td>290-400nm (F:965)</td>
<td>very, very rare (L)</td>
</tr>
<tr>
<td>1.2</td>
<td>Albinism</td>
<td>Genetic (M:2068)</td>
<td>Skin damage, skin cancers (M:2068)</td>
<td>Sunlight (M:964)</td>
<td>5 per 100,000 (F:577)</td>
</tr>
<tr>
<td>1.2</td>
<td>Bloom's syndrome</td>
<td>Genetic (R:121)</td>
<td>Skin lesions (HB:226)</td>
<td>Sunlight (R:121)</td>
<td>very rare (L)</td>
</tr>
<tr>
<td>1.3</td>
<td>Cutaneous (discoid) lupus erythematosus (DLE)</td>
<td>Unknown (M:1206)</td>
<td>Precipitation and aggravation of skin lesions (M:1206)</td>
<td>Sunlight (F:1274)</td>
<td>more common than SLE (F:1273)</td>
</tr>
<tr>
<td>1.3</td>
<td>Dermatomyositis</td>
<td>Unknown, autoimmune (M:1214)</td>
<td>Aggravation of skin lesions (F:1300)</td>
<td>Ultraviolet light (F:1300)</td>
<td>0.4 per 100,000 (F:1299)</td>
</tr>
<tr>
<td>1.1</td>
<td>Disseminated superficial actinic porokeratosis (DSAP)</td>
<td>Genetic, sun (R:2181)</td>
<td>Precipitation of skin lesions (R:2181)</td>
<td>Sunlight (R:2181)</td>
<td>reasonably frequent (L)</td>
</tr>
<tr>
<td>1.3</td>
<td>Herpes simplex</td>
<td>Viral infection (M:200)</td>
<td>Precipitation of herpetic sores (R:534)</td>
<td>250-320nm (HB:229)</td>
<td>420 per 100,000 (USDHEW:28)</td>
</tr>
<tr>
<td>1.3</td>
<td>Pemphigus follicaeus</td>
<td>Unknown, autoimmune (M:2061)</td>
<td>Aggravation of skin lesions (F:976)</td>
<td>Sunlight (F:976)</td>
<td>very rare (L)</td>
</tr>
<tr>
<td>1.1</td>
<td>Photoallergic and phototoxic reactions</td>
<td>Exposure to chemical, drug and subsequent exposure to sunlight (M:2027)</td>
<td>Dermatitis (M:2027)</td>
<td>most &gt;320nm, some &lt;320nm (HB:129)</td>
<td>very common (L)</td>
</tr>
<tr>
<td>1.1</td>
<td>Polymorphous light eruptions (inc. Hydroa aestivale, Hydroa vacciniforme, Actinic prurigo)</td>
<td>Unknown (HB:170)</td>
<td>Variable skin reaction (F:961)</td>
<td>mostly 290-320nm, some UV-A, UV-C (F:962)</td>
<td>quite common (L)</td>
</tr>
<tr>
<td>Category**</td>
<td>Disease</td>
<td>Etiology</td>
<td>UV Effects</td>
<td>Action Spectrum</td>
<td>Frequency</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>1.1</td>
<td>Solar urticaria</td>
<td>Unknown, autoimmune (HB:164)</td>
<td>Skin swelling, itching, discoloration (F:964)</td>
<td>290-480nm</td>
<td>very rare (L)</td>
</tr>
<tr>
<td>1.3</td>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Unknown, autoimmune (M:1207)</td>
<td>Precipitation and aggravation of skin lesions (HB:230)</td>
<td>Sunlight (F:1284)</td>
<td>Prevalence: 100 per 100,000 women; incidence: 2.8 per 100,000 white women, 7.5 per 100,000 black women (F:1282)</td>
</tr>
<tr>
<td>1.2</td>
<td>Xeroderma pigmentosum</td>
<td>Genetic (M:1918)</td>
<td>Skin damage, skin cancers (M:1918)</td>
<td>290-340nm</td>
<td>0.4 per 100,000 (F:390)</td>
</tr>
</tbody>
</table>


** 1.1=partially caused by UV-B; 1.2=genetic, complicated by UV-B; 1.3=aggravated by UV-B

N/A = information not available.
DISEASES MOST LIKELY NOT AFFECTED ADVERSELY BY INCREASED UV-B EXPOSURE

The diseases listed in Table 7 can be classified into four categories: those that are improved by, or are not affected by, UV-B exposure (Category 2.1); those that are aggravated by UV radiation outside the UV-B spectrum (Category 2.2); those that are primarily nutritional deficiency diseases (Category 2.3); and those that may be affected by UV-B but more information is necessary before classification is possible (Category 2.4). Category 2.1 includes acne, atopic dermatitis, and transient acantholytic disease (TAD). The first two in this group may actually be improved by UV-B exposure; TAD is probably unaffected by UV-B. The beneficial health effects of UV-B include improvement in acne, atopic dermatitis and other skin conditions (including small plaque type parapsoriasis and psoriasis). Category 2.2 includes erythropoietic coproporphyria, erythropoietic porphyria, erythropoietic protoporphyria, and porphyria cutanea tarda. These diseases are affected by UV radiation in the UV-A spectrum. Assuming a change in UV-B would not affect the reaction of persons with one of the porphyrias to UV-A, these conditions would remain unaffected. Category 2.3 includes kwashiorkor, pellagra, and Hartnup disease. Each of these diseases results from a nutritional deficiency; one of the symptoms of each is a skin condition that is aggravated by sunlight. The final category 2.4 includes lichen planus actinicus, and Darier's disease. As stated above, these two diseases must be investigated further before they can be classified. The number of deaths due to each disease that occurred in the United States during 1979 is shown in Table 8.
Table 7
Diseases Most Likely Not Affected By Increased UV-B Exposure

<table>
<thead>
<tr>
<th>Category***</th>
<th>Disease</th>
<th>Etiology</th>
<th>UV Effects</th>
<th>Action Spectrum</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Acne</td>
<td>Hormonal, skin type (M:2048)*</td>
<td>Possibly beneficial (M:2048)</td>
<td>Sunlight (M:2048)</td>
<td>6810 per 100,000 (USDHEW:28)</td>
</tr>
<tr>
<td>2.1</td>
<td>Atopic dermatitis</td>
<td>Unknown (M:2029)</td>
<td>Possibly beneficial (HB:226)</td>
<td>Sunlight (HB:226)</td>
<td>690 per 100,000 (USDHEW:28)</td>
</tr>
<tr>
<td>2.4</td>
<td>Darier's disease</td>
<td>Genetic (HB:190)</td>
<td>Possible aggravation of skin lesions (F:266)</td>
<td>Sunlight (F:266)</td>
<td>1 per 100,000 (R:1292)</td>
</tr>
<tr>
<td>2.2</td>
<td>Erythropoietic coproporphyria</td>
<td>Genetic (HB:190)</td>
<td>Skin lesions (HB:206)</td>
<td>around 400 nm (F:1079)</td>
<td>&lt; 1 per derm. practice (L)</td>
</tr>
<tr>
<td>2.2</td>
<td>Erythropoietic porphyria</td>
<td>Genetic (HB:190)</td>
<td>Skin lesions (HB:199)</td>
<td>around 400 nm (F:1079)</td>
<td>&lt; 1 per derm. practice (L)</td>
</tr>
<tr>
<td>2.2</td>
<td>Erythropoietic protoporphyria</td>
<td>Genetic (HB:190)</td>
<td>Skin lesions (HB:201)</td>
<td>around 400 nm (F:1079)</td>
<td>1 per derm. practice (L)</td>
</tr>
<tr>
<td>2.3</td>
<td>Hartnup disease</td>
<td>Inherited metabolic disorder (F:975)</td>
<td>Skin rash, other symptoms (M:1579)</td>
<td>N/A</td>
<td>Very, very rare (L)</td>
</tr>
<tr>
<td>2.3</td>
<td>Kwashiorkor</td>
<td>Severe protein deficiency (M:887)</td>
<td>Aggravation of skin lesions (M:888)</td>
<td>N/A</td>
<td>Very, very rare in U.S. (L)</td>
</tr>
<tr>
<td>2.4</td>
<td>Lichen planus actinicus</td>
<td>Unknown (M:2056)</td>
<td>Skin lesions (M:2056)</td>
<td>Unknown (HB:229)</td>
<td>N/A (L)</td>
</tr>
<tr>
<td>2.3</td>
<td>Pellagra</td>
<td>Severe niacin/tryptophan deficiency (M:900)</td>
<td>Precipitation of skin reaction (F:975)</td>
<td>N/A</td>
<td>Very, very rare in U.S. (L)</td>
</tr>
<tr>
<td>2.2</td>
<td>Porphyria cutanea tarda</td>
<td>Alcoholism, toxic agents, hepatic disease (M:962)</td>
<td>Skin lesions (M:962)</td>
<td>around 400 nm (F:1079)</td>
<td>&gt; 1 per derm. practice (L)</td>
</tr>
</tbody>
</table>
### Table 7 (continued)

<table>
<thead>
<tr>
<th>Category**</th>
<th>Disease</th>
<th>Etiology</th>
<th>UV Effects</th>
<th>Action Spectrum</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Transient acantholytic dermatosis (TAD)</td>
<td>Unknown (R:1294)</td>
<td>Skin lesions (F:976)</td>
<td>Sunlight (F:976)</td>
<td>Rare (L)</td>
</tr>
</tbody>
</table>


** 2.1=beneficial or no effect of UV-B; 2.2=aggravated by UV radiation other than UV-B; 2.3=nutritional deficiency; 2.4=more information necessary.

N/A = information not available.
Table 8
NUMBER OF DEATHS IN THE UNITED STATES DURING 1979 DUE TO SELECTED CAUSES

<table>
<thead>
<tr>
<th>Disease</th>
<th>ICDA-9 Category</th>
<th>Number of Deaths in U.S., 1979</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne vulgaris</td>
<td>706.1</td>
<td>0</td>
</tr>
<tr>
<td>Actinic keratitis</td>
<td>702</td>
<td>0</td>
</tr>
<tr>
<td>Actinic reticuloid</td>
<td>(a)</td>
<td>(a)</td>
</tr>
<tr>
<td>Albinism</td>
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<td>108</td>
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<td>(36)</td>
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<tr>
<td>Dermatomyositis</td>
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</tr>
<tr>
<td>Disseminated superficial actinic porokeratosis</td>
<td>757.3</td>
<td>(36)</td>
</tr>
<tr>
<td>Erythropoietic coproporphyria</td>
<td>277.1</td>
<td>(12)</td>
</tr>
<tr>
<td>Erythropoietic porphyria</td>
<td>277.1</td>
<td>(12)</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td>277.1</td>
<td>(12)</td>
</tr>
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<td>Hartnup's disease</td>
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<td>Pemphigus foliaceus</td>
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<tr>
<td>Photoallergic or phototoxic reaction</td>
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<tr>
<td>Polymorphous light eruption</td>
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<td>(7)</td>
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<td>Xeroderma pigmentosum</td>
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<tr>
<td>Melanoma of skin</td>
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<td>4,749</td>
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<tr>
<td>Other malignant neoplasms of skin</td>
<td>173</td>
<td>1,407</td>
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</table>


aNot listed in the International Classification of Diseases, Ninth Revision index.

NOTE: Numbers in parentheses represent deaths due to listed disease or other disease included in the same numerical category of the Ninth Revision International Classification of Diseases (ICDA-9). For example, deaths due to Bloom's syndrome and Darier's disease are coded as 757.3; thus, each death can be attributed to only one cause in that category.
V. SUGGESTIONS FOR FURTHER RESEARCH

This Note provides an overview of those human diseases thought to be related to ultraviolet radiation. Although much research has been conducted on topics related to these diseases, many topics need to be investigated further before definitive conclusions can be reached. The NAS report (NRC, 1984) recommends further research on the following topics (as well as others):

- Effect of ultraviolet radiation on immunological processes in humans;
- Relationship between immunological changes induced by ultraviolet radiation, and skin cancers and other diseases in humans;
- Further work on predicting the expected number of cases of nonmelanoma skin cancer in humans with increased UV-B;
- Periodic surveys to determine the incidence of nonmelanoma skin cancer and year-round measurement of UV-B insolation at different latitudes;
- Laboratory studies of the effect of ultraviolet radiation on the activity of melanocytes and on the development of malignant melanoma in animals;
- Epidemiologic studies to determine risk factors for malignant melanoma;
- Development of models to predict change in the incidence of malignant melanoma in humans with increased UV-B;
- Laboratory studies to further define the relationship between UV-B exposure and nonmelanoma skin cancer in animals.

In addition to these topics, a complete evaluation of the possible human health effects of increased ultraviolet radiation exposure would require detailed study of UV-related diseases other than nonmelanoma and melanoma skin cancer; many of these were discussed briefly in this Note, but there may be others.
Finally, research is needed to determine the potential economic costs of UV-related diseases. In addition to the pain and suffering that accompanies these diseases, they also necessitate expenditures for hospital and nursing home care, physicians' and nurses' services, drugs and medical equipment. These direct costs are accompanied by indirect costs associated with these diseases, such as lost income due to premature mortality and time lost from work because of illness and disability. The direct and indirect costs together comprise the economic cost of disease -- an economic loss that must be considered the lower limit on the true cost of the disease to society. The information in this Note on the incidence, treatment methods, and patient contact within the medical care system for nonmelanoma and melanoma skin cancer provide the basis for further work on economic costs.
GLOSSARY

Acne vulgaris: A chronic inflammatory disease of the hair follicles and sebaceous glands, with lesions appearing on face, chest, and back. The cause is unknown, but several factors, including foods, stress, heredity, hormones, drugs, and bacteria play a causal role.

Actinic keratosis (A.K.): A sharply outlined, red or skin colored, flat or elevated, warty skin growth, that may develop into a horn-shaped growth, and may give rise to a squamous cell carcinoma; it usually affects the middle-aged or elderly, especially those of fair complexion, and is caused by excessive exposure to the sun.

Actinic reticuloid: A skin disease aggravated by exposure to light, usually affecting elderly males, characterized by redness, itching, oozing, and crusting, followed by scaling and thickening of the skin, predominantly on the exposed skin of the face, hands, and forearms and extending to contiguous unexposed areas. The eruption clears slowly on avoidance of light.

Adjuvant therapy: Treatment used in conjunction with the main treatment.

Aggressive therapy: Strong treatment measures used when a patient is affected by severe disease.

Albinism: Congenital absence of pigment in the skin, hair, and eyes, due to absence or defect of the process producing melanin. It is accompanied by photophobia and astigmatism.

Atopic dermatitis: A chronic itching skin rash occurring during childhood and adolescence, of unknown cause, although allergy, heredity, and psychogenic factors appear to be involved. The itchy rash occurs mainly on the knees and elbows, but may be found in other areas, and is characterized by dryness of the skin, and irritation due to scratching.

Basal cell carcinoma (B.C.C.): Type of nonmelanoma skin cancer characterized by incomplete maturation of basal epidermal cells.

Biopsy: A tissue sample used for microscopic diagnosis.

Bloom's syndrome: Dwarfism, photosensitivity, and redness of the face, with defects of skin pigmentation, teeth, and general development; it is transmitted as an autosomal recessive trait.

Cutaneous (discoid) lupus erythematosus: A chronic, superficial inflammation of the skin, marked by red spots up to 3 or 4 cm. in width, and covered with scales; healed lesions may leave scars.
Darier's disease (keratosis follicularis): A rare hereditary condition manifested by areas of crustig, itching, and rough bumps, usually appearing symmetrically on the trunk, arm pits, neck, face, scalp, and behind the ears.

Dendrites: The branches projecting out from a cell (in this context, a melanocyte).

Dermis: Layers of skin tissue just below the epidermis.

Disseminated superficial actinic porokeratosis (DSAP): A rare, chronic hereditary disease of the skin, usually limited to sun-exposed areas; usually occurring in persons 30 to 40 years of age; the lesions are small and disc-shaped, bordered by a margin of scaly skin. It is transmitted as an autosomal dominant trait.

DNA: Deoxyribonucleic acid, the genetic material inside the nucleus of a cell responsible for the cell's functions.

Edema: Swelling of the skin.

Enzymes: Proteins critical for certain chemical pathways of metabolism to occur.

Epidermis: The layer of human skin above the dermis.

Erythropoietic porphyria (and E. coproporphyria): A rare, chronic hereditary disease caused by a disturbance of the metabolism of porphyrin, and resulting in skin lesions from exposure to sunlight, hemolytic anemia, discoloration of the teeth, and enlargement of the spleen. The prognosis is poor, most patients dying before middle age. It is transmitted as an autosomal recessive trait. Erythropoietic coproporphyria is a very rare form of e. porphyria, clinically resembling e. protoporphyria (below).

Erythropoietic protoporphyria: A milder form of e. porphyria (above) characterized by skin lesions due to photosensitivity, and possible formation of gallstones, anemia and hepatic disease. It is transmitted as an autosomal dominant trait.

Hartnup disease: A hereditary condition seen in children characterized by skin rash, lack of muscle control, high levels of amino acids in urine, and other biochemical abnormalities. It is transmitted as an autosomal recessive trait.

Herpes simplex: A viral infection which may recur periodically as herpes labialis, a condition characterized by groups of blisters, each about 3 to 6 mm. in diameter, on the the borders of the lips or nostrils. Precipitating factors for herpes labialis include fever, serious illness, sunburn, skin abrasions, and emotional disturbances.
Histologic: Related to the minute structure of animal and plant tissues as discernible with a microscope.

In situ squamous cell carcinoma: Early stage of squamous cell carcinoma in which malignant changes are confined to the epidermal layer of skin.

Keratinocytes: Non-pigment-producing skin cells containing keratin surrounding melanocytes.

Kwashiorkor: A condition caused by severe protein deficiency, characterized by retarded growth, changes in skin and hair, swelling, and liver pathology. Other findings are mental slowness, changes in pancreatic and gastrointestinal functions, anemia, and dermatoses. Kwashiorkor occurs throughout the world, but mainly in the tropics and subtropics.

Lentigo maligna melanoma: A type of melanoma typically occurring in older people, usually on sun-exposed skin.

Lichen planus: An inflammatory skin disease with small purple, itchy bumps that are often persistent. Lichen planus actinicus is a form of the disease thought to be related to sun exposure.

Malignant melanoma (NOS): Melanoma, but type is not specified.

Melanocytes: The cells that produce melanin pigment in human skin that can result in tanning of skin.

Melanosomes: Packages of melanin pigment found inside human melanocytes.

Metastasis: Spread of malignant disease to another part of the body which may be far from the primary tumor.

Mitosis: Cell division.

Nodular melanoma: A type of melanoma with poor 5-year survival.

Pellagra: A syndrome due to the deficiency of niacin and characterized by dermatitis, inflammation of mucous membranes, diarrhea and psychic disturbances. The dermatitis occurs on the portions of the body exposed to light or trauma.

Pemphigus foliaceus: A chronic, generalized, blistering, and scaling skin eruption on the scalp, face, or upper chest and back; may be affected by emotional upset or exposure to sunlight.

Photoallergic or phototoxic reaction: A skin reaction characterized by an exaggerated response to sunlight following topical application of certain chemicals; may range from transient redness to severe swelling with large blisters; may also result from photosensitizing drugs that are administered systemically.
Polymorphous light eruptions: Breaking out of the skin, the appearance of which varies considerably from patient to patient; it is confined to the sun-exposed surfaces of the skin and cannot be attributed to photosensitizing agents or to systemic disease.

Porphyria cutanea tarda: A condition characterized by chronic skin lesions ranging from slight skin fragility to severe chronic scarring, enlargement of the liver, and excretion of uroporphyrin; it is usually associated with alcoholism or hepatic disease, but other toxic agents may be causal. Malignant hepatoma has been associated with the condition.

Progression: Sufficient changes in the condition to merit relabeling it as the next stage of disease, in the absence of medical intervention.

Recurrence: Occurrence of disease at the exact same location indicating treatment did not cure disease.

Squamous cell carcinoma (S.C.C.): Type of nonmelanoma skin cancer.

Solar urticaria: A vascular reaction of the skin marked by transient swellings that are often attended by severe itching. The eruption can exist in a chronic form. It is caused by sunlight.

Stage I melanoma: Malignant melanoma lesion localized to a certain body site.

Stage II melanoma: The spread of melanoma to nearby lymph nodes.

Stage III melanoma: The spread of melanoma to other organs of the body.

Superficial spreading melanoma: The most common type of melanoma.

Systemic lupus erythematosus: A generalized connective tissue disorder, affecting mainly middle-aged women, ranging from mild to severe, and characterized by a butterfly-shaped rash over the bridge of the nose, joint pain and inflammation, low white blood cell count, anemia, problems with heart, lung, kidneys.

Systemic treatments: Treatment administered by mouth, intravenously, or intramuscularly aimed at killing cancer cells.

Transient acantholytic dermatosis (TAD): A condition characterized by small bumps, or blisters with itching, often on the upper chest, the base of the neck, and the back, and sometimes on the upper arms and thighs. The disease lasts from a few weeks to over three years.

UV-A: Ultraviolet radiation of long wavelengths (320-400 nanometers).

UV-B: Ultraviolet radiation of middle wavelengths (290-320 nanometers).
UV-C: Ultraviolet radiation of short wavelengths (200-290 nanometers).

Xeroderma pigmentosum: A rare and frequently fatal pigmentary disease in which the skin and eyes are very sensitive to light. It begins in childhood and progresses to early development of freckling, and other skin lesions including benign and malignant skin tumors. The disease is inherited as an autosomal recessive trait. Total protection from sunlight prevents development of lesions completely.

5-year survival: The probability of living for 5 years after the diagnosis of a disease.
REFERENCES


