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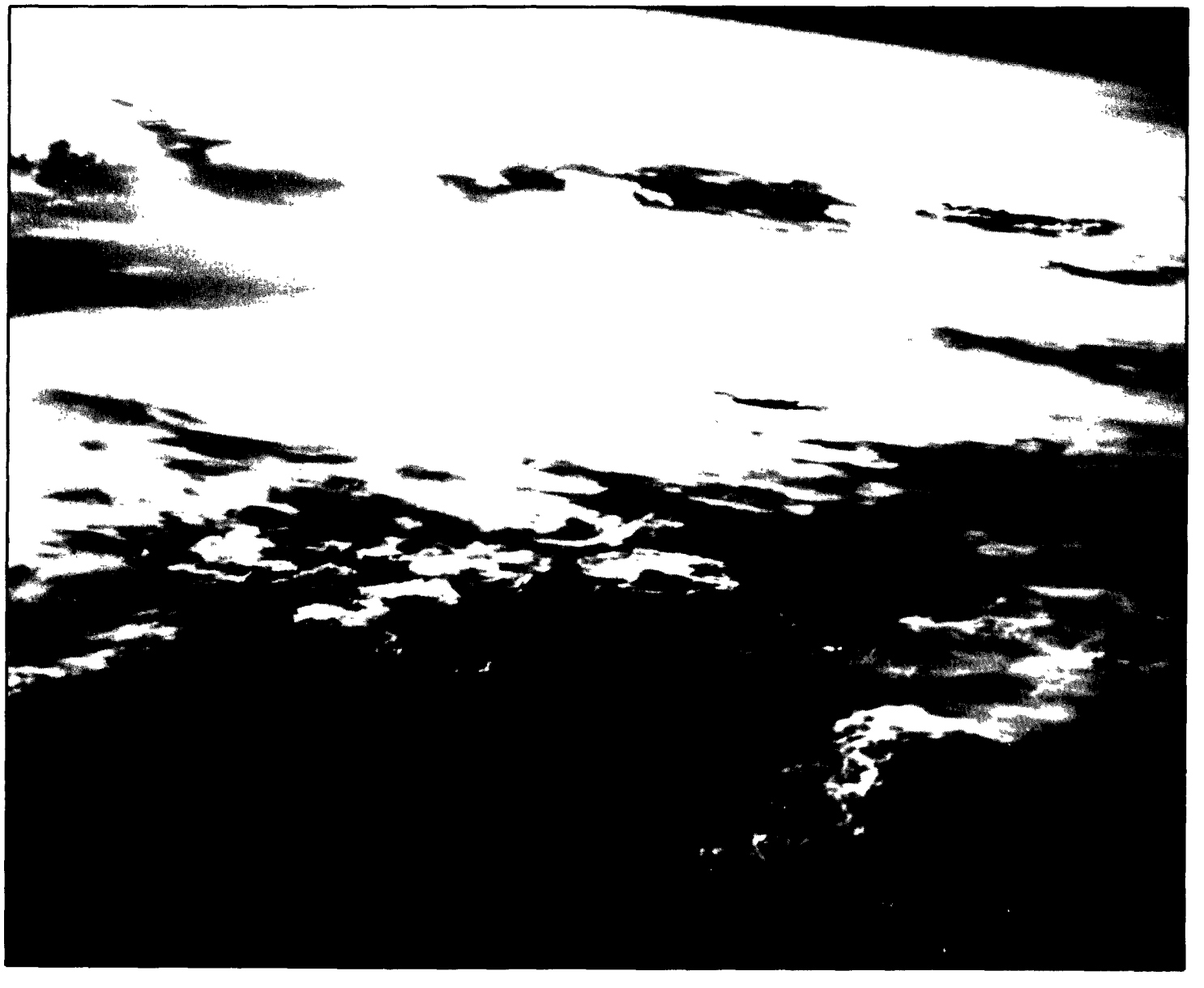
Ultraviolet Radiation and Melanoma

With a Special Focus on Assessing the Risks of Stratospheric Ozone Depletion



Ultraviolet Radiation and Melanoma

With a Special Focus on Assessing the Risks of Stratospheric Ozone Depletion

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SECTION I

INTRODUCTORY MATERIAL

INTRODUCTION

WHY MODIFICATION OF THE OZONE LAYER IS AN ISSUE

In the early 1970's, researchers hypothesized that proposed fleets of supersonic transports could unintentionally deposit nitrogen oxides directly into the stratosphere, depleting the ozone layer and allowing more ultraviolet-B radiation (UVB or UV-B) to reach the earth's surface (Crutzen 1970; Johnston 1971). Because of long known effects of UV-B on biological organisms, this possibility led to immediate concern about the potential effects of ozone depletion on health, ecological, agricultural, and aquatic systems.

Depletion of the ozone layer is a possibility because stratospheric ozone levels depend on physical and chemical processes that are constantly producing and destroying ozone molecules. In the stratosphere, high-energy ultraviolet radiation that does not reach the earth's surface photodissociates bimolecular oxygen (O2). The single oxygen atom that results chemically recombines with O2 to form ozone (O3). Ozone does not accumulate endlessly. Some ozone is lost when it is physically transported to the troposphere, where it is more easily destroyed. Other ozone is lost when O3 combines with single oxygen atoms to form O2, or in other chemical processes. Generally the various physical and chemical processes that produce and remove ozone in the stratosphere are in approximate balance, although shifts in climate and solar activity do cause seasonal and yearly variations around long-term mean ozone values.

OZONE ABUNDANCE AND ULTRAVIOLET RADIATION

The ozone layer acts as a shield for the earth, protecting its surface from all UV-C radiation (UV below 290 nanometers) and some but not all of the UV-B (UV-B in the range of 295 to 320 nanometers). Figure 1 (adapted from NAS 1982) shows how the ozone layer blocks radiation differently for various wavelengths of UV-B.

The quantity of ultraviolet radiation reaching the earth's surface varies with location because ozone density and the zenith angle describing the path of solar photons to the earth varies with latitude, creating a strong gradient for UV-B radiation. For example, models predict that the yearly dose of radiation from 295 to 299 nanometers at Nairobi, just south of the equator, is 5.2 times the energy received at Washington, DC (latitude = 38°N) and 34.5 times the radiation at Oslo (latitude = 60°N). Because ozone does not effectively filter other solar radiation, latitudinal variations in UV-A and visible light are much smaller, as shown in Figure 2. In addition to latitude, clouds can reduce the UV-B radiation reaching the earth's surface, and altitude can increase it. UV-B also varies with time of day. If the ozone layer depletes, ultraviolet radiation would increase everywhere on the earth's surface, with the largest percentage increases occurring at 290 to 300 nanometers and the smallest at 310 to 320 nanometers.

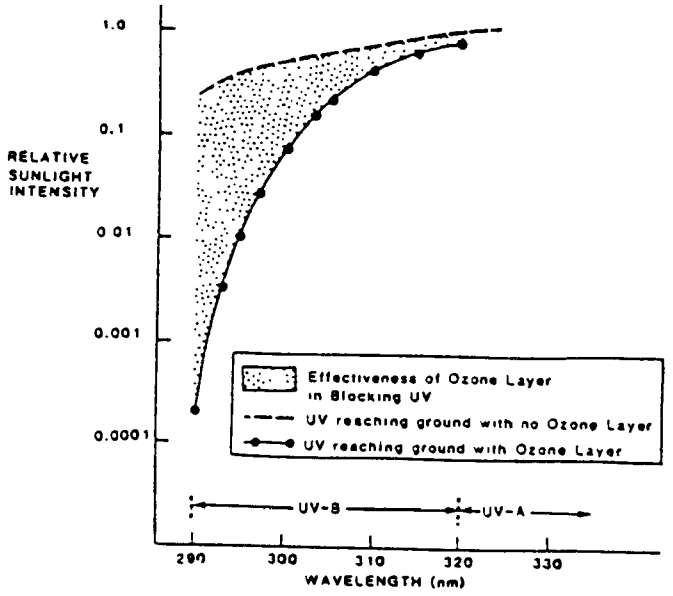


FIGURE 1
UV RADIATION WITH AND WITHOUT THE OZONE LAYER

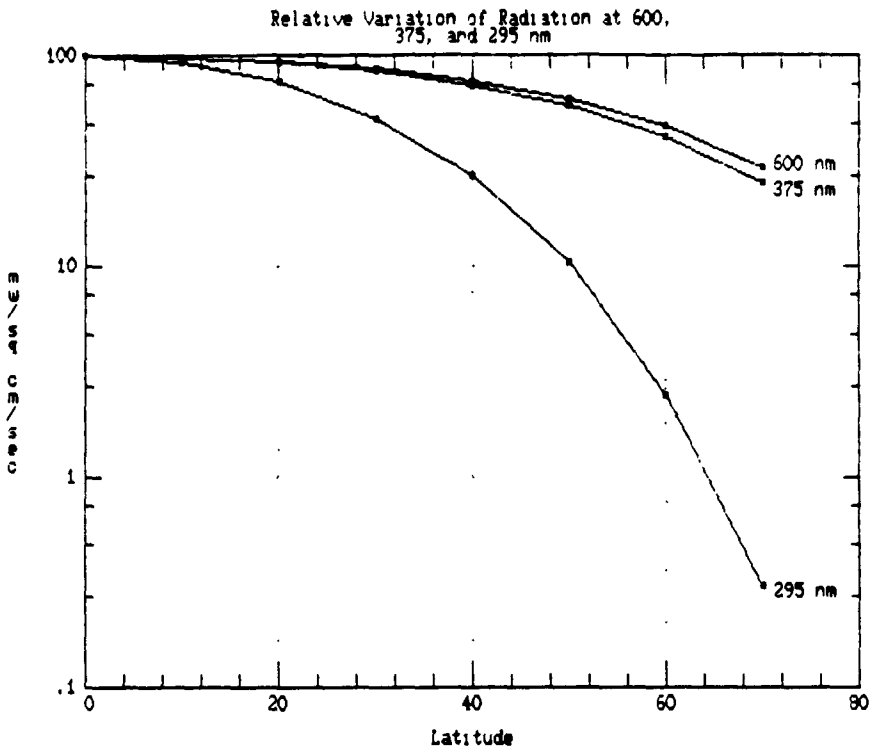
Source: Adapted from NAS (1982).

This figure shows that the effectiveness of the ozone layer in blocking UV is poor at 320 nm and improves to complete effectiveness at 290 nm.

CONCERN ABOUT CHLOROFLUOROCARBONS

In the early 1970's, Lovelock (1973) discovered that chlorofluorocarbons (CFCs) were not destroyed in the lower atmosphere (the troposphere). Instead, they were observed to accumulate, so that concentrations increase with time. Chlorofluorocarbons are used as aerosol propellants (in many countries other than the United States), refrigerants, solvents, foam blowing agents, and in many other industrial processes. In 1974, Molina and Rowland (1974) hypothesized that CFCs would not accumulate endlessly, but would, in small quantities, be transported to the stratosphere, where they would be photodissociated by high-energy radiation, releasing their chlorine. The chlorine would then enter into a catalytic cycle that would destroy ozone molecules, reducing mean ozone levels. Particular concern was expressed about this threat, because CFCs have long lifetimes: 75 years for CFC-11, 110 years for CFC-12 (NASA 1986), and 90 years for CFC-113 (NAS 1984). Because of these long lifetimes, ozone depletion due to CFCs would be almost irreversible.

Public reaction to the potential threat of chlorofluorocarbons to the ozone layer was swift. Between 1974 and 1978, the U.S. banned the use of CFCs



This figure shows that radiation varies with latitude much more for UV-B (295 nm) than UV-A (375 nm) or visible (600 nm).

FIGURE 2

VARIATIONS IN SOLAR RADIATION WITH LATITUDE

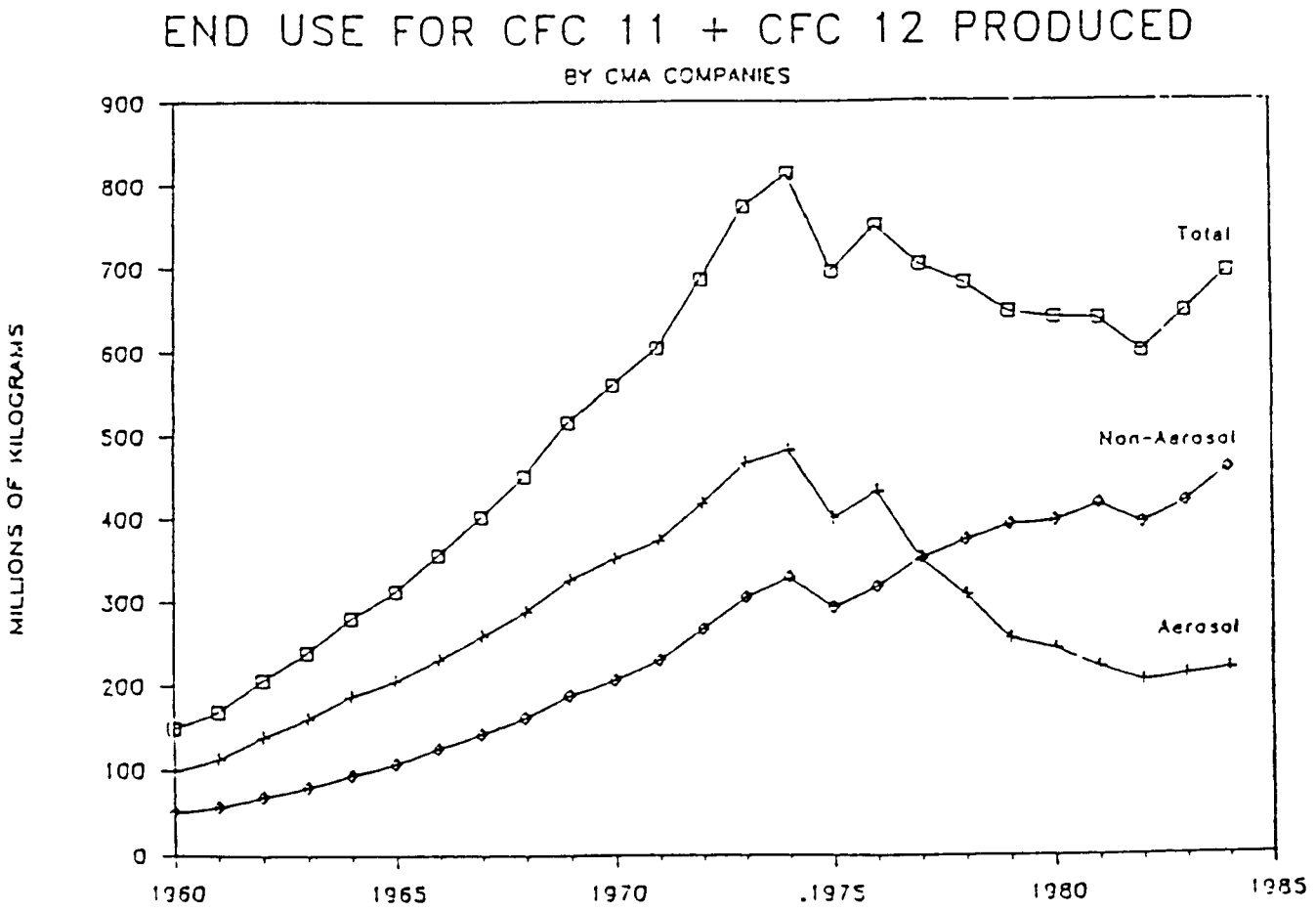


FIGURE 3
HISTORICAL PRODUCTION OF CFCs

This figure demonstrates that the flattening of the emission curve for CFC use in the last decade consists of two opposing trends: a decrease in aerosol uses and a steady increase in non-aerosol uses.

Source: Chemical Manufacturers Association (CMA) (1985).

in non-essential aerosols, the quantity of CFCs used in aerosols declined 60 percent, as consumers and producers alike abandoned CFC-propelled aerosols for hydrocarbon-propelled aerosols. After the U.S. ban of non-essential uses in 1978, CFC use in aerosols fell to negligible quantities (Kavanaugh 1986). Some but not all nations also took action to ban or reduce CFC use in aerosols. Until recently, the decline in aerosol use of CFCs worldwide had offset the steady increase in non-aerosol uses (Figure 3).

Throughout the 1970's, scientific research on ozone modification intensified. Many new studies were done on various aspects of stratospheric chemistry and dynamics, including more sophisticated analyses of the rate at which chemical reactions took place, and the types of chemical reactions that could influence the balance of ozone in the stratosphere (NAS 1976; 1979; 1982; 1984). During this period, the convention arose of using constant emissions for comparing stratospheric depletion models and for estimating future ozone depletion in assessments (NAS 1982). This standard assumption allowed easy intercomparison of models, and it seemed like a "reasonable" assumption of future CFC emissions, since growth did not seem to be occurring in that period. As stratospheric science matured, estimates of ozone depletion for constant emissions went up and down (Figure 4); the predictions are sensitive to the accuracy of a large number of factors that are subject to uncertainty.

In 1983, the assumption that CFC use would not grow in the future began to be questioned. Examination of the total trend in CFC use revealed that, while aerosol use had been falling, the use of CFCs in non-aerosols had been growing in a manner that seemed highly related to economic growth (Figure 5). As a result of this "discovery," scientists began to examine what would happen to ozone if there was sustained growth in chlorofluorocarbons. In addition, as global measurements revealed that many other potential stratospheric perturbants were also changing on a global scale, the atmospheric science community began to consider the possible influence of other gases on the stratosphere (Figure 6). Preliminary results indicated that significant global depletion might occur with higher CFC growth, and at least one model claimed that depletion may even be non-linear, once some threshold value of CFCs is exceeded (Prather et al. 1984).

Since 1983, a number of scientific studies have analyzed the risks of ozone depletion, including a large international assessment (WMO 1986). The WMO assessment examined the state of knowledge about the upper atmosphere and concluded that with sustained growth in CFCs, serious risk of ozone depletion still exists. Recent modeling efforts by Isaksen (1986) indicate that stratospheric ozone depletion is a real risk (Figure 7). This time-dependent model shows significant depletion at different altitudes. Furthermore, the recent discovery that ozone has been depleted over 50 percent in the last six years in the Antarctic region raises new concerns about the vulnerability of the ozone layer (Farman et al. 1985). This has spurred intensive scientific efforts to ascertain the causes and potential implications of this unexpected

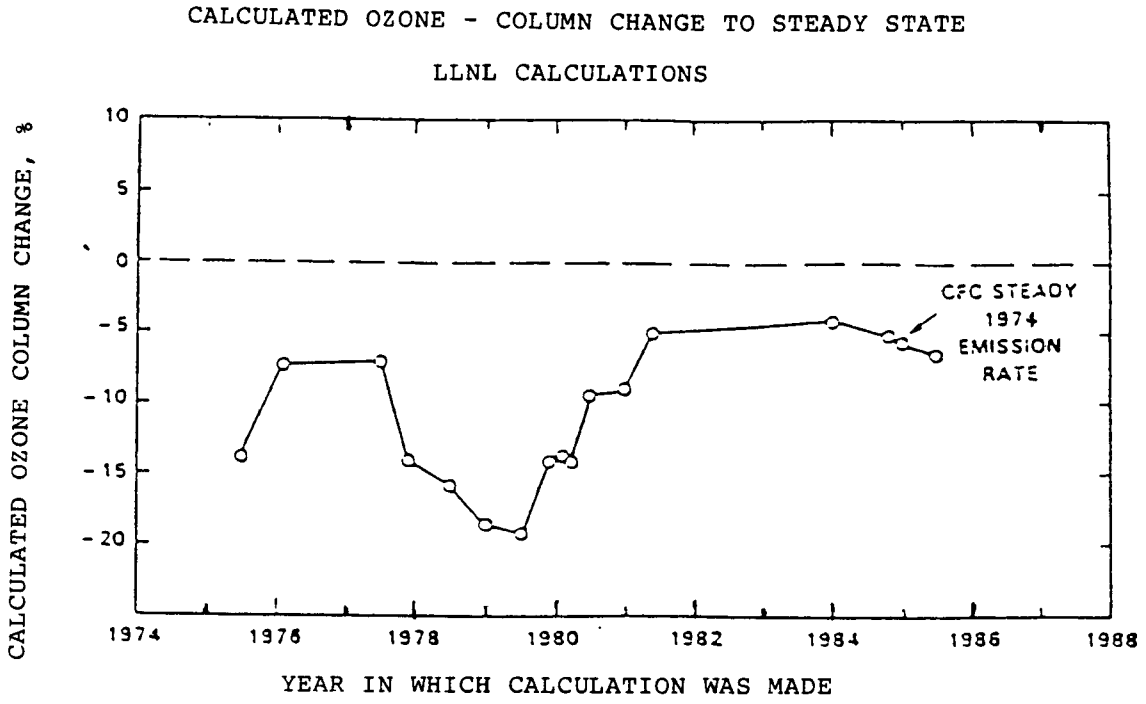


FIGURE 4

DEPLETION ESTIMATES FOR THE LAWRENCE LIVERMORE ATMOSPHERIC MODEL OVER TIME

This figure shows how "best case" depletion estimates for steady emissions at 1974 level of CFCs have shifted over time with changes in kinetics, cross sections, and chemistry.

Source: Connell and Wuebbles (1986).

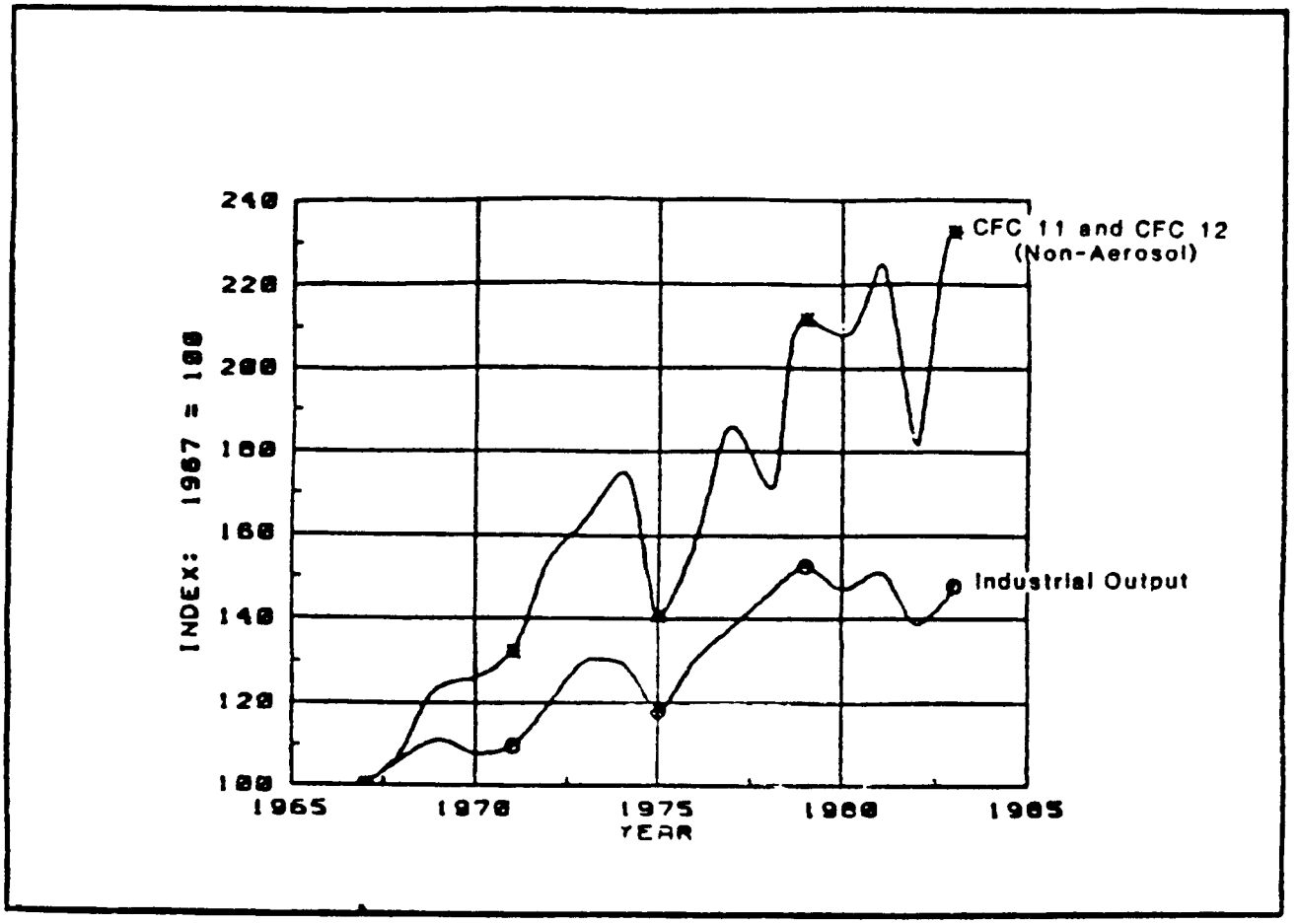


FIGURE 5
U.S.: NON-AEROSOL CFC PRODUCTION VERSUS
TOTAL INDUSTRIAL OUTPUT

Correlation coefficient = 92%.

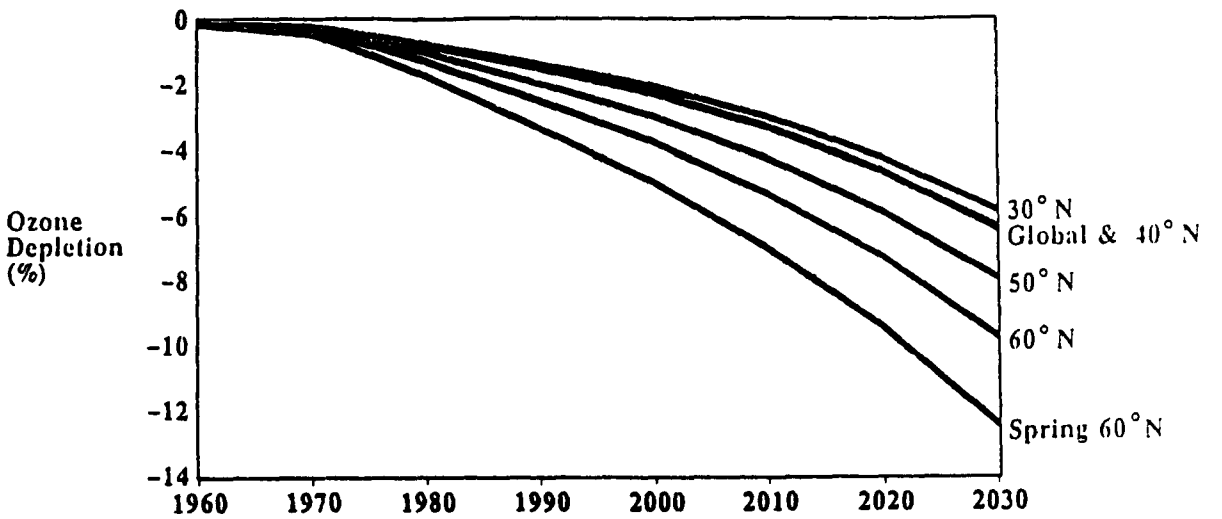
This figure shows that non-aerosol CFC production has been closely associated with aggregate industrial output, growing at approximately twice its rate.

Source: Based on Council of Economic Advisors (1984), Palmer et al. (1980), and USITC (1968-1984).

Compounds	Rate of Increase Per Year	Stratospheric Ozone	Global Temperature
Chlorofluorocarbons	about 5% per year	Depletes	Increases
Halons (Bromine)	about 22% per year	Depletes	Increases
Methane (CH_4)	about 0.017 ppm per year	Counters Depletion: Adds Ozone (Troposphere)	Increases
Nitrous Oxide (N_2O)	about 0.25% per year	Counters Depletion in High Chlorine Cases	Increases
Carbon Dioxide (CO_2)	about 0.6% per year	Adds Ozone (by cooling stratosphere)	Increases

FIGURE 6

GASES INCREASING GLOBALLY THAT INFLUENCE THE STRATOSPHERE AND GREENHOUSE EFFECT



Scenario of Growth Rates

CFCs: 3%
CH4 : 1%
CO2 : 0.6%
N2O : 0.25%

FIGURE 7

DEPLETION ESTIMATES AT VARIOUS LATITUDES

Source: Isaksen (1986).

phenomenon. Efforts are being made, worldwide, to assess the risks posed by various substances to the stratosphere and the health and welfare risks that stratospheric modification might pose. This report assesses the risk that stratospheric modification will cause an increase in the severity or incidence of melanoma.

PREVIOUS REVIEWS OF THE RELATIONSHIP OF MELANOMA, UV-B, AND OZONE DEPLETION

The relationship between skin cancer and exposure to solar radiation has been a subject of interest for many years. The information relevant to assessing the role of UV radiation as a causal factor in skin cancer in man has been the subject of many reviews (Urbach 1969; CIAP 1975; Scott and Straf 1977; NAS 1979; NAS 1982) and it has generally been accepted that the likelihood of basal and squamous cell cancers increases with accumulated UV exposures (Fears at al. 1977; Fitzpatrick 1986).

The relationship of cutaneous malignant melanoma to solar radiation exposure has been considered to be less clear. A latitude gradient for CMM was reported as early as 1975 (Scott and Straf 1977); however, conclusions from review to review about the relationship of CMM to solar exposure have tended to ascribe different degrees of certainty to the relationship. Thus, in 1979, the NAS concluded "...UV-B exposure [however]...the dose-response relationship between skin melanoma and UV-B appears to be more complicated than that observed for non-melanomas of the skin" (NAS 1979).

By 1982, the NAS concluded, "Since 1976, the case for an association between UV-B and melanoma has been weakened rather than strengthened by the results of additional clinical pathological and epidemiological studies. Furthermore (with the exception of a single animal), it has not been possible to use UV-B alone to induce melanomas in experimental animals." (NAS 1982). Even within the same review, there has been uncertainty. For example, NAS (1982) stated:

> "The incidence of skin melanoma appears to depend on latitude, an indication that sunlight is a contributing factor. Circumstantial evidence such as occupational differences and location of cancers on the body suggests, however, that exposure to sunlight is only one of several factors."

Still more recent reviews (Fitzpatrick and Sober 1985; Clark et al. 1986; Holman et al. 1986) conclude that the relation between melanoma and solar radiation is different from that observed for non-melanoma in that the exposure parameter of concern is probably related to intense intermittent exposures, and there is a greater impact of precursor lesions.

Since the NAS review in 1982, a wealth of new information has been added to the data base. In assessing whether a decrease in column ozone with the resultant increase in UV-B will be associated with an increase in cutaneous melanoma, this review draws on the past literature to examine the data base which led to such diverse conclusions as those presented in the NAS reports, and adds to the examination an analysis of the new information and its impact on assessing the role of UV-B in melanoma development.

CHAPTER 1

GOALS AND APPROACH OF THIS RISK ASSESSMENT

Under Part B of the Clean Air Act, the Administrator of the Environmental Protection Agency (EPA) "shall propose regulations for the control of any substance, practice, process, or activity (or any combination thereof) which in his judgment may reasonably be anticipated to affect the stratosphere, especially ozone in the stratosphere, if such effect in the stratosphere may reasonably be anticipated to endanger public health or welfare" (42 U.S.C. 7457). This report seeks to provide the Administrator of EPA with a basis for making a judgment about whether cutaneous malignant melanoma (CMM) can be reasonably anticipated to increase in incidence or severity if there is a modification of the column density of ozone and consequent alteration in the flux of ultraviolet-B (UV-B) radiation reaching the earth's surface. This report seeks to determine what dose-response relationships are consistent with current epidemiological evidence on melanoma and UV, so that quantitative estimates can be made of how an alteration in the flux of UV would change the incidence and mortality of various populations for melanoma.

LEGAL BACKGROUND AND FRAMEWORK

In January 1986, the EPA issued a Federal Register Notice (51 FR 1257: January 10, 1986) that announced a program of domestic and international activities aimed at reaching domestic and international decisions on the need to take additional action to control stratospheric perturbants. EPA announced that it will issue a Federal Register Notice in May 1987 that either proposes regulations or proposes that no regulations are needed. Under the auspices of the United Nations Environmental Programme, an international diplomatic conference is also scheduled in April 1987, at which time an attempt will be made to achieve agreement on an international protocol on chlorofluorocarbons (CFCs).

As part of the preparation for those decisions, the staff of EPA is submitting this risk assessment to the Science Advisory Board (SAB) in October 1986. The review analyzes all aspects of the stratospheric protection issue. The SAB will review this document and after revision it will be used by the Administrator of EPA as the scientific foundation for analysis of various risk management options. This report is an appendix of that review that assesses the likelihood that ozone could alter the incidence or severity of melanoma. The Administrator will use the risk assessment document and later risk management analyses to decide what is to be done.

THE FOCUS OF THIS REVIEW

Cutaneous malignant melanoma is a complex disease, with a complex etiology. For several decades, concern has been expressed about the relationship of sunlight, UV-B, and melanoma, with a large body of literature hypothesizing a strong relationship. The etiology of melanoma, however, is

far from being completely understood. There is no irrefutable proof that solar radiation (including ultraviolet radiation) is among the causes of the disease. Some evidence seems to support the hypothesis that solar radiation (and UV-B in particular) is one of many factors that cause melanoma. Some evidence seems to undermine the hypothesis that solar radiation (and UV-B in particular) is among the causes of melanoma. This report weighs and balances the evidence that melanoma incidence could increase if there is a change in UV-B radiation, applying the standard that Congress legally mandated--whether "it may be reasonably anticipated" that the particular effect will occur if there is a change in the ozone layer. In making such a judgment, one must decide whether available information supports the view that melanoma incidence or mortality will vary if ozone density varies, not whether the evidence provides certainty or a complete understanding of the etiology of the disease. Consequently, this report focuses on the weight of evidence, not the specific etiology or mechanisms by which people get melanoma. From the perspective of the public health decision mandated by Congress, the issue is not whether we understand the exact mechanisms by which UV might indicate or promote melanoma, or whether we are certain or almost certain of the relationship, but rather, whether the weight of all evidence appears to support a judgment that there is a reasonable probability that variations in UV-B can cause variations in melanoma incidence or severity.

APPROACH

To address whether a change in UV-B may be reasonably anticipated to alter melanoma incidence or mortality, we will try to answer three distinct questions:

1. **Does the evidence support the hypothesis that for susceptible populations, solar radiation is a cause of melanoma?**

2. **Does the evidence support the hypothesis that UV-B is a major component of solar radiation which causes melanoma?**

3. **What dose-response relationships between melanoma and UV-B are consistent with the epidemiological and experimental data?**

To address these questions, the literature review has been organized around a variety of commonly held assertions or "findings" about melanoma. For example, many studies have "found" that melanoma varies with latitude; other studies have claimed differences between males and females; other studies have "found" that migrants differ from natives in their likelihood of getting melanoma. Our report first analyses such "findings" to determine the scientific rigor of studies that support or deny each finding. In Chapter 19 (Conclusions) we consider the implications of these findings (to the extent they are supported) for each question.

REPORT ORGANIZATION

This review starts with three background chapters, then goes on to eleven epidemiological chapters, three chapters on animal, cell, and molecular evidence, and one chapter on plausible dose-response relationships. Finally, the last chapter presents our conclusions with regard to the three questions raised above: is solar radiation probably one cause of CMM in sensitive populations, is UV-B a likely component of solar radiation responsible for this disease; what dose response relationship(s) is (are) appropriate for predicting future incidence and mortality?

This chapter has discussed the legislative framework and focus for this review. Chapter 2 discusses how the energy delivered at different wavelengths of UV varies by season, time of day, latitude, and altitude, and how the energy delivered relates to what is biologically effective. The third background chapter provides information necessary for understanding the nature and magnitude of melanoma as a disease, along with key aspects of skin biology and photobiology useful for interpreting other chapters.

Chapter 4 reviews information on time trends in melanoma incidence and their relationship to age, period, and birth cohort effects. Chapter 5 examines the anatomic site distribution of melanoma, analyzing potential implications of this information for understanding the character of the solar radiation melanoma relationship. Chapter 6 reviews the geographic distribution (latitude and altitude of CMM). Since latitude and altitude are surrogates for variations in solar radiation, with UV-B varying far more than UV-A or visible light, this chapter will have relevance both to the issue of the relationship of solar radiation and melanoma and to the issue of whether UV-B is a component of sunlight that may be an agent. Chapter 7 examines the trends in melanoma incidence among persons migrating from lower to higher sunlight areas. Chapter 8 examines the relationship of intermittent or severe exposure to solar radiation and melanoma incidence. Chapter 9 summarizes information from studies which examined measures of cumulative solar exposure. Chapter 10 examines the relationship between pigmentation and the incidence of melanoma. This information has a bearing on how to interpret other epidemiologic evidence, and provides information on an interesting "natural" experiment in how the skin transmission qualities of different populations modify their reaction to solar radiation. Chapter 11 evaluates information on the correlation between melanoma incidence rates, and socioeconomic status and occupational factors. Chapter 12 examines the potential relationships between variations in melanoma incidence rates in certain populations and a variety of environmental factors including steroid hormones and immunosuppression regimens. This information is also useful for interpreting data presented in other chapters. Chapter 13 examines several predisposing lesions for melanoma, providing important information for interpreting the data from epidemiologic studies. Chapter 14 compares and contrasts the behavior of nonmelanoma and melanoma skin cancer in order to investigate what the differences in behavior mean relative to an etiologic agent or mechanism.

The chapters on animal, cellular and molecular, and immunologic studies then focus on solar radiation effects as determined in experimental studies. Chapter 15 reviews information on the effect of UV-B as interpreted through studies of cells, and also reviews studies of the effects of UV-B at the molecular level, particularly with regard to impacts on DNA and urocanic acid. Chapter 16 reviews the information on the role of UV-B as a causal agent in animal tumors and indicates that animals can be induced to develop melanomas but that as yet there is no animal model for melanoma induction by UV-B. Chapter 17 reviews information on the immunosuppressive effects of UV-B and how this may affect melanoma. Chapter 18 reviews the epidemiologic literature to determine what relationship(s) can best be used to determine how much increase in melanoma to expect if the density of column ozone is altered. Chapter 19 summarizes our conclusions about solar radiation and UV-B as an agent for melanoma in susceptible populations, bringing together all the evidence, examining what conclusions can be made, and the uncertainties remaining.

Appendix A reviews the process used to develop this report, available data bases developed (including a description of the keyword system developed), and a bibliography of articles reviewed. Appendix B reviews, in detail, several major epidemiologic studies considered crucial to these analyses, for their scientific rigor and applicability, and presents detailed reviews of many other epidemiologic studies. While these studies are discussed in earlier chapters, these reviews go into much greater depth about methodology and design of the studies. There are also reviews of other epidemiologic studies used in developing the analysis presented in subsequent chapters.

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CHAPTER 2

SOLAR RADIATION AND ITS POTENTIAL BIOLOGICAL EFFECTIVENESS

In order to understand the potential of solar radiation, and ultraviolet-B (UV-B) radiation in particular, as etiologic agents in the development of cutaneous melanoma, the characteristics of solar radiation in the environment and its effect on biological targets must be understood. This chapter examines the physical and biological concepts relevant to understanding how potential exposure and biologically effective doses of solar radiation might be measured and might differ. An analysis of the role of UV-B in CMM based on the epidemiologic and experimental evidence presented in this document requires an understanding of the material covered in this chapter.

The chapter is divided into three parts:

- An overview of key concepts:
  - -- an explanation of the spectrum (wavelengths and energy);
  - -- the various units of energy used in studies and their equivalencies;
  - -- the relationship of spectral characteristics of light to biological effectiveness (the action spectrum); and
  - -- an explanation of the difference between exposure dose and biologically effective dose.
- The key action spectra, with emphasis on potential targets in the skin:
  - -- the key targets in skin; and
  - -- the relative effectiveness of different wavelengths in inducing cell mutation, lethality, and transformation.
- Estimates of variation in solar radiation received at the earth's surface*:
  - -- variations in solar radiation with different times, locations, and conditions on the earth; and
  - -- variations expected with ozone depletion.

*Information on variation in solar radiation by wavelength comes from a model developed using the National Aeronautics and Space Administration (NASA) satellite data, detailed information for which is given on pages 2-16 and in Serafino and Frederick 1986.

AN OVERVIEW OF BASIC CONCEPTS OF SOLAR RADIATION AND BIOLOGICAL EFFECTIVENESS

The sun produces energy by the process of nuclear fusion. Energy is transferred from the sun to the earth by radiative processes in the form of electromagnetic energy. Electromagnetic energy can be divided into a spectrum, in which photons that transfer energy have both a wavelength and energy level. Figure 2-1 shows the electromagnetic spectrum; it is divided into ultraviolet, visible, and infrared regions. Ultraviolet radiation (UVR) has been further divided into three parts: UV-C, UV-B, and UV-A. With time, the definition of UV-B has been shifting; in this analysis we will adopt the convention that UV-C is all UV radiation below 295 nanometers (nm), that UV-B is radiation between 295 nm and 320 nm, and that UV-A is radiation between 320 nm and 400 nm. Early researchers used 280 nm to 320 nm as UV-B; however, the absorption of all radiation below 295 nm by the ozone layer makes the definition (adopted by many later researchers) of 295-320 nm as UV-B much more biologically useful as a cutoff point.

The quantity of ultraviolet radiation can be measured in a variety of units. Table 2-1 provides a table of units used and their definitions.

Most of the energy received by the earth is in the visible part of the electromagnetic spectrum. Figure 2-2 shows the energy received at the earth's surface. Clearly some filter acts to limit the amount of radiation below 320 nm that reaches the earth's surface; that filter is primarily the ozone layer. The ozone layer is and will continue to be, even if ozone depletion occurs, an effective shield for UV-C, preventing almost all of it from reaching the earth's surface.

Biological Effectiveness of Different Wavelengths

Some molecules have the capacity to absorb ultraviolet radiation and in so doing undergo changes which manifest as adverse biological effects. For any given molecule the probability of photon absorption will vary with the wavelength of radiation. Thus the relative effectiveness of radiation for producing a specified biological response is strongly dependent upon its wavelength. For example, radiation at 295 nm may be ten, a hundred, or even a thousand times more effective in producing a given effect on a target molecule than energy at 315 nm. In contrast, some wavelengths of radiation are totally ineffective at producing given biological effects. Figure 2-3 shows the relative effectiveness of three wavelengths in inducing pyrimidine dimers in DNA (that is, in facilitating the covalent bonding of two adjacent pyrimidine molecules) as compared to their effectiveness in inducing cellular transformation.

A plot of the relative effectiveness of different wavelengths of UVR in inducing a given endpoint is termed the action spectrum of that endpoint. It

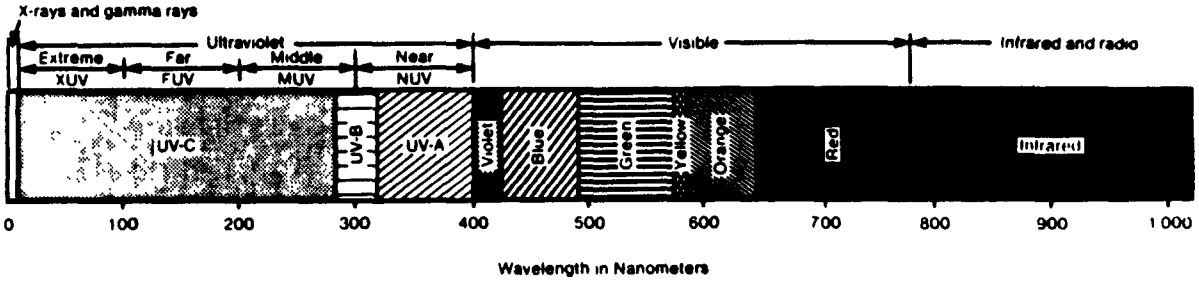

FIGURE 2-1

THE ELECTROMAGNETIC SPECTRUM

Source: Adapted from Scotto 1986.

TABLE 2-1

UNITS COMMONLY USED TO IDENTIFY QUANTITIES OF RADIATION

Quantity	Commonly Used Units	Symbol
Radiant energy	joule	J
	kilowatt-hour	kWh
Radiant density	joule per cubic meter	J/m^3
Radiant flux	watt	W
	joule per second	J/s
Radiant flux density at a surface	watt per square centimeter	W/cm^2
Radiant existence	joule per second per square centimeter	$J/s/cm^2$

Source: Weast and Astle (1978).

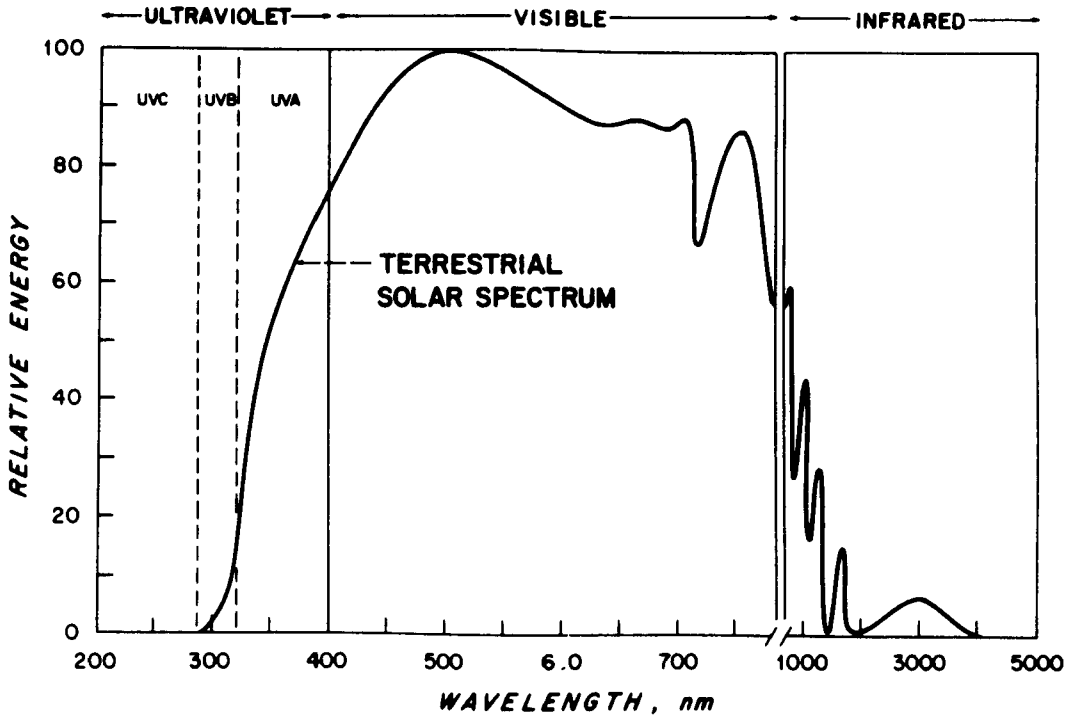

FIGURE 2-2

SPECTRUM OF ELECTROMAGNETIC RADIATION THAT REACHES THE EARTH'S SURFACE FROM THE SUN. WAVELENGTHS SHORTER THAN ABOUT 290 NM ARE ABSORBED BY OZONE IN THE STRATOSPHERE

Source: Kochevar (1983), Plenum Publishing Corp. Reproduced by permission.

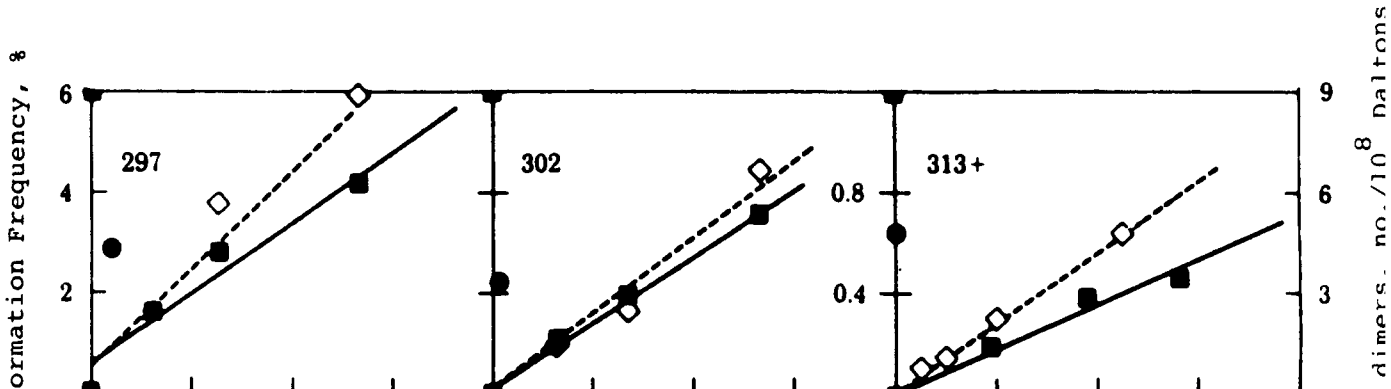

FIGURE 2-3

EFFECTIVENESS OF 297, 302 AND 313+ NM UV-R
AT INDUCING PYRIMIDINE DIMERS, (□) AND TRANSFORMATION (■)

Source: Adapated from Doniger et al. (1981).

provides a clear picture of the relative efficiency of various wavelengths of radiation in producing a specified effect in a molecule, cell, organ, or entire organism. The action spectrum plots the dose of radiant exposure necessary to produce an effect versus the wavelength at which that dose occurs; it will differ for different cells or organs because radiation absorption is determined by the chemical composition of the photoreceptors in the exposed tissue. The presence of absorbing molecules or chromophores determines the relative effectiveness of the incident radiation (Pitts et al. 1977).

Several general approaches have been used by researchers to derive action spectra for different biological effects. One common approach relies on monochromatic radiation sources. The relative effectiveness of individual wavelengths (or bands of wavelengths) is determined by measuring the dose of radiation needed to produce a specified biological response at each wavelength. The response generally is defined as a threshold value. For example, the response defining the effective dose at each wavelength often is set at the dose which causes a 50 percent or greater occurrence of some effect (e.g., mortality), in the biological system under investigation. Thus, the dose causing a 50 percent or greater response rate describes the relative effectiveness of each wavelength. The most "effective" wavelength (which is defined as that wavelength which requires the least amount of radiant energy to cause the specified effect) is then chosen as a reference point and its corresponding dose measurement assigned a unit value. The other dose levels at the different wavelengths are then normalized to correspond with the reference point. The compilation of dose levels at the various wavelengths thus forms a spectrum over which the relative effectiveness of each wavelength for producing a particular effect is compared.

The Difference Between Exposure Dose and Biologically Effective Dose

There are certain concepts that are critical to understanding the dosimetry associated with exposure to solar radiation and its possible role in cutaneous malignant melanoma. Table 2-2 presents four dose concepts designed to address the difference between the energy which is delivered and that which is effective. The total amount of energy across all wavelengths that an individual could possibly receive--equivalent to the energy delivered during the sunlit hours--is defined as the potential exposure dose. The actual exposure dose is defined as that fraction of the energy present in the sunlit hours which is actually delivered to skin--the potential exposure dose modified by clothing and sun exposure habits. The potential biologically effective dose will be defined as the amount of effective energy present in the actual exposure dose. The potential biologically effective dose is determined by using a weighting factor for each waveband which is based on the action spectrum for the effect of concern. The weighting factor for a waveband times the amount of energy delivered in the actual exposure in that waveband is equal to the amount of effective energy delivered per waveband. The sum of the products across all wavebands present in the actual exposure dose is equal to the potential biologically effective dose. The actual biologically effective dose--the amount of energy actually delivered to the target cell or molecule--is the potential biologicially effective dose

TABLE 2-2

DOSE CONCEPTS IN PHOTOBIOLOGY USED IN THIS DOCUMENT

Potential exposure dose	--	the total amount of solar energy that an individual could receive--equivalent to the amount of solar energy delivered in the sunlit hours at place(s) of work or residence.
Actual exposure dose	--	the amount of total solar energy delivered to the skin surface--the potential exposure dose modified by clothing and behavior patterns.
Potential biologically effective dose	--	the amount of biologically effective energy present in the actual exposure dose--determined by applying a weighting function based on an action spectrum to the actual exposure dose.
Actual biologically effective dose	--	the actual amount of biologically effective energy delivered to the target in the skin--the energy in the potential biologically effective dose modified by the absorptions of energy by competing chromophores (e.g., keratin and melanin) prior to its reaching the target.

modified by additional factors such as an individual's pigmentation characteristics and the amount of other competing photoreceptors.

ACTION SPECTRA OF CONCERN IN HUMAN SKIN

UVR induces a number of effects in the skin which could influence the induction and growth of cutaneous melanoma. Each effect has its own action spectrum; thus there are a number of weighing functions which potentially could be important to estimating the biologically effective dose. Presented below are action spectra from a number of different effects that could be important to the etiology of sunlight in CMM. Detailed discussions of these effects are presented in subsequent chapters.

Figure 2-4 shows the average action spectrum for DNA damage proposed by Setlow (1974); its importance lies in the role DNA damage plays in carcinogenesis (see Chapter 15 for detailed discussion). Figure 2-5 shows the erythema action spectrum (which is related to those wavelengths most effective in causing sunburn) as compared to that for melanogenesis (tanning); the weighting function derived from the erythema action spectrum would be similar to that for the Robertson-Berger (R-B) meter. Figure 2-6 shows the action spectrum for edema in mice as compared to that of Setlow for DNA damage and that of the R-B meter. Cole et al. (1986) found the edema action spectrum to provide the most appropriate weighting function for assessing the carcinogenic impact of UVR in mice. Figure 2-7 shows the absorption spectrum* for urocanic acid and the action spectrum for the induction of systemic suppression of contact hypersensitivity (CHS), two possible mediators of the effect of solar radiation on the immune system (DeFabo and Noonan 1983). A key characteristic of the action spectra presented here is that energy in the UV-B (295-320 nm) wavelengths tend to be much more biologically active than UV-A or visible light.

VARIATIONS IN AMBIENT SOLAR RADIATION

The total amount of energy from ultraviolet radiation that any target receives in a given amount of time (the actual exposure dose) will depend, in part, on the variations in ambient radiation that occur in the natural environment. One effect of the earth's rotation and revolution is the modification of potential exposure doses from place to place over time. Ambient solar radiation incident on various sites on the earth's surface varies significantly with the latitude, altitude, season (day of the year), time of day, cloudiness, reflectiveness of surfaces (albedo), and atmospheric aerosols. More important, these variations differ in intensity for different wavelengths of the UVR. Understanding these variations in UVR is critical to predicting the effectiveness of solar radiation and its role in cutaneous melanoma induction. In general, ambient UV-B varies much more than UV-A or

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* An absorption spectrum only measures the amount of incident radiation absorbed by a molecule at individual wavelengths, whereas an action spectrum relates the amount of energy absorbed at each wavelength to an effect.

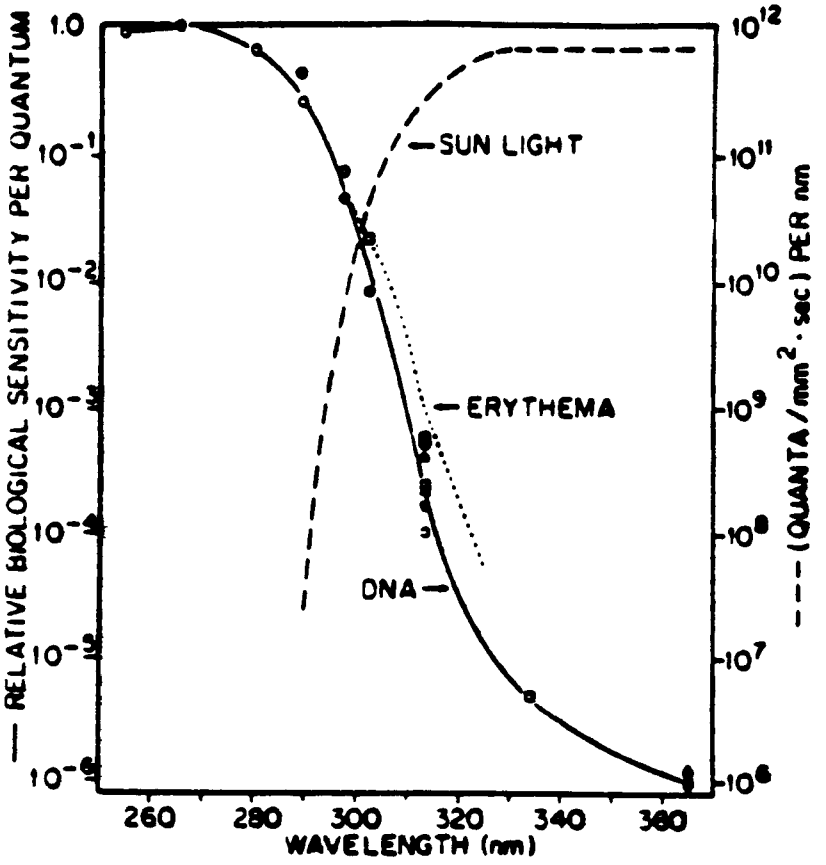

FIGURE 2-4

AVERAGE DNA ACTION SPECTRUM

Source: Adapted from Setlow (1974).

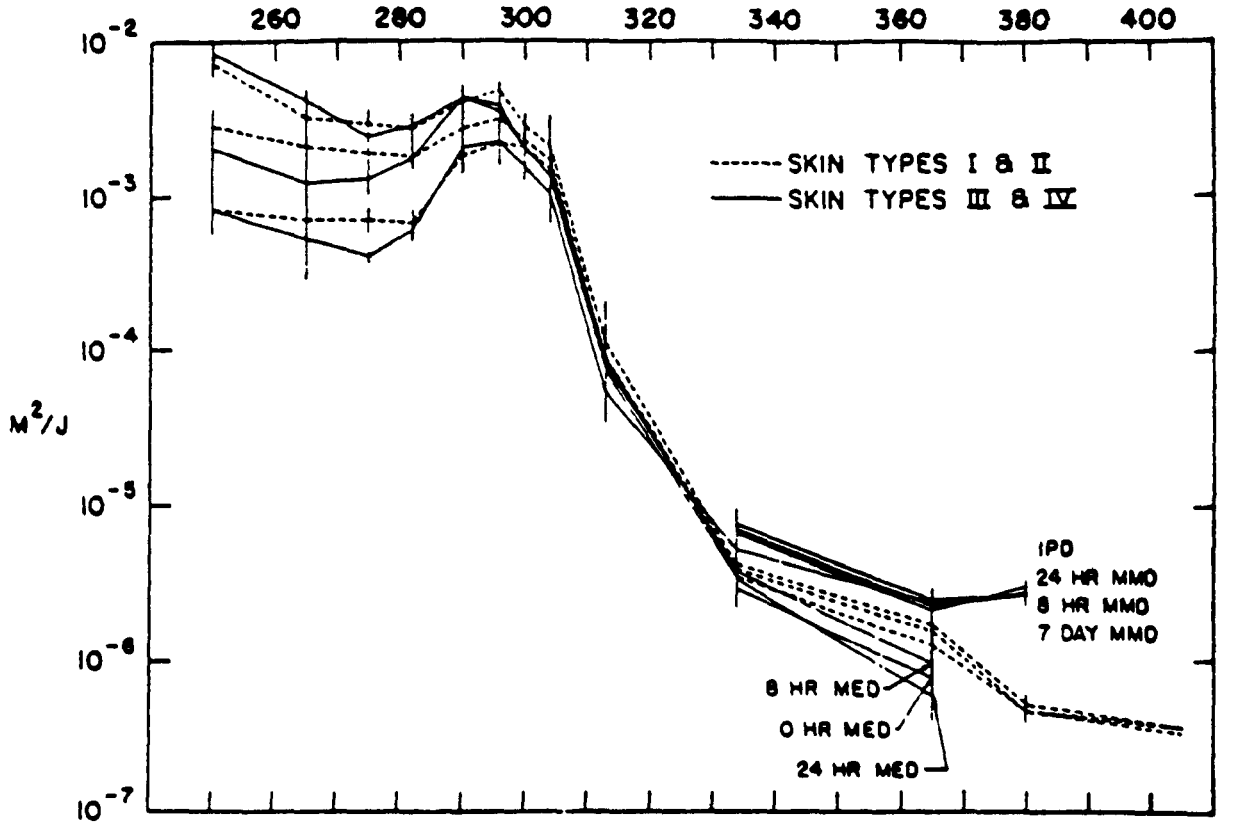

FIGURE 2-5

ACTION SPECTRA FOR ERYTHEMA AND MELANOGENESIS

MED = minimum effective dose; MMD = minimum melanogenic dose, skin types I, II, III, IV discussed on pg. 3-22

Source: Gange et al. (1986).

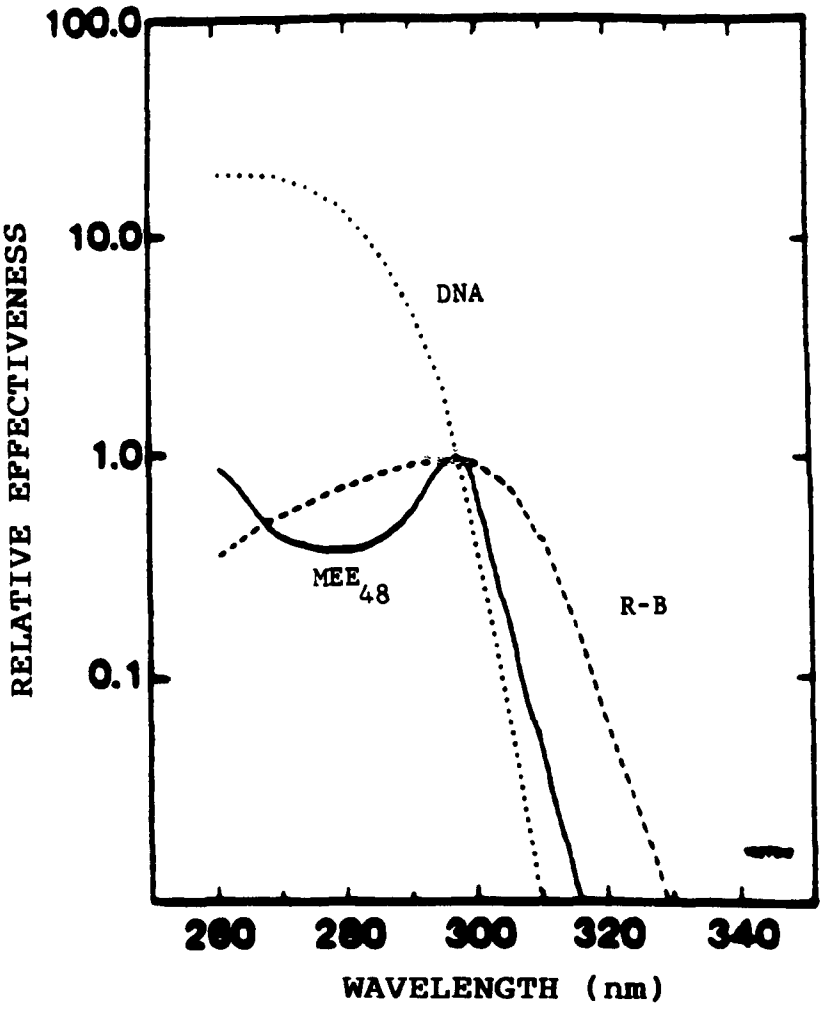

FIGURE 2-6

ACTION SPECTRUM OF MOUSE EDEMA (MEE48)
AS COMPARED TO THAT OF DNA DAMAGE
AND THE ROBERTSON-BERGER (R-B) METER

Source: Cole et al. (1986), Pergamon Press, Inc. Reproduced by permission.

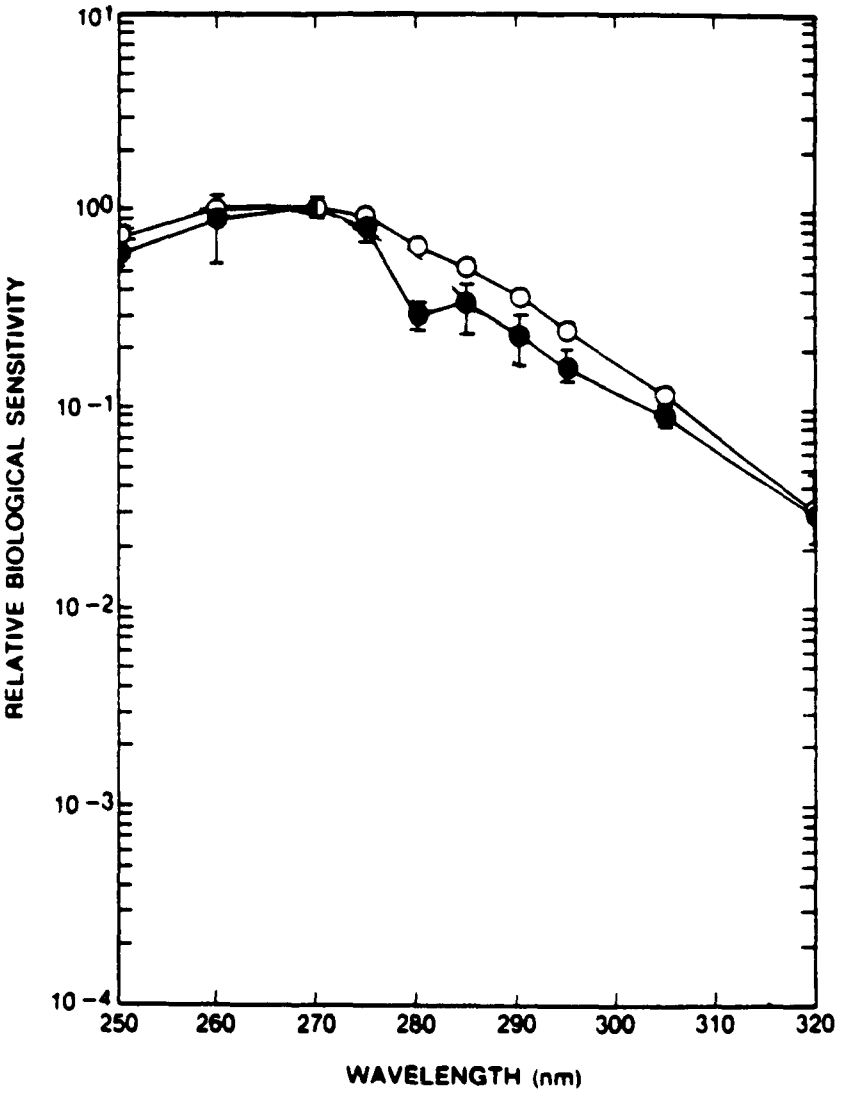

FIGURE 2-7

THE ACTION SPECTRUM FOR THE INDUCTION OF CONTACT HYPERSENSITIVITY (-•-) AS COMPARED TO THE ABSORPTION SPECTRUM OF UROCANIC ACID (-o-)

Source: Adapted from DeFabo and Noonan (1983).

visible light. The potential biologically effective dose a person receives will depend not only on the action spectrum of concern for potential skin targets, but also on the distribution of energy in the various wavebands. Differential variation is very important to understanding or computing this dose. For example, if total sunshine hours were the only consideration, that is, if photons in the UV-B, UV-A, and visible wavelengths were equally effective, then outdoor workers would clearly receive a larger dose of effective energy than indoor workers. However, if UV-B is more important biologically, then the situation could be different; since the amount of energy delivered in the UV-B range is highest at noon, an office worker who intentionally exposes himself to sunlight on the beach from 11:00 a.m. until 2:00 p.m. on weekends may receive greater radiation at 295 nm than an outdoor worker who eats in the shade every noonday and wears protective clothing. Thus, in order to calculate the actual biologically effective dose of solar radiation an individual receives, one must consider not just sunlit hours, but also the exposure to particular wavelengths as they are related to particular effects of concern.

Modulators of Actual Exposure and Biologically Effective Doses

The actual biologically effective dose of solar radiation a person or target molecule receives at a given wavelength depends on several factors other than the potential exposure dose at a certain location. One important factor is the amount of time a person spends outside during certain periods of the day. The total amount of energy delivered at a given location provides an upper bound of exposure, not the actual exposure. Few individuals are out in the sun during all daylight hours; therefore, actual exposure is correspondingly reduced. As indicated in a subsequent section, seasonal and hourly variations in incident solar radiation are quite significant, particularly in those wavelengths that are most biologically effective (295-299 nm), so all hours in the sun cannot be considered equal. People living in areas having the same number of sunlit hours may have additional behavioral differences that modify the amount of radiation reaching the skin (the actual exposure dose). For example, some people wear a great deal of clothing; others do not. Some people wear sunscreens; others use sun reflectors to gather more solar radiation.

In addition to these difficulties in determining the actual exposure dose for an individual, the transition from an actual exposure dose to a potential biologically effective dose also involves technical problems. The determination of the potential biologically effective dose is influenced principally by the choice of weighting function. Using different weighting functions (based on different action spectra) will result in differing estimates of the potential biologically efffective dose. Estimating a biologically effective dose via the use of a weighting function based on the action spectrum for erythema would probably overestimate the role of UV-A if the effect of concern was related to DNA damage because the DNA damage action spectrum lies more in the UV-B range than does that of erythema.

The actual biologically effective dose is the result of still additional factors which modify the potential biologically effective dose. Probably the

most important such factor is the degree of pigmentation. As discussed in detail in Chapter 3, melanin, the major pigment in the skin, absorbs UV radiation; the more energy absorbed by melanin, the less energy there is available to be absorbed by target molecules. The quantity of melanin in black skin is much more effective in preventing solar radiation from reaching targets than the lower quantity of melanin present in an olive-skinned white person; the quantity of melanin in the skin of a fair-skinned redhead is probably the least effective. A person who is tanned receives a lower dose of solar radiation to the basal layer than someone who is not tanned. Since tanning can take place in different seasons, when UV-B varies, the actual dose received is not invariant with the time of year when the first sun exposure started. Wavelengths of solar radiation vary differentially with season; someone who starts getting significant sun exposure in March or April (outdoor workers, for example) may receive relatively high quantities of UV-A and low quantities of UV-B while tanning. Conversely, someone whose significant exposure starts in June or July (some indoor workers, for example) receive high UV-B with the quantities of UV-A, allowing penetration of UV-B before tanning occurs.

In addition to pigmentation there are additional properties of the skin which can influence the transmission of UVR to the basal layer. One such important property is the thickness of the epidermis, particularly the stratum corneum. As discussed in detail in Chapter 3, keratin, the major protein of the keratinocyte, absorbs strongly in the UV region. A thicker stratum corneum thus provides more keratin to act as a UVR absorber. Other optical properties of the skin (for example, scatter) can vary with its condition, and may also affect the delivery of radiation to targets within the skin.

It is clear from the above information that an understanding of the factors that can lead to variations in biological effective doses is important to the interpretation of epidemologic data. Information on ambient variations in UV flux is discussed in the remainder of this chapter; Chapter 3 provides information on how the tanning process and skin pigmentation can influence the transmission of UV-C through the skin to the target cells (melanocytes) in the basal layer.

Background on the NASA Model

The radiation numbers used in this chapter are estimates taken from a satellite-based model developed by John Frederick and George Serafino while both were at the National Aeronautics and Space Administration (NASA). Detailed explanations of how the model works by Serafino and Frederick (1986) are included in this report and accompanies this document. Information which demonstrates its validations with the ground-based Robertson-Berger meters is presented in the report by Pitcher (1987).

At any particular location it is difficult to predict exactly what the levels of solar radiation have been because appropriate data to model cloud cover are not yet available in a form which would allow the UV data in the model to be fully exploited in estimating radiation under cloudy skies. Work

is progressing in this regard, however, and should be facilitated by the use of data from the International Cloud Climatology project.

Latitude as a Cause of Variation

The angle between a location and the sun determines the amount of the atmosphere that photons must pass through before reaching that part of the earth. The lower the angle, the longer the path the photons must pass through in the stratosphere, where ozone differentially absorbs solar radiation of various wavelengths. Furthermore, a longer passage through the troposphere also provides a longer exposure to aerosols, which results in greater scatter of radiation, thereby reducing delivery of the energy to the earth's surface. Since latitude determines the average angle between a location and the sun, the latitude of any location has a strong effect on the amount of radiation received at that location, producing differential gradients for various wavelengths that vary quite systematically across the earth's surface.

Figure 2-8 shows estimates from the NASA model which predict that at 12 noon on March 21, the flux of UV-B at 295-299 nm can be expected to vary from the equator to 70°N by a factor of over 100, while UV-A at 335-339 nm can be expected to vary by a factor of 5. Clearly, the flux of UV-B varies by latitude more than that of UV-A. Figures 2-9a and 2-9b present a comparison for UV-B (295-299 nm) and UV-A (375-379 nm) of how variations in UV flux by latitude change by season. They indicate that north of the equator the variation in UV-B by latitude in June is much greater than that seen for UV-A, but that the rate of change for each waveband stays relatively constant.

Another point worth noting from Figure 2-9a is that the model estimate of peak instantaneous flux of UV-B (295-299 nm) does not vary much from the equator to 30°N and to 60°N. At latitudes between the equator and 30°N, the highest peak value of UV-B flux is 2×10^{-2} mw/cm^2 (occurring in June at the equator) and the lowest peak is about 1.7×10^{-2} mw/cm^2 (occurring in March and June at about 14°N). From 30°N to 60°N the highest peak goes from about 1.8×10^{-2} mw/cm^2 to about 0.7×10^{-2} mw/cm^2 (June at 60°N)--about a 60 percent drop. This becomes an important consideration if, as some researchers have suggested, it is the high-intensity, peak exposures to solar radiation which are important, because the information presented above suggests that there will be little variability in peak exposures to UV-B below 30°N and much variability from 30°N to 60°N.

Variation by Season

There are tremendous variations in the flux of solar radiation by season. Figure 2-10 reinforces the conclusions from Figures 2-9a and b, showing model estimates of how the various wavelengths vary by month for Washington, D.C. Energy at 295 nm increases by about a factor of 10 from winter (December) to spring (March) and by about another factor of 10 by mid-summer (July). For UV-B at 305 nm, there is an increase by a factor of 2 from winter to spring and another factor of 4 by mid-summer. Over the same period, UV-A does not vary much at all.

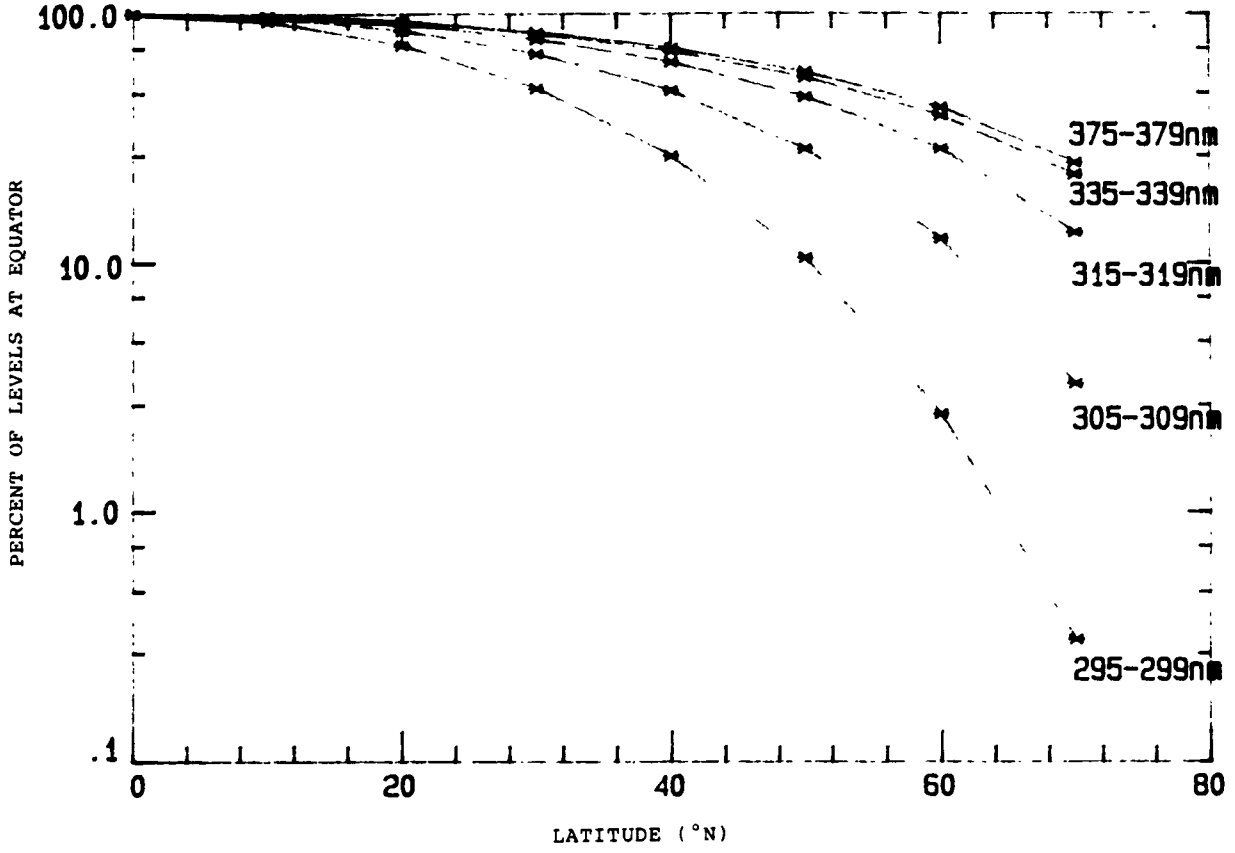

FIGURE 2-8

VARIATION IN UV RADIATION BY LATITUDE AS PERCENT OF LEVELS AT THE EQUATOR ON MARCH 21 AT NOON

The variation estimated by the NASA model for five wavebands of ultraviolet radiation for a single day, high noon, in March is shown. The variation would be different for other days.

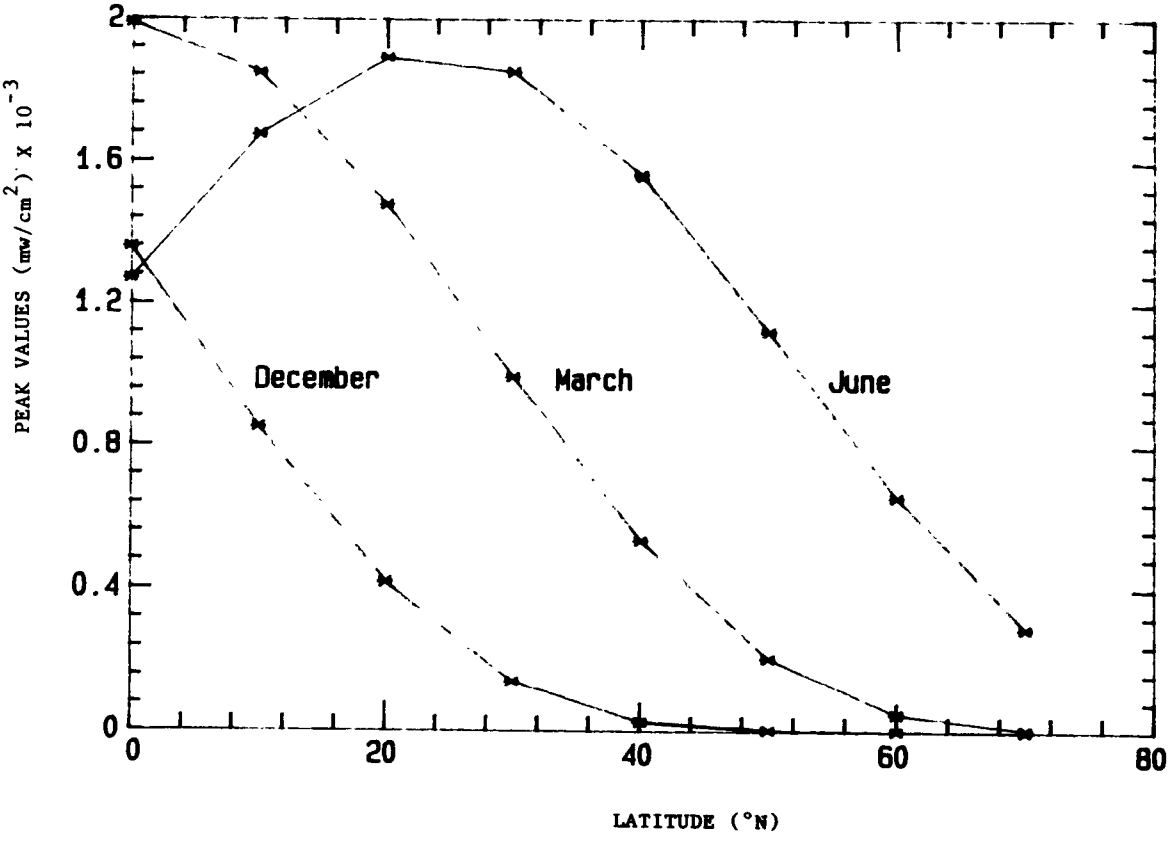

FIGURE 2-9a

SEASONAL PATTERN OF UV BY LATITUDE,
295-299 nm, CLEAR INSTANTANEOUS FLUX

The NASA model estimates that the peak values of 295-299 nm radiation are reached at different times of the year at different locations. Note that the peak value falls very little from 0° (the equator) to 30°N, then falls precipitously.

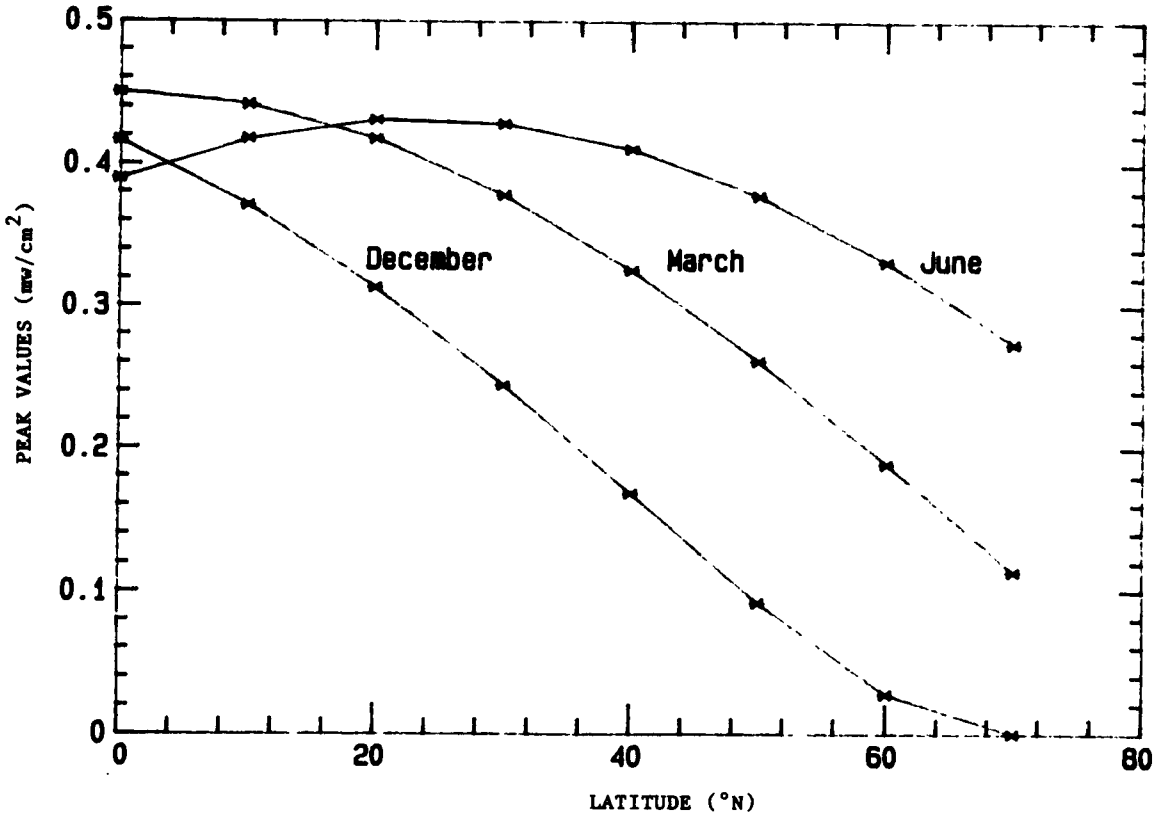

FIGURE 2-9b

SEASONAL PATTERN OF UV BY LATITUDE,
375-379 nm, CLEAR INSTANTANEOUS FLUX

The NASA model estimates that the peak values of UV-A at 375-379 nm are reached at different times of the year at different latitudes. The peak varies very little between 0° and 40°N, and not much more at 70°N.

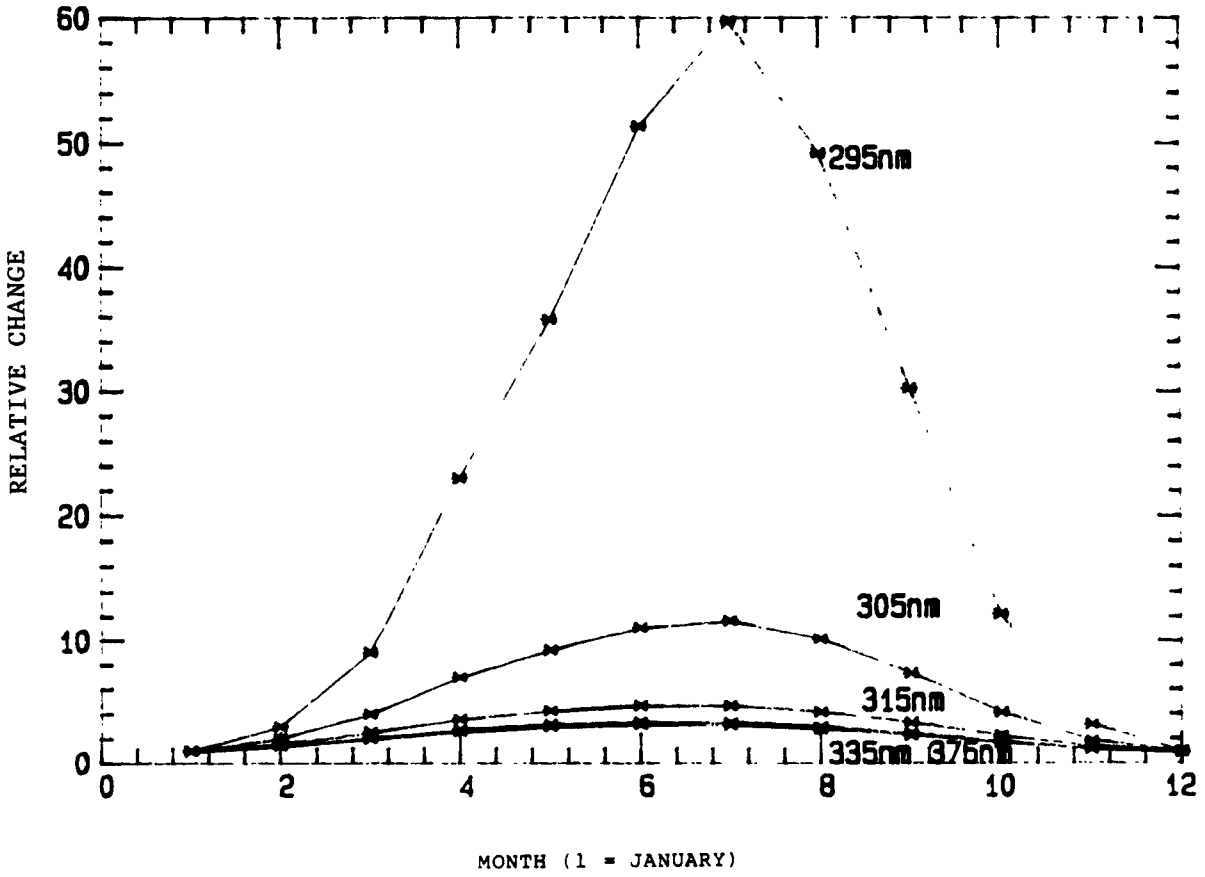

FIGURE 2-10

UV RADIATION BY MONTH IN WASHINGTON, D.C.

The NASA model estimates that radiation at 295 nm has a much larger proportional gain than at 305 nm or higher. Note that the 335 nm line is almost coincident with the x axis, indicating a low monthly variation in Washington, D.C.

Variation by Time of Day

The relative amount of UV-B at 295 nm also varies tremendously with time of day. Figure 2-11 shows the NASA model predictions for the variation in UV flux by hour in Washington, D.C. on June 21. From 8:36 a.m. to 12:00 noon radiation at 295 nm increases by a factor of five. A large proportion of total daily radiation at 295 nm arrives between 11:00 a.m. and 1:00 p.m. Wavelengths of UV-A (e.g., 335-339 nm) hardly varies with time of day, so that the quantity of radiation delivered between 11:00 a.m. and 1:00 p.m. is a small fraction of total daily radiation. For example, the model predicts that from 5 a.m. to noon UV-A (335 to 339 nm) will vary about 20-fold (data not shown) whereas UV-B (295-299 nm) will vary about 2500 fold (Figure 2-12). Thus the time of day of exposure is a very important factor in determining the biologically effective dose.

Variation in Ambient UV as a Function of Cloud Cover or Surface Albedo

Solar radiation varies tremendously with cloud cover (Figure 2-12). In this case, however, there is not much differential variation with wavelength. Increasing cloud cover decreases solar radiation fairly equally at all wavebands, shorter wavelengths of UV-B are affected slightly more than UV-A or longer wavelengths of UV-B. An increase in percentage cloud cover from 0 to 40 percent can reduce solar radiation 20 percent.

Another factor which can cause variations in ambient UV is albedo. Albedo is that property of a surface which is defined as the ratio of the light reflected from it to the total amount incident on it. For instance, water, sand, and snow have much higher albedos than asphalt and grass. Figure 2-13 examines the effects of changing the albedo of UVR incident on Washington D.C.; it indicates that although there is variation in ambient UV at different albedos, there is little difference by wavelength.

Variation by Altitude

Because higher altitudes have less atmosphere to pass through, scattering due to aerosols is reduced and the amount of UV incident on the surface increase. Figure 2-14 presents results based on the hypothetical assumption that San Francisco's altitude was raised from sea level to 4,000 meters. In this instance, San Francisco would receive 1.35 and 1.25 times the UV-B at 295 nm and 315 nm, respectively, and UV-A at 375 nm would only increase by a factor of 1.07.

Differences in Peak Versus Cumulative Potential Exposure

Diverse locations have differential variation in peak and cumulative exposure. Figure 2-15 demonstrates this point using El Paso as the reference point for 3 wavelengths. For 295 nm, the difference between Minneapolis and El Paso for cumulative exposure is about 3.5 fold. For peak exposure, the difference is only about 2 fold. For a longer wavelength of UV-B, 315 nm, the variation in peak exposures between these two cities is only about a 1.7 fold (about 50% lower than that seen at 295 nm). For cumulative exposure at 315 nm,

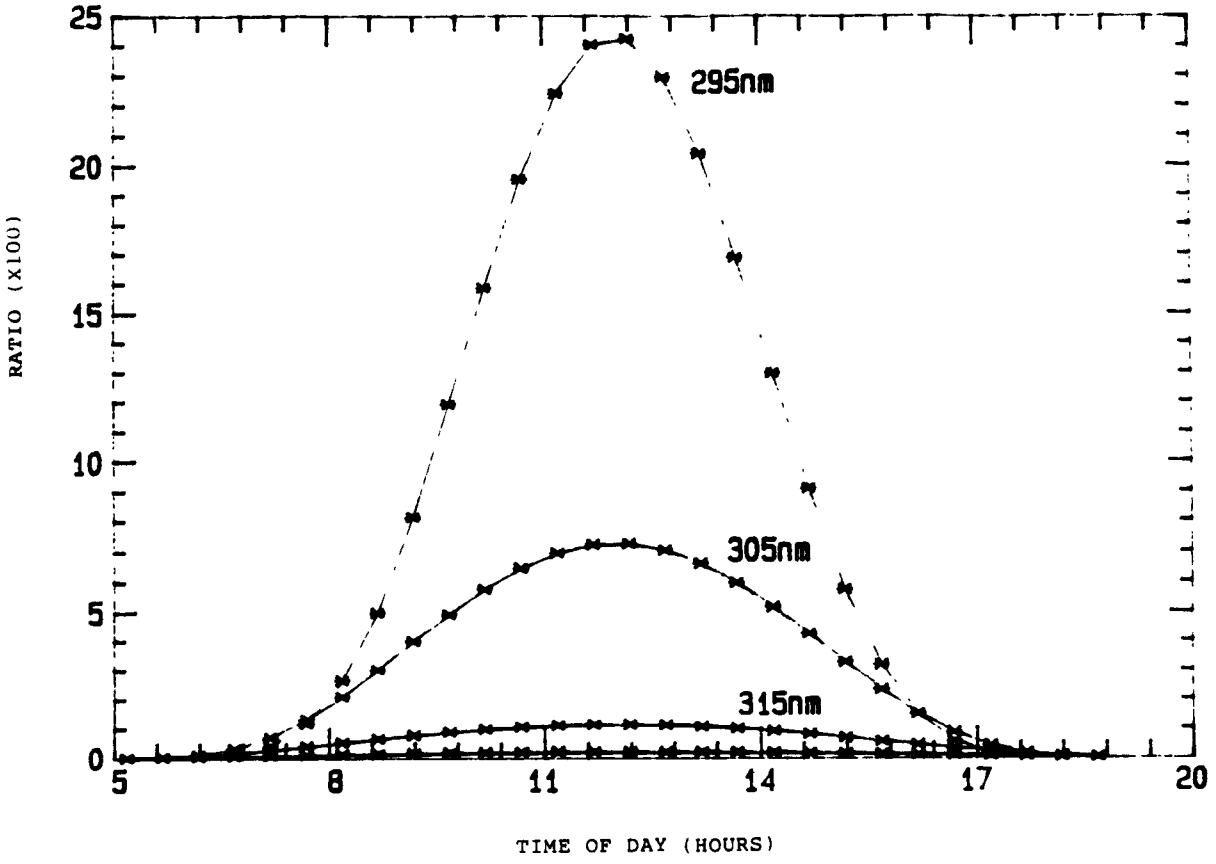

FIGURE 2-11

RATIO OF INSTANTANEOUS FLUX THROUGHOUT THE DAY TO FLUX AT 5:15 A.M. IN WASHINGTON ON JUNE 21 (ASSUMES A CLEAR DAY)

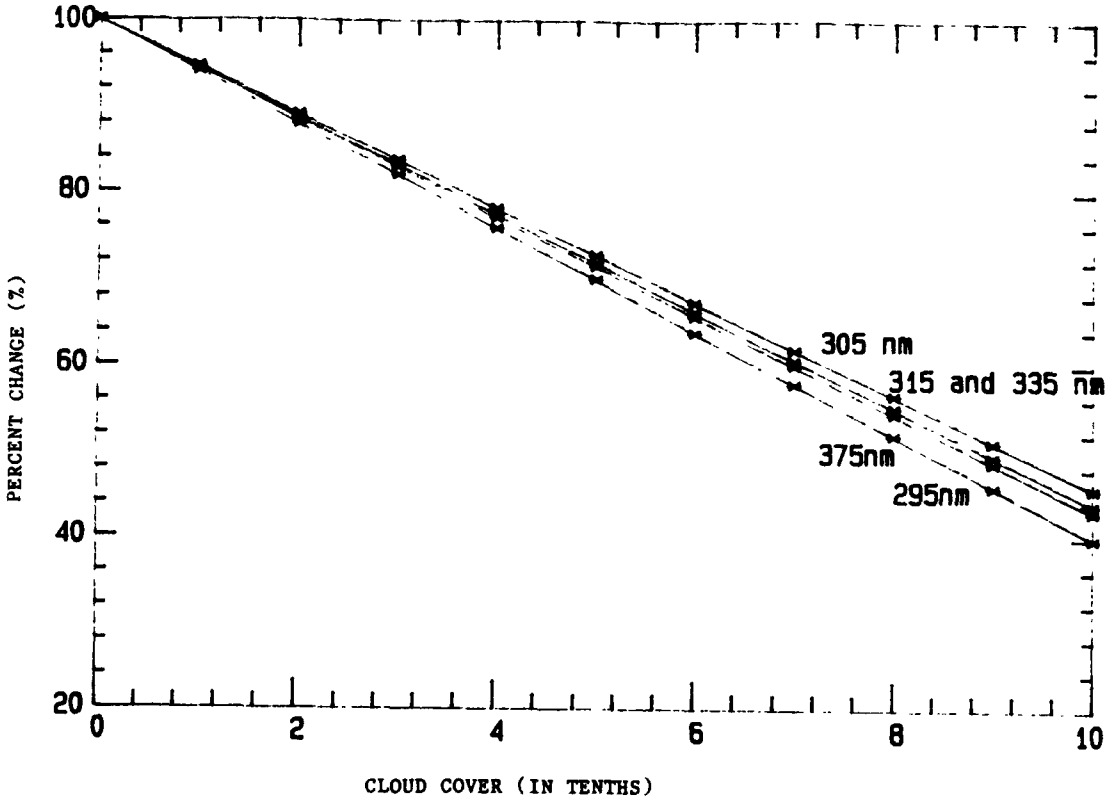

FIGURE 2-12

MODEL ESTIMATES OF UV AS A FUNCTION OF CLOUD COVER

Cloud cover can reduce the percent of UV-B and UV-A reaching the earth's surface quite effectively.

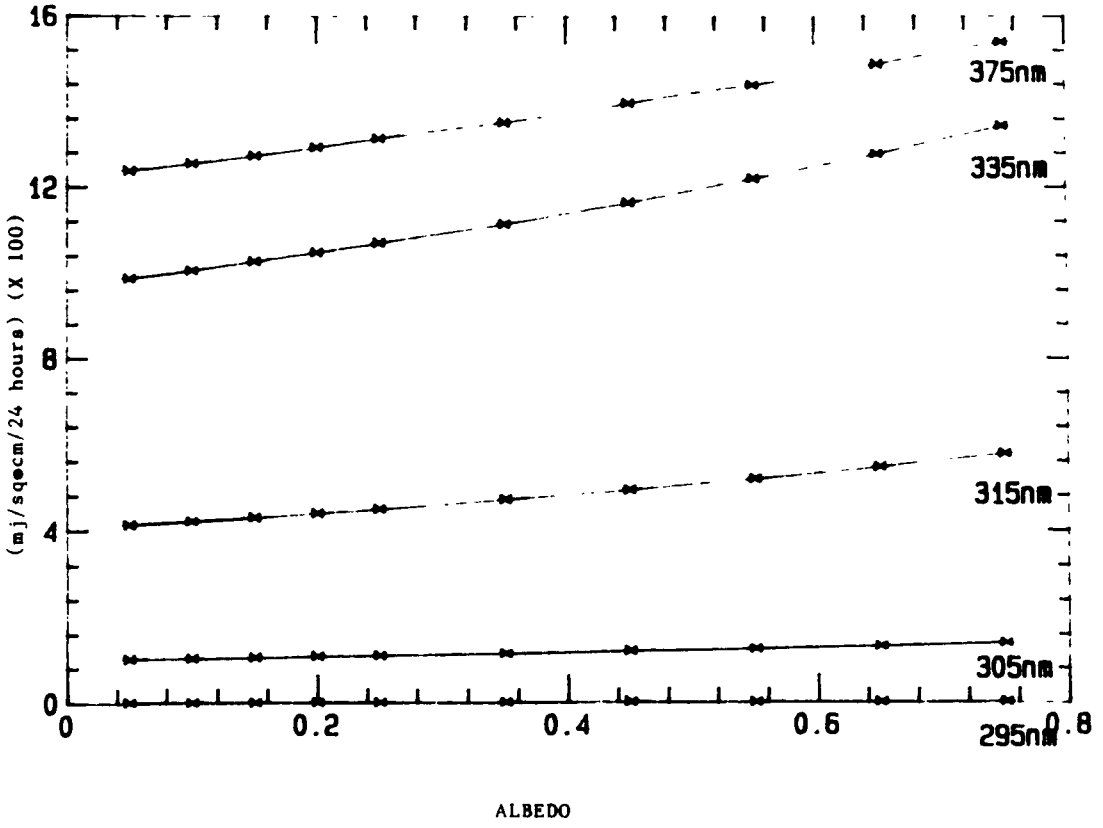

FIGURE 2-13

CHANGES IN UV RADIATION AS THE SURFACE ALBEDO IS INCREASED AT WASHINGTON, D.C.

As the Albedo (that is, reflectiveness) of surface areas increase, then ambient UV increases. The lower the wavelength, the greater the relative increase.

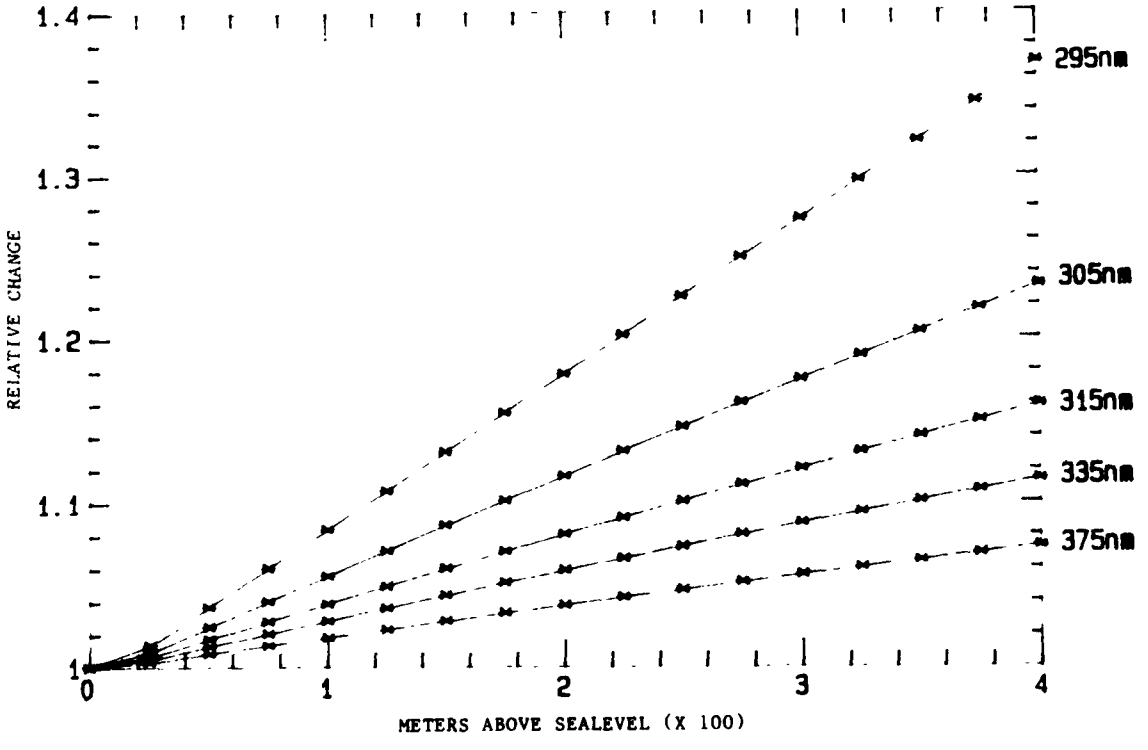

FIGURE 2-14

RELATIVE INCREASE IN JUNE CLEAR SKY DAILY UV FLUX BY WAVELENGTH WITH CHANGES IN ALTITUDE HOLDING LATITUDE (=SAN FRANCISCO) CONSTANT

Increases in altitudes can mean increases in the radiation at any location, with the proportion of change inversely related to decreasing wavelength.

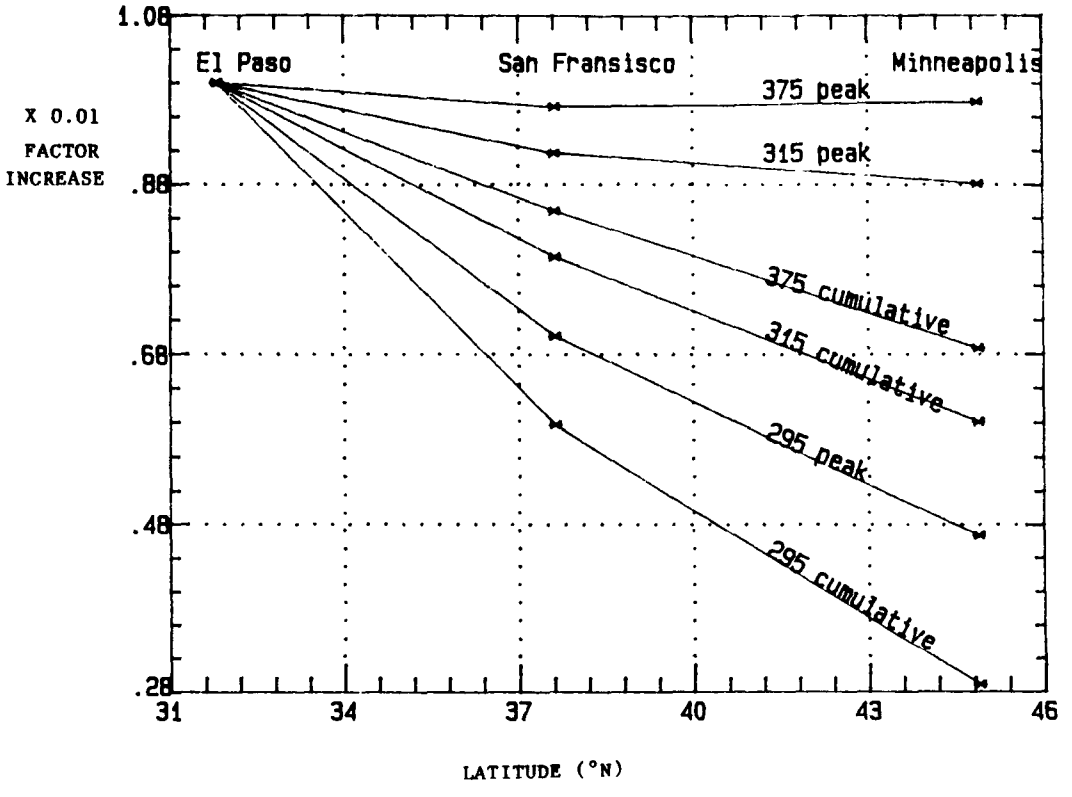

FIGURE 2-15

PERCENT CHANGE IN PEAK AND CUMULATIVE ENERGY FOR EL PASO, SAN FRANCISCO, AND MINNEAPOLIS

There is a greater proportional decrease in cumulative exposure than peak exposure, with variation decreasing from 295 nm to 375 nm, to the point that peak exposures at 375 nm do not vary with latitude.

the ratio between the cities drops to a 1.3. For UV-A at 375 nm, the variation is even less; 68:100 for the cumulative and 100:100 or no variation for peak.

An important implication of this pattern of variation is that if peak exposure were the critical factor in the etiology of a disease, the expected variation in incidence would be less than if cumulative dose were the important factor. Furthermore, if peak exposures were the key etiologic factor, one would expect no variation in incidences from place to place if UV-A radiation is the biologically effective portion of the UV spectrum.

IMPLICATIONS OF VARIATIONS IN AMBIENT SOLAR RADIATION FOR THE INTERPRETATION OF EPIDEMIOLOGIC STUDIES

Information on ambient variation in UV can have important implications in interpreting epidemiologic studies. Such studies can be done on matched groups (i.e., case control studies) or ecologically. Ordinarily, matched groups are preferred since it is believed that better control of variables can be achieved. In ecological studies, three approaches to estimating doses have been used to attempt to evaluate the relationship between solar radiation and melanoma: a) those in which exposure was estimated based on consideration of predicted or measured wavelengths; b) those in which sunlit hours at place of residence was used; or c) studies in which latitude as a surrogate for UV exposure was used. In most case-control studies, hours of sun exposure, as assessed by questionnaire, have generally been used to estimate dose.

Different approaches have important implications for evaluating the epidemiologic studies and their utility. In particular, the substitution of hours of sun exposure for actual information on time of day and year of exposure creates real problems in ascertaining either the actual exposure dose or the biologically effective dose. At any given latitude, merely counting the hours of sunshine will not allow one to know whether a person has received a higher exposure or biologically effective dose than another. In fact, to the extent that the case and the control populations differ in their expected time/day of exposure and in the temporary pigmentation they are likely to have at times of high UV-B flux, sunshine hours of exposure might be negatively correlated with biologically effective dose. Thus one group (outdoor workers, for example) might spend more total hours in the sun, but less time with untanned skin at periods of high UV-B than a group of office workers. Data on this point are lacking, but an understanding of variation in ambient UV should lead to real concern about the issue.

The systematic variation of UV-B and other solar radiation with latitude also has implications for interpreting ecological studies that use latitudinal variation as a surrogate for effective dose. If the populations being evaluated are large enough to show little systematic variation by latitude, then the real difference between populations at two different latitudes would be in the actual biologically effective dose. As such, ecological studies might actually control better for exposure than matched studies. Of course, it would not be possible without additional data to distinguish whether the effective dose stems from peak or cumulative exposure. And the danger exists

that there could be other factors (e.g., dietary or cultural habits) that also vary by latitude, and thus could confound the association of latitude (as a surrogate for dose) with CMM incidence. Clearly, in ecological studies, one would expect much variation to go unexplained simply because the determination of actual exposures in a population will be affected by noisiness in potential exposure variables (e.g., altitude, cloudiness, albedo), as well as differences in behavioral (recreation, clothing) and pigmentary characteristics in the population.

As a consequence of the systematic differential variation of solar radiation in the environment, the possibility needs to be considered that well-designed ecological studies may provide a reasonably well-controlled natural experiment in countries where there are few apparent biases in the ways humans with different skin colors and behavior have arranged themselves. Matched studies that fail to consider the details of hours of exposure and rely on small groups that differ in critical ways may actually provide weaker data than ecological studies.

OZONE DEPLETION AND CHANGES IN SOLAR RADIATION

Clearly, the best epidemiologic study and possibly the only adequate way to estimate an accurate and precise UV-B dose-response relationship would be a study in which much effort had been expended to estimate the biologically effective dose received by both cases and controls. This would require careful attention to details about when, where, and how an individual acquired his/her sun exposure, as well as information on tanning and clothing habits, and normal pigmentation.

Understanding the effect of depletion of the ozone layer on the peak flux of UV-B, the total potential dose of UV-B, and the relative amount of various wavelengths of UV-B will be critical to estimating future incidence and mortality of UV-induced malignancy. If ozone is depleted, there will be an increase in the amount of UV-B that reaches the earth's surface, but not UV-A or visible light. Figure 2-16 shows NASA model predictions for how ozone depletion would affect UV flux in Minneapolis. The figure indicates that a 10 percent depletion would result in a 50 percent increase in UV-B at 295 nm, a 20 percent increase at 305 nm, and a 10 percent increase at 315 nm; at 335 nm there is no increase.

SUMMARY

There are several critical summary points:

2.1 Ozone differentially absorbs various wavelengths of UV-B and affects UV-A very little and visible light not at all.

2.2 Wavelengths between 295 nm and 300 nm are generally much more effective at inducing adverse biological effects, e.g., mutation, transformation, and cell death, in target cells in the skin than the longer

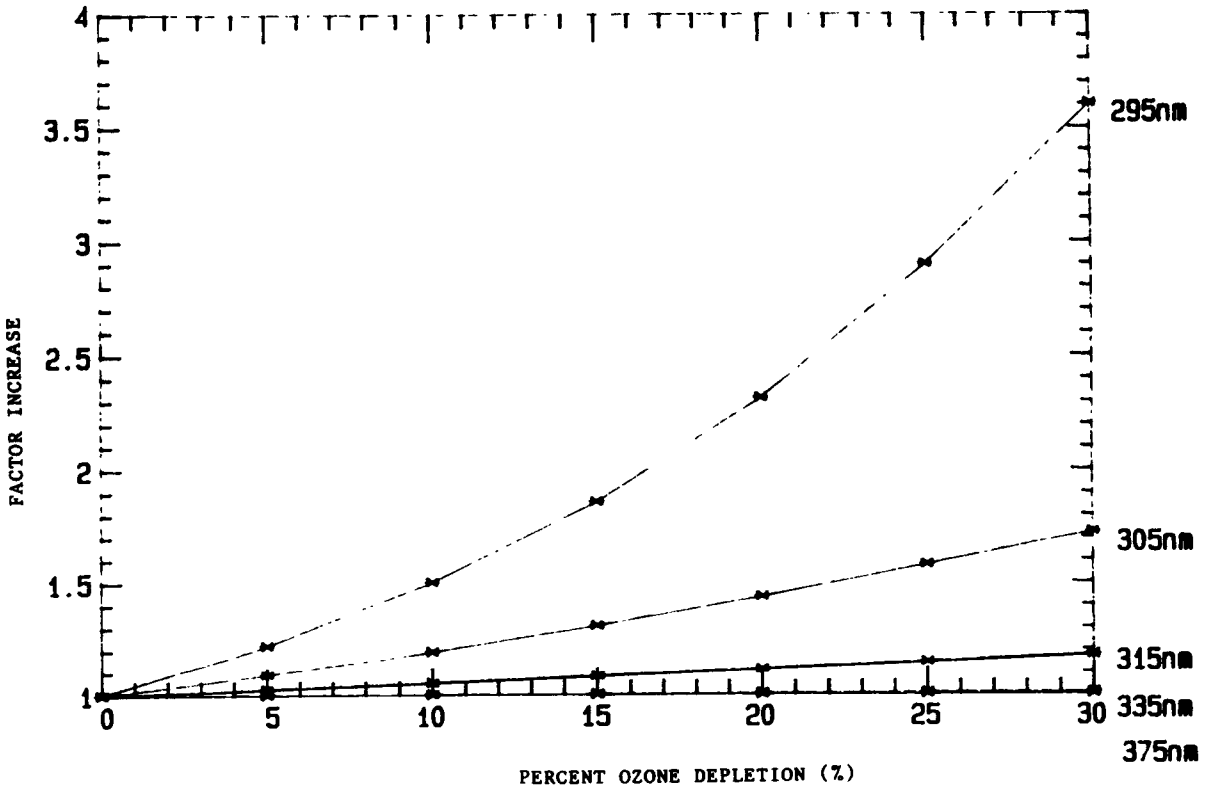

FIGURE 2-16

MINNEAPOLIS: TOTAL YEARLY FLUX VS. OZONE DEPLETION

wavelengths of UV-B and even more so than radiation in the UV-A.

2.3 The biologically effective dose depends on the number of photons of appropriate energy that are actually absorbed by target molecules. This is influenced by the duration of exposures at particular locations, time of day, and time of year, by behavior in terms of clothes and sunscreens, by pigmentation, permanent and temporary, and by the action spectrum of the target molecule.

2.4 The flux of radiation at 295-299 nm varies more than other UV-B wavelengths, and much more than UV-A by latitude, altitude, time of day, and time of year.

2.5 The differential variation between UV-A and UV-B is greater for cumulative potential exposure than potential peak exposure.

2.6 Cloudiness and albedo can cause large variations in UV-A and UV-B flux, but they affect all wavelengths relatively equally.

2.7 Ozone depletion would cause the largest increases in UV-B (particularly in the 295-299 nm range) and little change in UV-A.

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CHAPTER 3

BACKGROUND INFORMATION ON CUTANEOUS MALIGNANT MELANOMA

This chapter introduces the concepts in dermatology, photobiology, and carcinogenesis deemed necessary to evaluate the role of solar radiation, and in particular, the wavelengths between 290 and 320 nm (ultraviolet-B; UV-B), in the induction and progression of the dermatologic cancer known as cutaneous malignant melanoma (CMM). Particular attention has been paid to the presentation of information which may help explain variations in the incidence or mortality of the disease among various populations. The first section of the chapter outlines the extent of the public health problem presented by CMM: its incidence and mortality in the U.S. It also briefly presents information on the time trends observed in incidence and mortality of the disease. The second section presents a summary of normal skin biology, reviewing skin structure, component cells, and macromolecules. This is then followed by a review of what is known about the interaction of solar radiation with the skin and the skin's mechanisms for the reduction or repair of solar damage. This information is necessary to understanding and interpretation of the data presented on racial and skin color differences as well as that derived from cellular and molecular studies. The final section is a discussion of the biology of CMM, including information on the differences in biology that might help explain the behavior of the disease in various populations. This information may help resolve some of the apparent contradictions and complexities in the relationship of melanoma and sunlight. In particular, it is clear that there are several forms of melanoma which have different natural histories, including different relationships to sunlight.

EXTENT OF THE PUBLIC HEALTH PROBLEM

Malignant melanoma is a form of cancer whose cell type is the melanocyte. Most melanomas arise in the skin, although they may also arise in other sites, e.g., the eye. In the U.S., melanoma accounts for 1 percent of all cancers excluding non-melanoma skin cancer and about the same proportion of cancer deaths. Although melanoma represents only 3 percent of cutaneous neoplasms, it is responsible for 65 percent of all skin cancer deaths (Mastrangelo et al. 1982). In 1940, the 5-year overall survival was 40 percent (Sober et al. 1979). The National Cancer Institute (Sondik et al. 1985), based on SEER data, found 5-year survival rates of 60 percent (1960-1963), 68 percent (1970-1973), 78 percent (1973-1976), and 80 percent (1977-1982).

Melanoma incidence has been rising steadily in the U.S. In the mid-1930's, the incidence was 1 per 100,000; however, by 1980 the incidence had risen to 6 per 100,000. It has been estimated that there will be 25,800 melanoma cases and 5,800 melanoma deaths in the U.S. in 1987; the life time risk of contracting melanoma is now 1 in 135 (Kopf 1987). Similar calculations based on incidence data from 1974 in New South Wales, Australia indicate that

by the age of 74, one out of every 66 residents will develop melanoma (Holman et al. 1980). Scotto (1985) predicted that the current trend would produce 24,000 cases of CMM in the U.S. in 1985, and that by 1989 this number would rise to 30,000.

THE BIOLOGY OF SKIN

CMM is one of several skin cancers. The other predominant ones are basal cell (BCC) and squamous cell carcinomas (SCC). Comparative incidence rates for these three tumors are given in Table 3-1. There are some interesting differences in the apparent relationship of solar radiation to these various skin cancers (for details see Chapter 14) which may be related to differences in the way the various normal epidermal cell types (and/or their principal molecular products) function in the epidermis. In order to understand and assess the role of solar radiation (and in particular UV-B) in CMM, it is necessary to have some knowledge of the normal structure and function of the skin and the comparative relationship of melanocytes to other epidermal cells, in particular basal and squamous cells. It is also important to have an understanding of the impacts of solar radiation on the skin, the skin's response mechanisms to solar radiation, and the role played by each of the different cell types in these processes. The next sections present a brief review of information in these areas.

Skin structure and function

The skin is the largest organ of the body. Weighing 3 to 4 kg (which is two to three times the weight of the liver), it constitutes 6 percent of the body weight (Fitzpatrick and Soter 1985). There are three principal layers of skin: the epidermis, the dermis, and the panniculus adiposus (Figure 3-1). The layers vary in thickness depending on their location. The epidermis is typically 70 to 170 micrometers (μm) thick (maximum thickness: 1560 μm); the thinner epidermis on the head, trunk, and upper limbs, and the thicker epidermis on the lower limbs. The epidermis on the palms and soles is as much as ten times thicker than that on the head and trunk. The stratum corneum generally comprises between 8 to 15 μm of the epidermis' thickness (Pearl 1984; Fitzpatrick and Soter 1985). The dermis is typically between 1700-2000 μm thick (minimum: 600 μm; maximum: 3000 μm) and the subcutaneous layer between 4000 and 9000 μm (minimum: 600 μm; maximum: 30,000 μm) (Fitzpatrick and Soter 1985).

The epidermis is populated by a mixture of three cell types of different embryonic origin and function: these are (in order of percent composition) the keratinocyte (80 percent), the melanocyte (5-10 percent), and the Langerhans cell (5-10 percent). The dermis is composed mainly of connective tissue fibers. These fibers are secreted by cells called fibroblasts and are responsible for the skin's resilience and elasticity. Many of the skin changes associated with aging are due to the impact of solar radiation on these dermal fibers although there are also radiation-independent, age-related changes in the chemistry of these fibers. The subcutaneous layer, or panniculus adiposus, is a specialized layer of connective tissue which

TABLE 3-1

AGE ADJUSTED INCIDENCE RATES[a] OF BASAL CELL CARCINOMA (BCC) SQUAMOUS CELL CARCINOMA (SCC) AND CUTANEOUS MALIGNANT MELANOMA (CMM) AMONG WHITE POPULATIONS IN THE UNITED STATES

	Males	Females
BCC[b]	246.6	150.1
SCC[b]	65.4	23.6
CMM[c]	9.2	7.7

[a] Rates per 100,000 per year.

[b] Source: Scotto and Fraumeni (1982).

[c] Source: Sondik et al. (1985) - based on 1978 data.

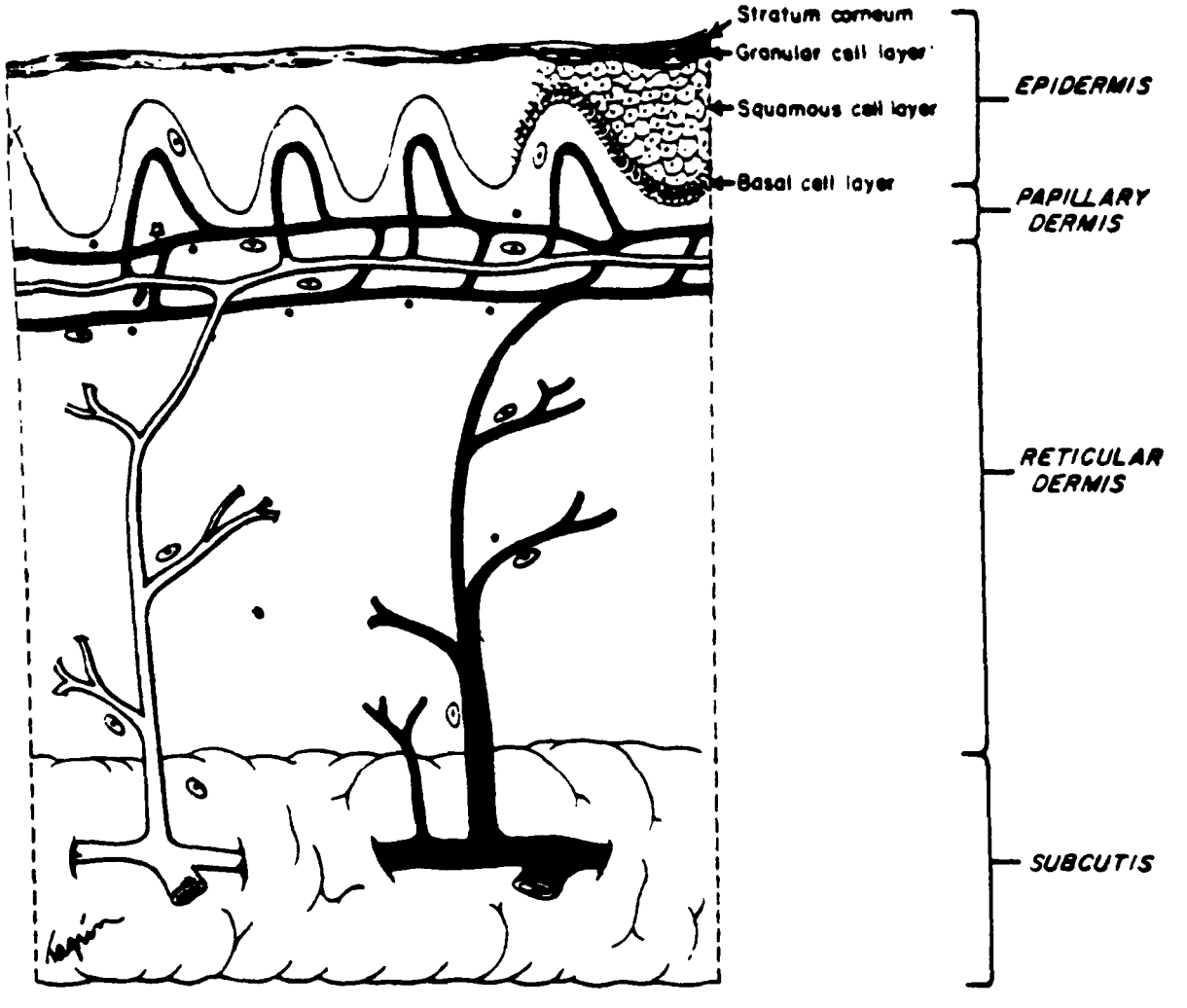


FIGURE 3-1

STRUCTURE OF THE SKIN

Source: Adapted from Fitzpatrick and Soter (1985).

functions as a cushion between the bone and the epidermis and dermis. It consists primarily of fat cells; it is a reservoir for caloric energy (Fitzpatrick and Soter 1985).

Skin Cell Types and Their Major Products

Keratinocytes comprise the major cell population of the epidermis. Embryologically, these cells trace their lineage back to the ectoderm, which differentiates into the neural crest, the neural plate, and the epidermis at the time of neurulation (Balinsky 1965). As indicated below, melanocytes are derived from the neural crest so that although both melanocytes and keratinocytes are of embryonic ectodermal original, additional differentiation has occurred before precursor melanoblasts are generated.

In the epidermis, keratinocytes are organized vertically by various stages of differentiation. In its first stage, the keratinocyte is termed a basal cell. Basal cells are organized in a basal cell layer which is oriented along a basement membrane that demarcates the interface of the dermis and the epidermis. There are structurally and functionally distinct populations of basal cells; some may represent the epidermal stem cell population whereas other may serve an anchoring function (Fitzpatrick and Soter 1985). Those basal cells that serve as epidermal stem cells divide to produce daughter cells that migrate outward, differentiating into squamous cells, which lose their nucleus to finally become corneocytes in the stratum corneum (Anderson 1983). In normal skin the transition from basal cell layer to stratum corneum takes about 2 weeks. The cells then pass through the stratum corneum and are sloughed off in an additional 2 weeks (Pearl 1984).

Both basal cell and squamous cell carcinomas are of keratinocyte origin. It is currently believed that BCC is derived from undifferentiated pluripotent stem cells; ultrastructural studies indicate that BCC cells are very similar to primitive ectodermal cells and that they can simulate both epidermal and adnexal development. In contrast, SCC consist of cells which are differentiated to the point that they tend to produce keratin. Individual SCC may show different degrees of keratinization. Growth rate of the two types of nonmelanoma skin tumors varies tremendously. Generally, basal cell tumors are slow growing, with a cell cycle time that has been estimated at 82 and 217 hours in two studies. For SCC of the head, the cell cycle time has been estimated at between 51 and 88 hours (Laerum and Iversen 1981).

Keratinocytes produce a number of different proteins at least three of which have biologic activity important to the skin: keratin, histidine-rich proteins, and interleukin 1 (IL-1, also known as epidermal-derived thymocyte activation factor [ETAF]). Keratins, the primary structural proteins of the epidermis, consist of a family of helically configured, disulfide-rich polypeptides which strongly absorb photons in the UV-B and UV-C range (Harber and Bickers 1981); their molecular weights range from 40 to 70 kilodaltons.

In the basal layer, where keratinization begins, keratin is organized into intracellular intermediate filaments. As cells ascend the epidermis, synthesis of new fibers stops, and the bundles of fibers become oriented in

alignment with the surface of the skin. The keratinocytes at this point have a thick deposit of keratin underneath a much thickened cell membrane. The final transition is to a corneocyte in the stratum corneum layer -- an enucleated dehydrated keratinocyte whose water content drops from 70 percent to 10 percent (Fitzpatrick and Soter 1985).

Another group of proteins produced by keratinocytes are called histidine-rich proteins (HRPs). In keratinocytes, HRPs are sequestered with keratin into keratohyalin granules. As keratinocytes differentiate into corneocytes, the HRPs break down, releasing free histidine which is subsequently converted to urocanic acid (Scott et al. 1982). The degradation of HRPs is a multistep process involving at least three species of HRPs. The initial molecule is about 94K molecular weight (MW); it is subsequently broken down first to HRP-II (32K MW), then to HRP-I (15-20 K MW) (Horii 1983). Ultimately the HRPs are degraded to histidine.

Apparently it is only the enucleated, keratinized corneocyte which has the ability to convert the free histidine released by the HRP degradation into urocanic acid. Experiments have localized 93 percent of epidermal histidenase to a cell compartment which contains the smallest percentage of epidermal DNA (Scott 1981; Scott et al. 1982). The rate of conversion of histidine to urocanic acid is pH-dependent: the further towards the surface of the skin a corneocyte moves, the more acid its environment becomes, and the more slowly the urocanic acid is produced.

IL1/ETAF is a protein which functions as a major mediator in both immune and inflammatory responses. Originally thought to be a solely macrophage-produced lymphokine, characterization of its biological properties indicates that it is a potent inducer of lymphocyte activation and chemotaxis, that it enhances production of acute phase proteins by the liver, increases the number of circulating macrophages, and can result in elevated temperatures (fevers). Production of IL1/ETAF by UVR-irradiated keratinocytes is only depressed at irradiation levels which are cytotoxic. It has also been recently noted that human and murine stratum corneum contain substantial amounts of IL1/ETAF (Daynes et al. 1986).

There is some evidence that different populations within the keratinocyte lineage may have differential sensitivity to solar radiation. This conclusion is based on the observation that, fairly early after irradiation, a population of so-called "sunburn cells" appears. These cells are hyperatotic cells which when stained with hemotoxylin and eosin exhibit dark, pyknotic nucleic and shrunken homogenous eosinophilic cytoplasm (Gschnait and Brenner 1982; Ley and Applegate 1985). The pathogenesis of sunburn cell development was originally thought to involve sensitization of keratinocytes by melanin. This was based on the work of Johnson et al. (1972), who observed that sunburn cells contain more melanin than their neighboring keratinocytes, that vitiligenous skin produces fewer sunburn cells with the same relative doses of UVR, and that macrophages laden with squid melanin exhibit greater sensitivty to UVR.

Subsequent work suggested that DNA might be the target molecule as an action spectrum for sunburn cell formation was consistent with DNA as a target

(Woodcock and Magnus 1976), and autoradiographic studies showed that sunburn cells exhibited less DNA repair activity than normal keratinocytes (Brenner and Gschnait 1979). In addition, studies performed in the marsupial Monodelphis domestica (which has the ability to photoreactivate pyrimidine dimers in its epidermal DNA) indicated that pyrimidine dimers are the major photoproduct involved in the induction of sunburn cells and hyperplasia in this species (Ley and Applegate 1985).

The **melanocyte** is the second cell type in the epidermis. Figure 3-2 presents three increasingly magnified versions of the structure of the skin which focus down on the melanocyte and its positional relationship in the epidermis (Fitzpatrick and Soter 1985; Pearl 1984; Nordlund 1981). Melanocytes are pigment-producing cells derived from the embryonic neural crest which, in the case of skin, have migrated to the basal layer of the epidermis or the matrix of hair follicles (Romsdahl and Cox 1976). Melanocytes may also migrate to the oral and nasal cavities, the upper third of the esophagus, the vaginal mucosa, and the eye (Briele and Das Gupta 1979; Nordlund 1981). In the skin, melanocytes tend to reside at the interface of the dermis and the epidermis, where they interact with keratinocytes via long extensions of their cell bodies called dendritic processes (Romsdahl and Cox 1976).

Melanocytes in the basement membrane at the interface of the dermis and the epidermis rarely divide, although there is some evidence that UV irradiation may cause melanocyte proliferation (Pathak et al. 1985). One report in the literature indicated that there is about a 10 percent reduction in melanocyte numbers per decade of life (Snell and Bischitz 1963). This reduction probably parallels that seen in hair follicles which is expressed as graying of the hair (Fitzpatrick and Soter 1985).

The major function of the melanocyte is the production and distribution of melanin to the keratinocytes. Melanocytes which migrate to the hair follicles produce the melanin which gives hair its characteristic color, and it is melanin which has been purified from hair which is used most often in analytical studies (Menon et al. 1983a).

In the skin, each melanocyte distributes melanin, packaged in an organelle termed a melanosome, to about 36 keratinocytes. Figure 3-3 shows the close association between a melanocyte and its keratinocytes; this grouping is frequently referred to as an "epidermal melanin unit" (Fitzpatrick and Soter 1985).

Melanin is a pigment that absorbs light in the broad range of 250 to 1200 nm; its absorption increases steadily towards the shorter, more biologically active wavelengths (Anderson 1983). As such, it has been suggested that melanin's major role in the skin is to protect against the adverse effects of UVR (Briele and das Gupta 1979). Other hypotheses (reviewed in Morison 1985) include camouflage and heat absorption.

There are qualitative and quantitative differences in the melanin present in human skin. These differences may be important to an understanding of the difference in melanoma incidence among different races and among Caucasians of

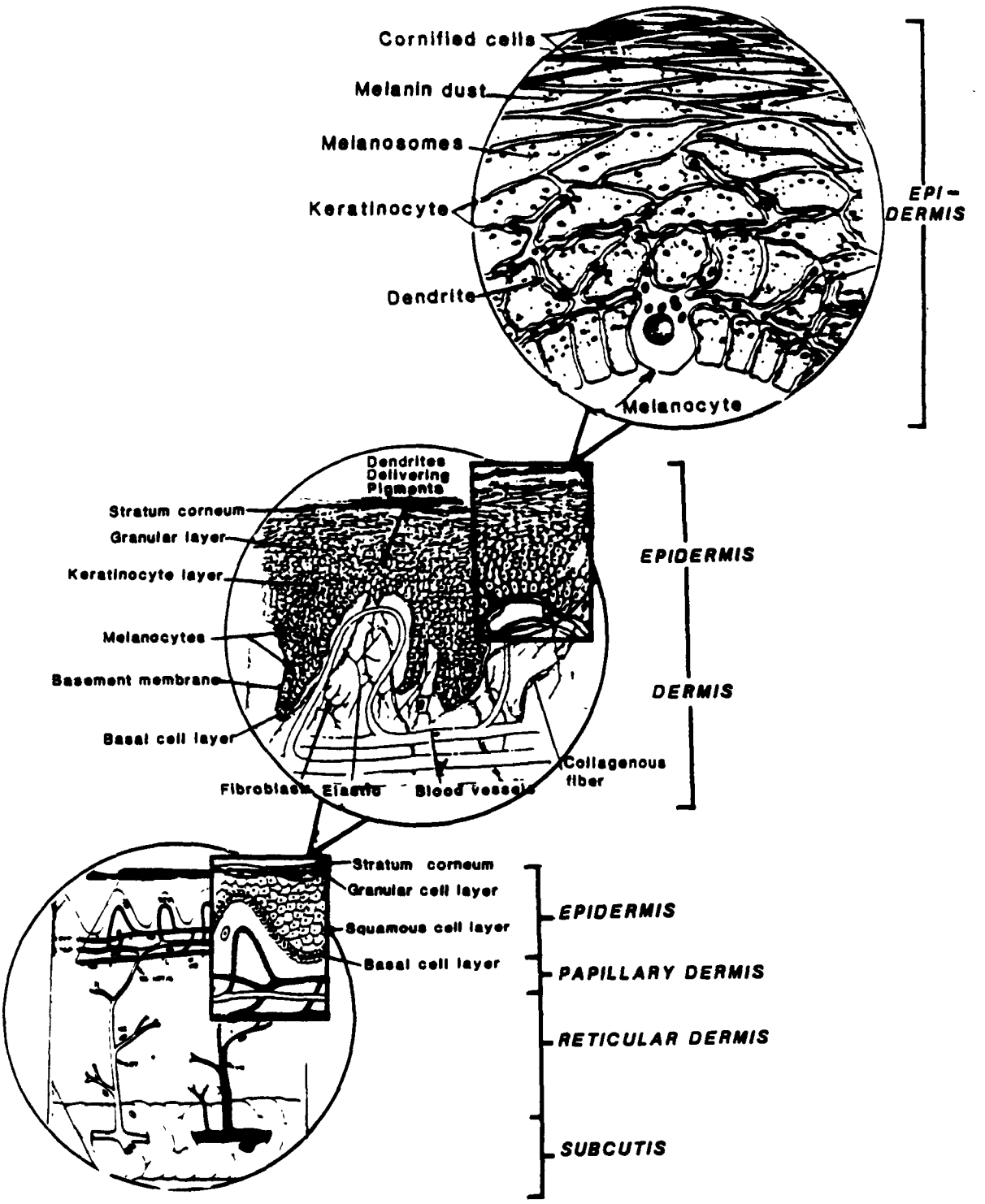
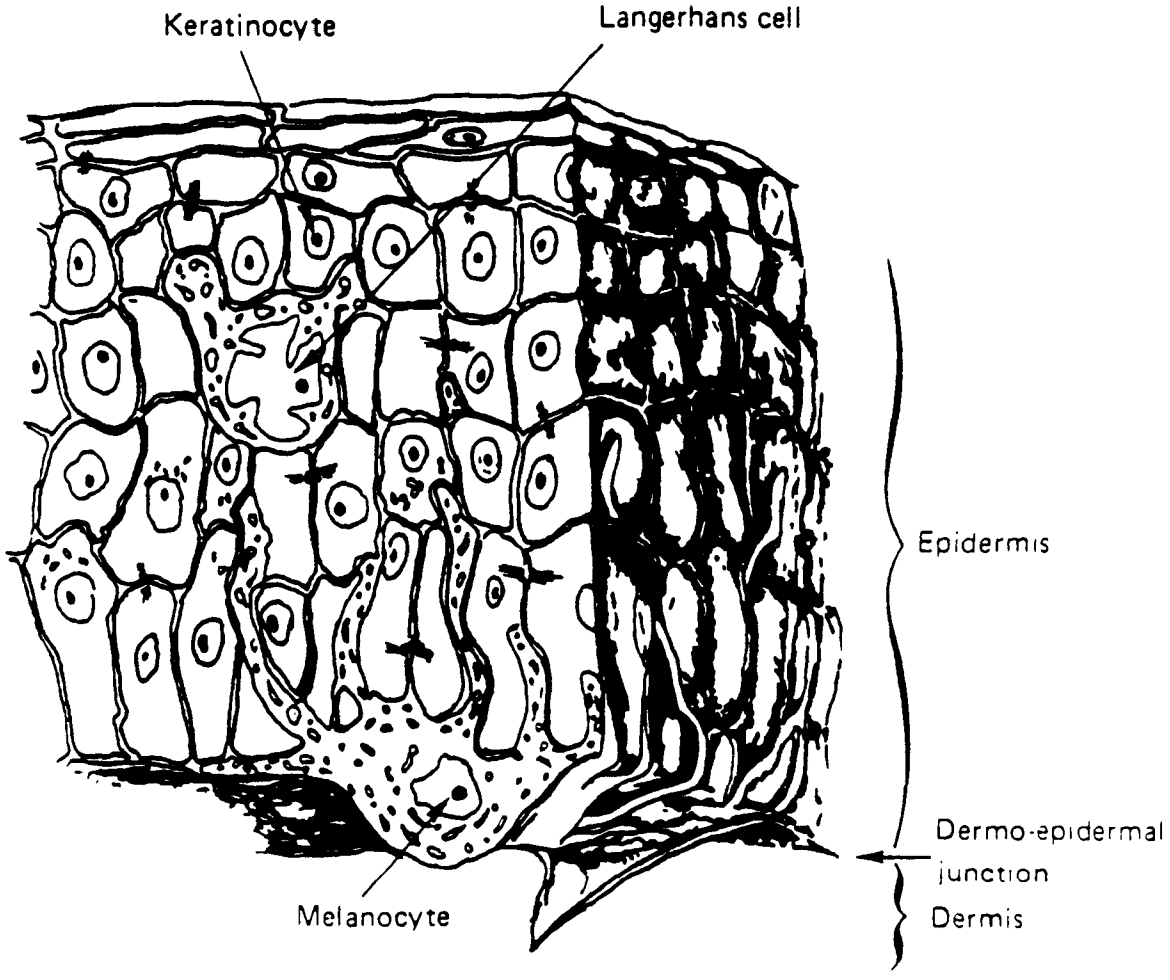


FIGURE 3-2

THREE INCREASINGLY MAGNIFIED VERSIONS OF THE STRUCTURE OF THE SKIN SHOWING THE RELATIONSHIP OF THE MELANOCYTE

Source: Adapted from Fitzpatrick and Soter (1985); Pearl (1984); and Nordlund (1981).



Source. NAS (1984).

FIGURE 3-3

THE EPIDERMAL MELANIN UNIT

different genetic heritages. For this reason, a somewhat detailed review of melanin biology and chemistry is presented here.

In melanocytes, melanin is synthesized from tyrosine and becomes complexed with a protein matrix (Romsdahl and Cox 1976) inside membrane-bound structures termed melanosomes. The chromophoric backbone of the melanin complex is very stable and can withstand attack from proteases, acids, and bases (Anderson 1983).

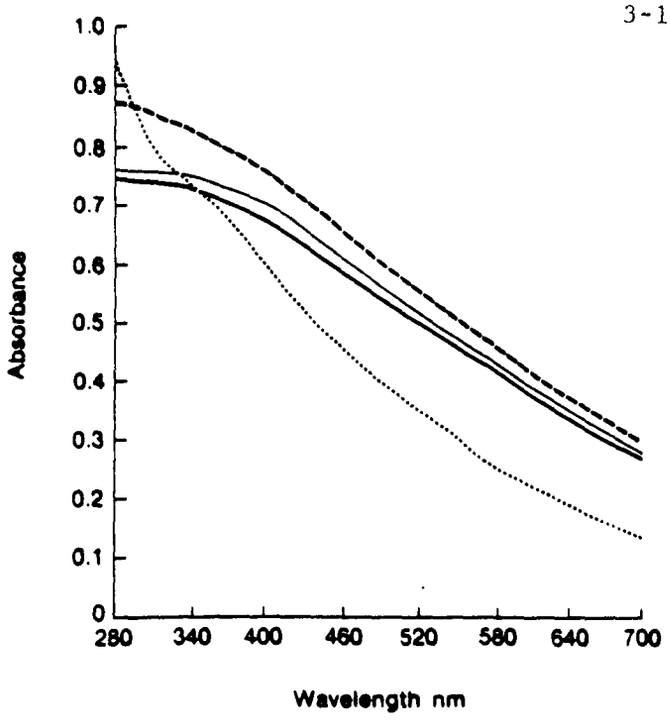
In humans and other mammals there are two predominant forms of melanin -- eumelanin, which is brown or black, and pheomelanin, which is yellow or auburn, and is the pigment responsible for red hair. In normal skin pigmentation, tyrosine is the starting point for both types of pigment (Nordlund 1981). Tyrosinase oxidizes tyrosine to dopa (3,4-dehydroxyphenylalanine) and dopa to dopaquinone (Nordlund 1981; Romsdahl and Cox 1976). The dopaquinone then undergoes a series of spontaneous oxidative changes forming a variety of indoles and quinones which polymerize and are deposited on the lamellar protein matrix of the melanosome. To form pheomelanin, dopaquinone is shunted by some unknown control mechanism into a pathway in which it is covalently bonded to cysteine; thus pheomelanin is a polymer of indole cysteine (Nordlund 1981).

The melanosomes containing these two types of melanin differ structurally. Those with pheomelanin are round and have a protein matrix with a "tangled" appearance, whereas eumelanin-containing melanosomes are round and have a characteristic lamellar structure (Nordlund 1981).

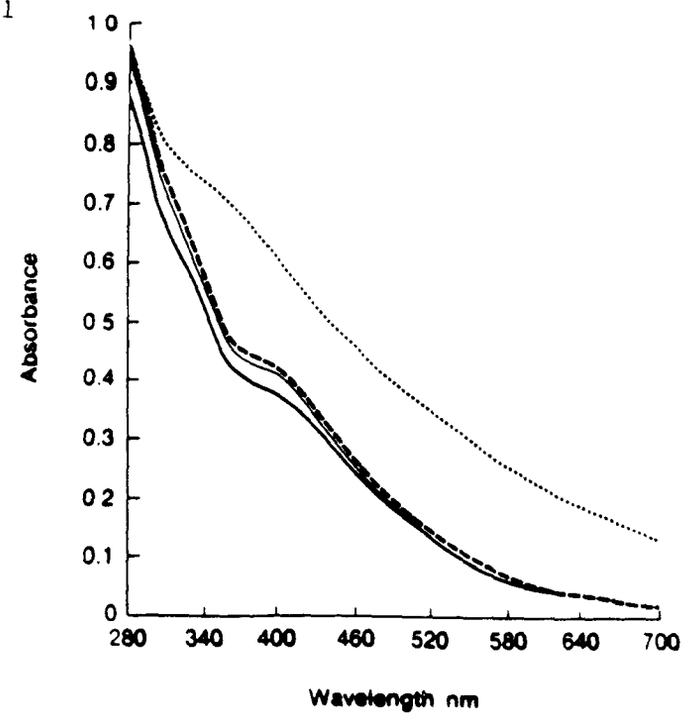
The two melanins have different UV and visible absortion spectra (Figure 3-4), with the eumelanin looking much like the dopa melanin and the pheomelanin absorption decreasing more rapidly in the 280-370 nm range. (Dopa melanin is a synthetic melanin generally produced in the laboratory by allowing a solution of dopaquinone to spontaneously polymerize.) Pheomelanin has not been found in normal epidermal melanocytes. Pheomelanin also has a quite different infrared absorption spectrum showing an increased transmittance at almost every wavelength (Figure 3-5) (Menon et al. 1983a).

The two melanins also show different behaviors when subjected to UV-visible irradiation in vitro. Irradiation of pheomelanin produces considerable amounts of superoxide (a free radical) under conditions in which the irradiation of eumelanin does not. It has also been shown that while irradiation of cells in the presence of either melanin produced cell damage, pheomelanin was much more effective than eumelanin in producing this effect (Menon et al. 1983b).

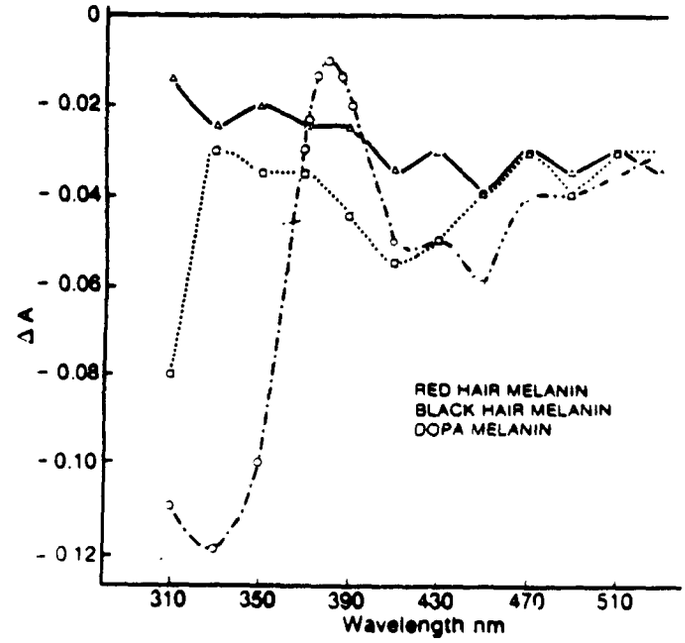
Extensive studies have indicated that the number of melanocytes varies very little from one racial group to another. There are variations, however, by anatomic region, with the highest concentration of melanocytes occurring in the cheek (2,310 $\pm$ 150 melanocytes mm^2) and the lowest occurring in the back and thigh (890 $\pm$ 70 and 1,000 $\pm$ 70 per mm^2, respectively) (Briele and das Gupta 1979). Instead, the pigmentary difference between races is apparently due to the quantity and quality of melanin deposited in melanosomes and the



Ultraviolet and visible spectra of black hair melanin and dopa melanin. Black hair melanin was irradiated for 30 and 60 min. Nonirradiated samples of black hair melanin and dopa melanin were used as controls. The melanins were precipitated by adding 3 M HCl to pH 1; the precipitates were dissolved in Solune-100 to give a final concentration of 200 μg/ml. .....: Dopa melanin; ———: nonirradiated black hair melanin; —— hair melanin irradiated for 30 min; ____: hair melanin irradiated for 60 min.



Ultraviolet and visible spectra of red hair melanin and dopa melanin. Red hair melanin was irradiated for 30 and 60 min. Nonirradiated samples of red hair melanin and dopa melanin were used as controls. The melanins were precipitated by adding 3 M HCl to pH 1, the precipitates were dissolved in Soluene-100 to give a final concentration of 200 μg/ml. .....: Dopa melanin; ------- nonirradiated red hair melanin; ——: hair melanin irradiated for 30 min; ____ hair melanin irradiated for 60 min.



. First derivatives of absorption spectra of dopa melanin, black hair melanin, and red hair melanin. . . .. Dopa melanin. —— black hair melanin; ------- red hair melanin.

FIGURE 3-4
DIFFERENCES IN THE UV-VISIBLE ABSORPTION SPECTRA FOR BLACK HAIR MELANIN (EUMELANIN) AND RED HAIR MELANIN (PHEOMELANIN)

Source: Menon et al. (1983a).

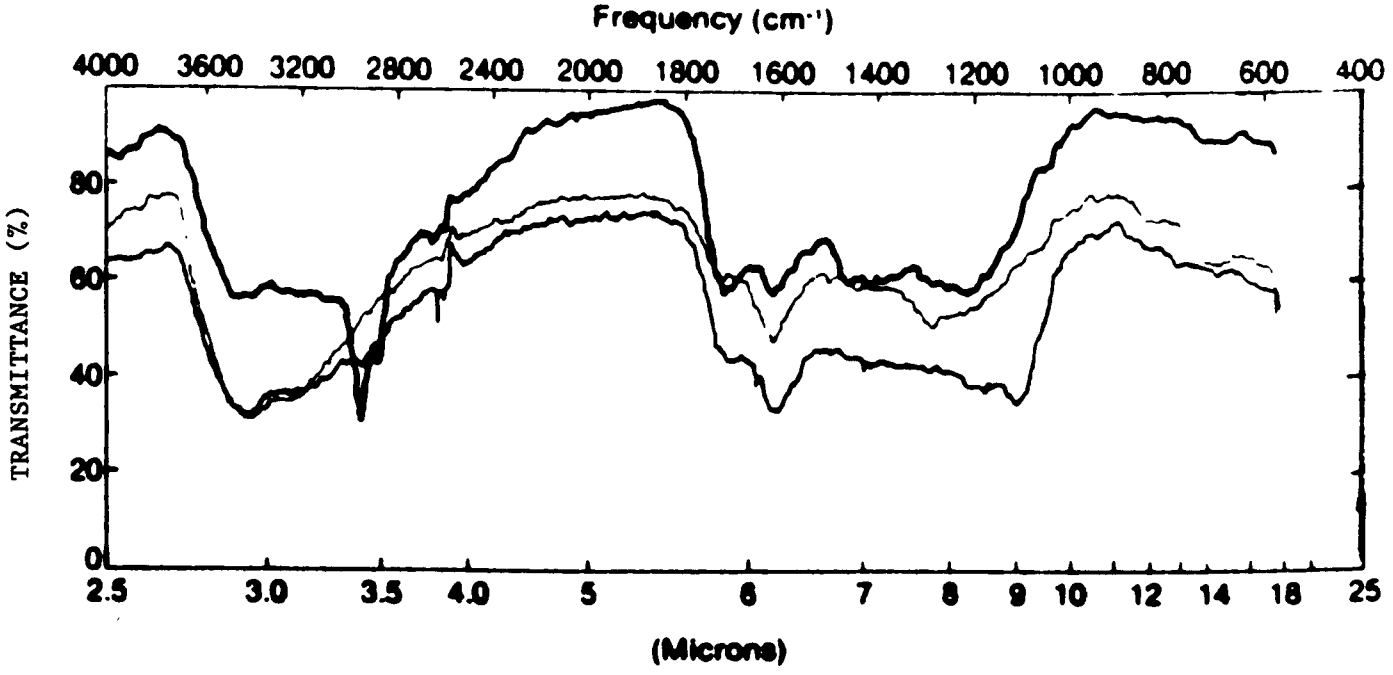


FIGURE 3-5

INFRARED ABSORPTION SPECTRA OF DOPA MELANIN
BLACK HAIR MELANIN, AND RED HAIR MELANIN

Dopa Melanin
Black Hair Melanin
Red Hair Melanin

Source: Menon et al. (1983a).

number of melanosomes transferred to keratinocytes. Table 3-2 shows the relationship between skin color, melanosome size, organization and skin type classification. Note that melanosomes in keratinocytes from lighter-colored skin are characteristically found as aggregates whereas melanosomes in keratinocytes from dark-skinned individuals, which are larger, generally occur singly. The table also indicates a greater tyrosinase activity in melanocytes from dark-skinned individuals, probably because there is more melanin per melanosome (Pathak et al. 1976). It has been suggested that the size of the individual melanosome may determine whether they are taken up singly or as aggregates by the keratinocytes (Hu 1981).

There are instances in which melanocytes and/or their embryonic precursors fail to reach the epidermis but come to reside in the dermis instead. In many such instances, as a result of unknown stimuli, they may lose their melanogenic properties and acquire the ability to contribute to the fibrous matrix of the dermis or to its neuronal network (Reed 1983; Elder et al. 1981). In so doing they become nevus cells. The factors that govern this change are unknown. One classification scheme considers the melanocytic nevus to be an evolving lesion in which melanocytes ("nevus cells") proliferate in the epidermis, drop into the dermis, and undergo further maturation there (Elder et al. 1981). Another scheme differentiates between acquired and congenital melanocytic nevi by whether the melanocyte precursor goes to the epidermis and then returns to the dermis or fails to achieve the epidermis because of arrested development in the dermis (Reed 1983). It has been suggested (Holman et al. 1983) that differences in behavior between histogenetic types of melanoma may be related to their having as precursor cells different differentiation states of the melanocytes.

Langerhans cells represent the third significant cell population present in the epidermis. It is generally accepted that Langerhans cells are bone marrow-derived cells which are functionally and immunologically related to the monocyte-macrophage series (Katz et al. 1979). These cells are present in the epidermis at a concentration similar to that of melanocytes--between 460/mm^2 and 1000/mm^2 (Lever and Schaumburg-Lever 1979). In contrast to melanocytes, the number of Langerhans cells does not increase with repeated exposure to ultraviolet light (Scheibner et al. 1986); however, these cells are very sensitive to UV light and lose their functional ability when exposed to very low doses. Their primary function appears to be one of antigen presentation (Stingl et al. 1978). A defect in this function is thought to be the cause of the immunosuppressive effect of UVR noted in studies of UV-induced cutaneous tumors (Kripke 1974) and the response of individuals to cutaneously applied antigens (Toews et al. 1980).

Skin photobiology

The interaction of sunlight with the skin is a complex process involving the transfer of energy from sunlight to various molecules in the various skin layers. As shown in Figure 3-6, the solar radiation reaching the earth contains wavelengths from about 290 to 4000 nm. This radiation is described as UV, visible, or infrared depending on the wavelength. The UV portion of the electromagnetic spectrum covers the range from 200 to 400 nm. Solar

TABLE 3-2

RELATIONSHIP AMONG SKIN COLOR, SIZE, DISTRIBUTION PATTERN OF MELANOSOMES AND SKIN TYPE CLASSIFICATION

Skin Color	Size of Melanosomes	Tyrosinase Activity in Melanocytes	Distribution of Melanosomes in Epidermal Keratinocytes	Approximate Number of Melanosomes per Basal Keratinocyte*	Skin Type**
Heavily pigmented skin of Africans, American Negros and Australian Aborigines	0.7-0.8 um x 0.3-0.4 um	Marked	Single, non-aggregated	400±35	VI
Moderately pigmented skin of Mongoloids (American Indians, Orientals)	0.5-0.7 um x 0.3-0.4 um	Moderate	Mixed non-aggregated as well as aggregated	250±50	V I
Moderately pigmented skin of Caucasoids (East Indians, Italians, Egyptians)	0.5-0.7 um x 0.3-0.4 um	Moderate	Predominantly aggregated	200±5	II III
Lightly pigmented skin of Caucasoids (fair-skinned Americans, British, French, Germans, etc.)	0.4-0.6 um x 0.3-0.4 um	Weak	Predominantly aggregated	100±50	I II III

* Based on random counts of 50 keratinocytes in basal layer.

** Estimate of sensitivity to UV-B erythema based upon history of sunburn and ability to tan.

Pathak MA, et al.: Sunlight and melanin pigmentation, in Smith KC (ed): Photochemical and Photobiological Reviews. New York: Plenum, 1976, pp. 211-239.

Source: Pathak et al. (1976).

radiation shorter than 290 nm is absorbed by ozone in the atmosphere and does not reach the earth's surface. The range from 200 to 400 nm is often divided into three categories: UV-A, UV-B, and UV-C. The UV-A portion (320 to 400 nm) is a longer wavelength, less energetic UV radiation which is not strongly absorbed by proteins and nucleic acids, and does not cause erythema in normal skin at moderate doses in the absence of photosensitizing chemicals (Anderson 1983). This range is also called black light and near UV radiation. UV-B (290-320 nm) is that portion of the spectrum responsible for solar erythema. It is also known as midrange UV and sunburn radiation. UV-C (200 to 290 nm) is biologically active but does not reach the earth's surface. However, radiation at 254 nm is frequently used in experimental biology to study the effects of UV on various systems.

About 95 percent of incident radiation penetrates the stratum corneum; the other 5 percent is reflected by the stratum corneum. Two processes, scatter and absorption, determine the penetration of radiation into the skin. Table 3-3 shows estimates of the epidermal transmission of various UV wavelengths through Caucasian or black skin. Note that the relative transmission of white to black is about fivefold, i.e., black epidermis is five times more effective than white epidermis at preventing radiation from reaching the basal layer. Figure 3-7 graphically shows these differences and indicates that, between 340 and 400 nm, black skin may be ten times better than white skin at preventing radiation from reaching the basal layer (Kaidbey et al. 1979). These authors also estimate that in blacks, the minimal erythemal dose (MED) is about 13 times that in fair-skinned humans. Figure 3-8 indicates that there are also great differences in the transmission properties of black versus white skin for wavelengths up to 800 nm (Wan et al. 1981). Data on a parameter related to transmission--diffuse spectral absorbance--indicate as well that "...above 1200 nm, the optics of the skin are essentially unaffected by melanin pigment" (Anderson 1983; Jacquez et al. 1955a,b).

The amount of radiation reaching the basal cells is a function of the thickness of the epidermis and stratum corneum as well as their content of radiation-absorbing molecules (chromophores). Although there are a large number of such substances in the skin, some of them as yet uncharacterized, most of the optical absorbance within the skin is attributable to melanin, proteins containing aromatic amino acids, urocanic acid, carotenoids (in the stratum corneum only), and nucleic acids (Anderson 1983). Figure 3-9 shows the ultraviolet absorption spectra of the major epidermal chromophores.

Only certain of the wavelengths present in sunlight are capable of stimulating or altering the functional state of melanocytes. The UV-A (320-400 nm) and UV-B (290-320 nm) wavelengths are the most active at stimulating the production of melanin, and are most effective at activating melanocyte function. Visible radiation (400-760 nm) and infrared radiation have some ability to stimulate or induce melanin pigment production; however, this response appears to be secondary to the damaging effect of the heat that such light transmits to the skin. The mechanism of the UV-B effects is unknown, although one author has suggested that it involves direct damage to the cell nuclei of melanocytes following direct absorption of photons by DNA, resulting in DNA base photoproducts and subsequent mitoses and proliferation

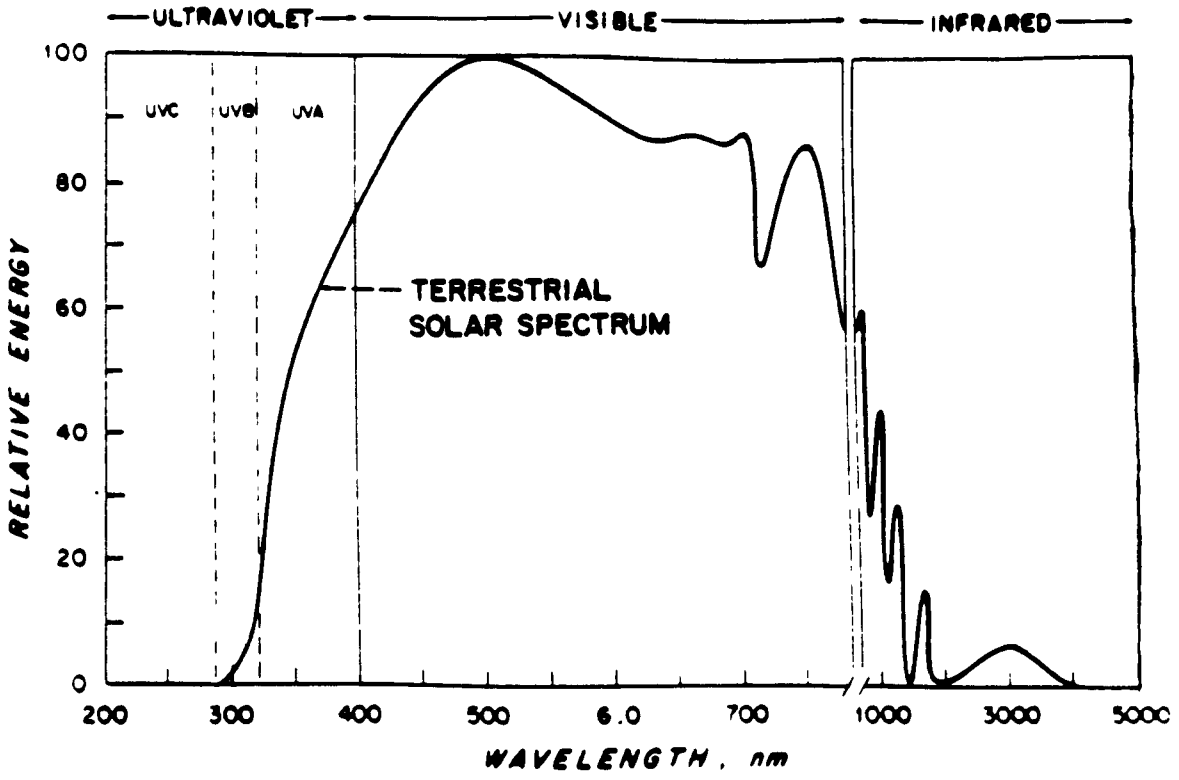


FIGURE 3-6

SPECTRUM OF ELECTROMAGNETIC RADIATION THAT REACHES THE EARTH'S SURFACE FROM THE SUN

Source: Kochevar (1983), Plenum Publishing Corp. Reproduced by permission.

TABLE 3-3

ESTIMATES OF THE PERCENT EPIDERMAL TRANSMISSION OF VARIOUS WAVELENGTHS OF UV-RADIATION

λ, nm	Percent Transmission White	Percent Transmission Black a/	Relative Transmission (%) Black Compared to White b/
290	0.083	0.011	13
295	0.171	0.025	15
300	0.270	0.041	15
305	0.348	0.056	16
310	0.407	0.068	17
315	0.453	0.078	17
320	0.488	0.086	18
325	0.515	0.092	18
330	0.537	0.097	18
335	0.550	0.100	18
340	0.562	0.103	18

a/ As reported in Kaidbey et al. (1979). Average values from Figure 3. Fluorescence radiation was not excluded.

b/ Based on values from Kaidbey et al. (1979).

Source: Adapted from Kubitschek et al. (1986).

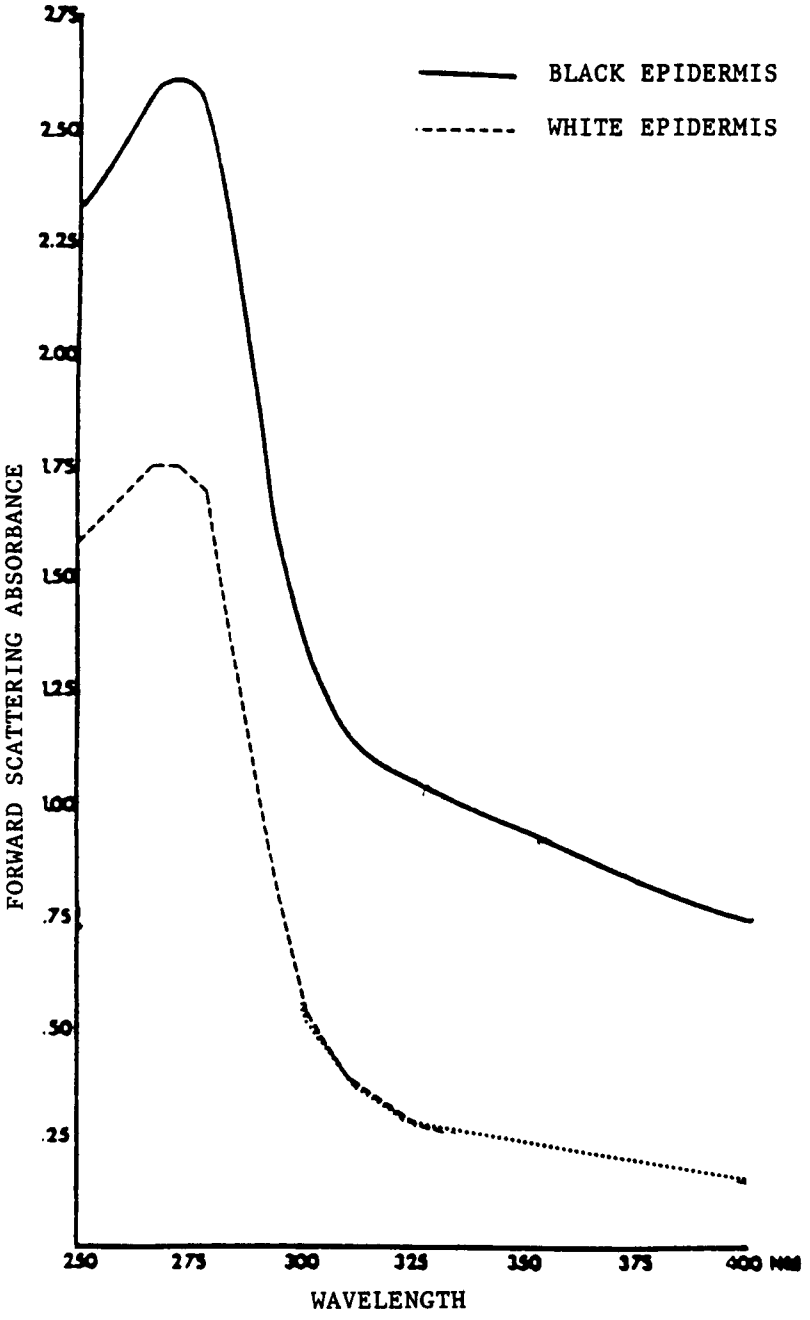


FIGURE 3-7

AVERAGE ABSORPTION SPECTRA FOR BLACK AND WHITE EPIDERMIS

Source: Adapted from Kaidbey et al. (1979), Reproduced by permission.

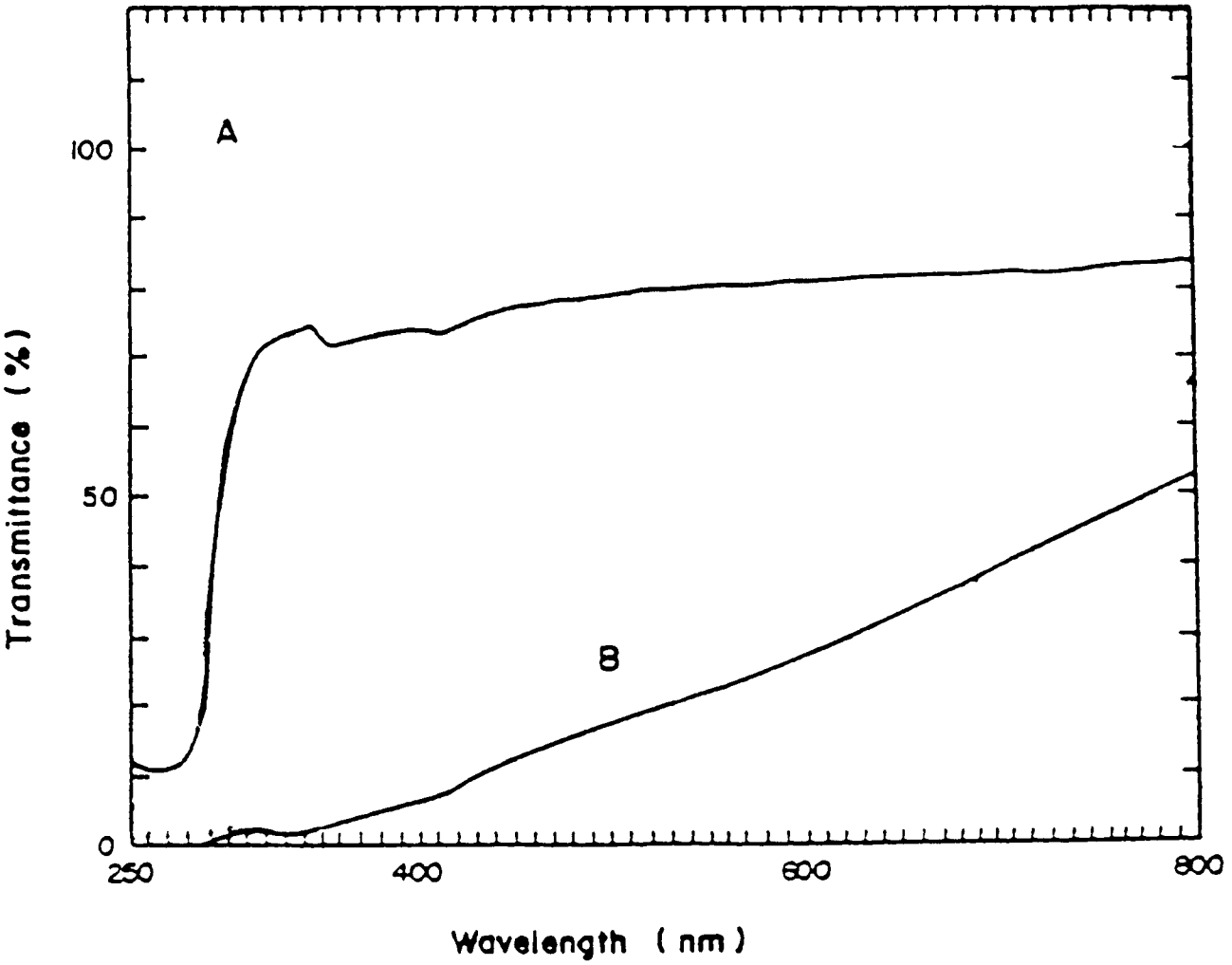


FIGURE 3-8

COMPARISON OF MEASURED EPIDERMAL TRANSMITTANCE
A, CAUCASIAN; B, DARK BLACK

Source: Adapted from Wan et al. (1981).

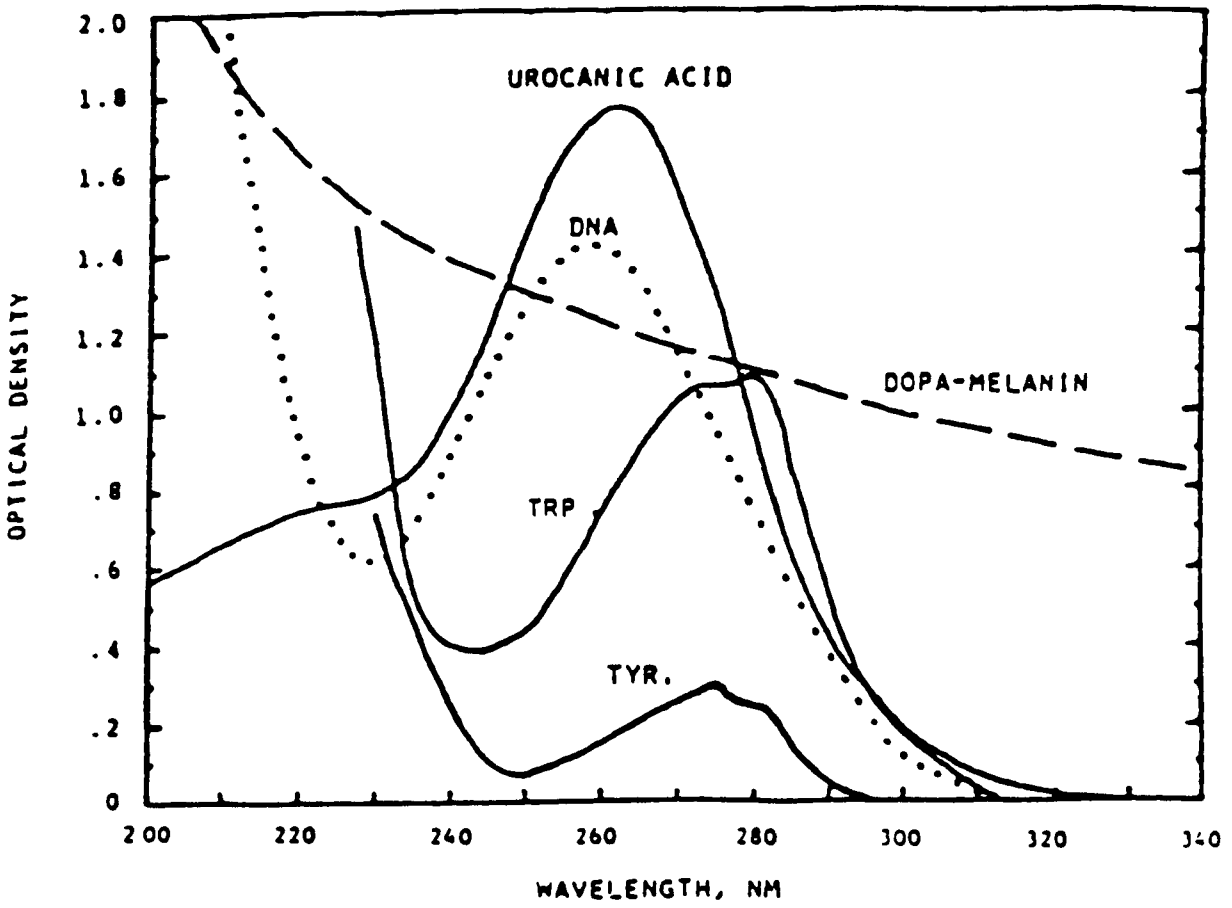


FIGURE 3-9

ULTRAVIOLET ABSORPTION SPECTRA OF MAJOR EPIDERMAL CHROMOPHORES

DOPA-melanin, 1.5 mg% in H2O);
Urocanic acid, 10^{-4} in H2O;
Calf thymus DNA, 10 mg% in H2O (pH 4.5);
Tryptophan (TRP), 2 x 10^{-4} M (pH 7);
Tyrosine (TYR), 2 x 10^{-10} (pH 7)

Source: Anderson (1983), Plenum Publishing Corp.

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of melanocytes. In contrast, the effects of the longer wavelength UV-A apparently involve the absorption of photons by non-DNA chromophores followed by the reaction of these excited species with molecular oxygen and the generation of reactive oxygen species which then interact with melanin, the cell membrane, or DNA, thereby exerting damage (Pathak 1985).

Skin response mechanisms

The skin has three response mechanisms for dealing with solar radiation: 1) dose reduction through the production of increased melanin (tanning) or through keratinocyte hyperplasia, 2) damage repair in which the cell's DNA repair mechanisms remove photoinduced damage, and 3) cell removal.

(1) Dose reduction via tanning is principally via a delayed response which is the result of the de novo synthesis of new melanosomes followed by their transport to keratinocytes to produce a skin darkening about 10 hours post exposure. This process may continue for several days, with the maximal skin darkening (tan) achieved in about a week. The most active wavelengths at inducing delayed tanning are in the UV-B range; however, UV-C, UV-A, and visible light can also cause delayed tanning. Along with the increased production of melanosomes, there is an increase in the number of active melanocytes, some of which are probably due to increased mitoses and others the result of the recruitment of dormant melanocytes. Mice repeatedly irradiated with UV-B showed a four- to sixfold increase in their melanocyte populations in 11 days; a smaller increase in non-irradiated sites was also observed, suggesting that a systemic growth factor might be involved. With time the tan wears off as the keratinocytes containing the extra pigment are sloughed off.

There is a wide variation in the tanning as well as the burning (erythema) response of individuals. This has been characterized through the classification of skin responses into six skin types as outlined below (Pathak 1985):

It was once thought than an immediate tanning response - immediate pigment darkening or IPD, also served a dose reduction function. However, very recent studies indicate that this process offers little or no protection (Blacket et al. 1985).

> Skin type I. These individuals are very sensitive; they tan little or not at all even with repeated exposure and may develop a moderate to severe sunburn reaction after exposure for an hour to solar radiation in the summer months. They are very fair, often have freckled skin, have red or blond hair, blue eyes, and have a low minimal erythemal dose (MED)--in the range of 15 to 30 mJ/cm^2. They do not show any IPD response.

Skin type II. These individuals are also very sensitive and burn frequently. They do not tan well, but upon repeated exposures may acquire a slight tan. They have a low MED in the range of 20-35 mJ/cm^2, and may show a weak IPD response.

Skin type III. These individuals generally burn first, then tan later after repeated exposure. They exhibit an IPD reaction upon exposure to light, and can generally acquire an average to good tan with two or three moderate exposures.

Skin type IV. These individuals generally have dark eyes and hair, and normally have lightly tanned skin. They burn minimally and have a strong IPD reaction. In the summer months, their facial skin color changes from light brown to olive or medium brown. This group includes pigmented Caucasoids, American Indians, Orientals, and people from the Mediterranean region.

Skin type V. These individuals generally acquire a deep tan and demonstrate an intense IPD reaction . Their eyes and hair are deep brown or black. This group includes Indians, Egyptians, Malaysians, Puerto Ricans, Mexicans, and other Spanish-speaking peoples.

Skin type VI. These individuals are darkly pigmented without exposure (e.g., American and African blacks and Australian aborigines) and become even more deeply pigmented upon exposure.

Gange et al. (1986) have compared the action spectra for tanning to that for erythema for skin types I through IV. Figure 3-10 presents the information provided by this group. The shorter UV wavelengths (250-296 nm) were more erythemogenic than melanogenic. Wavelengths of 296 nm to about 330 nm are equally erythemogenic and melanogenic to all skin types. In contrast, at wavelengths above 330 nm there is a divergence in response; for instance, individuals who tan well have a melanogenic dose at 365 nm, which is approximately one quarter of that required to induce erythema.

These authors also examined the photoprotective effects of visually identical UV-A and UV-B tans induced in the same individuals (Gange et al. 1986). They found that UV-B tans were much more protective, in that a UV-B tan could protect the skin from up to three times the normal MED whereas a UV-A tan could not.

The epidermis may also reduce the dose delivered to the basal layer by increased production of keratinocytes and a subsequent thickening of the epidermis. Studies in humans have shown that after a single exposure to UV-B, there is a sustained increase in epidermal mitoses, which leads to the epidermis and stratum corneum becoming 1.5 to 3 times as thick over the course of 1 to 3 weeks. The dose first induces a transient depression in

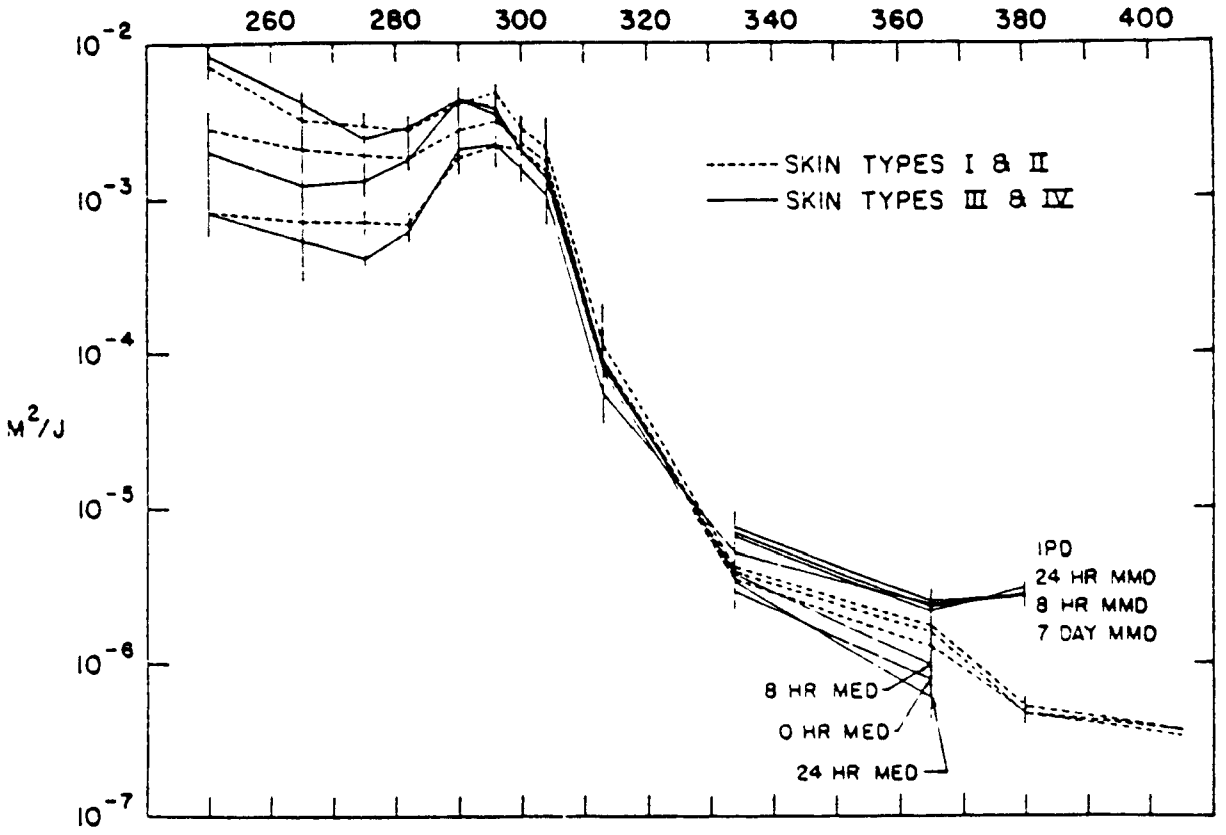

FIGURE 3-10

ACTION SPECTRA FOR ERYTHEMA AND PIGMENTATION

Source: Gange et al. (1986).

macromolecular synthesis in which DNA, RNA, and protein synthesis are markedly reduced and then elevated. The elevation of synthesis is a maximal 24 to 48 hours post-irradiation but may continue for as long as a week. UV-B and UV-C are the most effective at inducing this response but UV-A will also induce it. This additional skin thickness offers some measure of protection to individuals with a poor tanning ability because the disulfide-rich keratin synthesized by the keratinocytes absorbs photons in the UV-B and UV-C ranges. It is likely that, in lightly pigmented individuals, this skin thickening is the most important photoprotective or dose-reducing response, whereas in dark-skinned individuals, tanning is the more important response (Gange and Parrish 1983).

(2) The second mechanism by which the skin can respond to damage due to solar radiation is DNA repair. (A brief discussion of this subject is presented here; it is covered in much greater detail in Chapter 15.) The direct or indirect DNA damage inflicted on cells by UVR can be very detrimental. The most studied alteration in DNA structure by biologically relevant doses of UV is the cyclobutyl pyrimidine dimer (Spikes 1983). These dimers are formed between adjacent pyrimidines on the same DNA strand and their presence renders the phosphodiester bond joining the deoxyribose moieties resistant to nuclease digestion. The cell has three repair processes by which to correct damage to its DNA: photoreactivation, excision repair, and post-replication gap repair.

Photoreactivation involves UV-A-dependent, enzyme-mediated repair of pyrimidine dimers in which the enzyme binds to the dimer, forming an enzyme-substrate complex which absorbs photons of UV-A light; the dimer is then monomerized (Spikes 1983). Photoreactivation is an error free, nonmutagenic repair pathway which offers a number of advantages to the cell: it uses an outside energy source (UV-A photons), there is no incision into the DNA phosphodiester backbone (and therefore no risk of DNA degradation), and there is no polymerization (and thus no chance for the introduction of coding errors) (Spikes 1983).

Another efficient DNA repair process which works more slowly but may repair not only dimers but other kinds of damage, e.g., bulky carcinogens linked to DNA, is called excision repair. In the case of dimers, excision repair works via the activity of three enzymes, an endonuclease specific for dimers, a polymerase, and then a ligase. The endonuclease attacks the DNA at or adjacent to the dimer and introduces a nick in the DNA. The DNA polymerase removes the damaged DNA segments while utilizing the opposite strand as a template for new synthesis, and finally a ligase joins the newly synthesized DNA to the preexisting strand. Other kinds of damage, such as bulky carcinogens linked to DNA, require different endonucleases but the activities of the polymerase and the ligase remain the same (Spikes 1983).

There is a final repair process which may be available to the cell should the previous two mechanisms fail to repair a pyrimidine dimer. Termed post-replication gap repair, this mechanism is fairly well understood in bacteria such as Escherichia (E. coli) where it is invoked when, following DNA replication, there are gaps left in the DNA opposite the dimer. (The DNA

polymerase which faithfully transcribes one daughter strand to produce a new strand cannot interpret a dimer and consequently leaves a gap in the newly synthesized DNA.) Not much is known about post-replication repair in mammals, however. If mammalian cells use a mechanism similar to that observed in E. coli, then repair would proceed via a DNA recombinational mechanism which provides a good copy of the DNA needed to repair the damage; using this information, the cell can repair the damage with an excision repair mechanism (Spikes 1983). However, this mechanism is fairly error prone.

There are three possible outcomes as a result of the combined efforts of these repair systems: (a) the excision repair or photoreactivation process has worked properly, so that all photolesions are removed from the cell before DNA replication takes place and thus the cell suffers no mutations or other UV-induced DNA changes; (b) the photolesions in the DNA are not removed prior to DNA replications, so that mutations occur; or (c) misrepair or lack of repair of the DNA results in cell death. From the perspective of melanoma development it is the second category which is probably most important, because a non-lethal mutation could cause the cell or its progeny to take on the characteristics of a cancer cell.

(3) The third protective mechanism available to the skin is the removal of potentially harmful cells via either immune surveillance or, in the case of keratinocytes, programmed senescence and the shedding of dead cells from the stratum corneum. Immune surveillance may be compromised in chronically UV-irradiated individuals because UV-B experimentally induces a systemic immunosuppression to UV-induced tumor antigens (Kripke 1984). The skin is also protected in part from the development of mutant cells because the normal life history of keratinocytes is to move upward in the epidermis, gradually being removed from the nutrients provided by the basal layer, and eventually losing their ability to divide neoplastic, an essential property of cells. This latter mechanism does not apply to melanocytes, however.

THE BIOLOGY OF CUTANEOUS MALIGNANT MELANOMA

As mentioned in the first part of this chapter, malignant melanoma can be considered to be the neoplastic endpoint of melanocyte transformation. Transformation represents a disturbance in cell behavior; it is acquired over a finite time period through the slow and cumulative modification of different abilities in progressively growing groups of cells. Once a critical mass of cells with the appropriate properties is present, they can then be designated a neoplasm. The characteristics of a neoplasm are that "it is an abnormal new growth of tissue that is uncontrolled, has no expected endpoint and is aggressive to the host" (Perez-Tamayo 1984). An additional characteristic of malignancy that is acquired is the ability of a neoplasm to spread from its site of origin to other sites, i.e., to metastasize.

The biology of cutaneous malignant melanoma is complex in that there are several morphologic types of melanoma which may have different pathways of histogenesis; they tend to behave differently in terms of age at appearance and characteristic location, and yet have common elements in their tumor progression. What follows is a description of the various morphologic types,

information on their unique and similar characteristics, and finally a discussion of their similar method of tumor progression. This information is important to the interpretation of the epidemiologic and experimental studies discussed later in this document, because seeming incongruities in the relationship of sunlight (or UV-B) and the disease entity known as CMM may be explained by the different characteristics of these tumor types.

Morphology

Terminology for the various morphologic types was proposed by McGovern et al. (1973) and has been subsequently modified (Smith 1976; Elder et al. 1980). The descriptions that follow are composites drawn from these sources. There are four principal classes of melanoma:

(1) Melanoma arising in Hutchinson's melanotic freckle (HMFM) [also known as lentigo maligna melanoma]

(2) Superficial spreading melanoma (SSM)

(3) Nodular melanoma (NM)

(4) Unclassifiable melanoma (UCM)

Melanoma arising in Hutchinson's melanotic freckle begins with a characteristic pre-invasive lesion, the melanotic freckle, which is a linear proliferation of atypical melanocytes in the basal layer of the epidermis. The freckle is often marked by a profuse production of melanin, some of which may be taken up by cells in the dermis. A lymphocytic infiltrate may also be present. Such freckles generally occur in skin marred by solar degeneration, having atrophy of the epidermis and elastosis of the dermis. The freckle progresses to malignant melanoma via a characteristic course including gradually increasing numbers of melanocytes which are initially morphogenically normal in shape. As proliferation increases, the arrays of melanocytes begin to take on a palisade appearance and the cells begin to assume a spindle shape. Clusters of cells begin to form and the abnormal melanocyte development can be observed in the external root sheath of the hair follicle and sometimes even in the sweat ducts. The cell nests generally remain localized to the dermo-epidermal junction with a relative lack of invasion into epidermal areas outside the circumference of the freckle.

Superficial spreading melanoma develops as a flat, irregularly expanding, slightly palpable lesion which often has an irregular outline with prominent indentations. The color may vary considerably within the lesion, initially consisting of varying shades of brown, black, and bluish-grey. As the lesion grows, there may also be areas of grey-white, blue-grey, or whitish-pink indicative of complete or partial depigmentation following spontaneous regression.

The proliferating melanocytes of SSM are not, like those of HMFM, confined to the dermo-epidermal junction but rather invade the epidermis and then the dermis. Melanocytes of SSM in the dermo-epidermal region do not display the

pleomorphism seen in HMFM but rather are generally uniform in size and shape. Once they invade the dermis, however, they may retain their characteristic shape or may become epithelioid, spindle cell, or nevus cell-like. This flat, radially spreading stage of the evolution of a melanoma (either SSM or HMFM) is termed the "radial growth phase" (RGP). It is believed that most, if not all, melanomas which achieve the radial growth phase will progress to the next stage, the vertical growth phase, characterized by the appearance of a nodule within the pre-existing plaque of the RGP (Elder 1986).

Nodular melanoma is the third category of melanoma; it is used for those tumors which are never observed in the radial growth phase but are first observed in the vertical growth phase. Such "pure" vertical growth phase tumors are characterized by a much more rapid rate of evolution than SSM or HMFM. These aggressive tumors first appear as palpable nodules with no antecedent radial growth phase. The nodularity is evidently the result of a rapid focal proliferation of melanocytes in which cells at the dermo-epidermal junction invade the dermis from the onset of tumor development.

The fourth category of malignant melanoma is unclassifiable melanoma. Tumors are placed in this category when they do not fit readily into the other three categories. This may arise because of some distinctive characteristic, e.g., in hyperkeratotic papillary melanoma, or because tumors have components of more than one of the three classes, e.g., the pleomorphism of the cells seen in HMFM accompanied by the dermo-epidermal location normally observed in SSM.

In addition to the four histogenic types of melanoma reviewed above, several groups have suggested the need to distinguish a fifth variant: acral lentigenous melanoma (ALM). These melanomas occur in the palms, soles, subungual regions, and the mucocutaneous junction of the oral and nasal cavities and the anus (Briele and das Gupta 1979; Mastrangelo 1982; Clark et al. 1976; Arrington et al. 1977). Melanomas at these sites comprise 7 to 9 percent of all cutaneous melanomas, although in certain populations, e.g., blacks, this type of melanoma, and in particular melanoma of the soles, is the most common form of melanoma (Arrington et al. 1977). According to Clark et al. (1976), this type of melanoma is similar in its developmental pathway to SSM although, histologically, Arrington et al. (1977) indicate its characteristics to be more similar to HMFM. This discrepancy might be important in treatment because HMFM is considered by some to be a less aggressive tumor, which may be treated conservatively, whereas ALM is certainly, when fully evolved, an aggressive variant with a poor prognosis. ALM is of epidemiologic interest because although it occurs with approximately equal frequency in all races it is virtually the only type of melanoma observed in blacks and individuals who have never lived south of the Arctic Circle (Mark et al. 1986), and because of its location in sites protected from light by thick keratin layers, e.g., the palms and the soles.

COMPARATIVE INCIDENCE, SITE, SEX, AGE, AND RACIAL DISTRIBUTION

In the U.S., by far the most common type of melanoma is SSM; estimates of its contribution to the total number of cases range between 54 and 70 percent.

The mean age at diagnosis is 45 years and the tumor occurs about equally in both sexes. Estimates of the proportion of melanoma cases represented by nodular melanoma range from 12 to 32 percent (Adler and Gaeta 1979; Briele and das Gupta 1979) and the mean age at diagnosis is 50 years (Briele and das Gupta 1979). The least common form of melanoma is HMFM. It constitutes from 10 to 14 percent of the melanoma cases (Adler and Gaeta 1979; Briele and das Gupta 1979) and the median age at diagnosis is 70 years (Briele and das Gupta 1979). Figure 3-11 shows the age distribution by type of melanoma for 1978 data from the Melanoma Clinical Cooperative (Sober et al. 1979).

Table 3-4 indicates the distribution by sex and site of primary malignant melanoma observed in 4,868 cases from NCI's SEER data for the period of 1978 to 1981 (Scotto and Fears 1986). These data agree reasonably well with those presented on a population from M.D. Anderson by Smith (1976) in Table 3-5, which though from a much smaller sample, show a similar relationship. Table 3-6 gives the age, sex, and racial distribution observed by Smith (1976) in the M.D. Anderson population.

HMFM comprises almost one-half of the melanomas of the head and neck (Adler and Gaeta 1979) and is about twice as common in women as in men (Briele and das Gupta 1979). Superficial spreading melanoma accounts for about 70 percent of the melanomas of the lower extremities of women (Adler and Gaeta 1979) but occurs about equally among the two sexes (Briele and das Gupta 1979). Nodular melanoma is said to occur most commonly on the sole of the foot by one group (Adler and Gaeta 1979) and on the head, back, and neck by another (Clark et al. 1975). The latter group also indicates that nodular melanoma occurs about twice as often in men as in women.

Table 3-7 presents the histogenic distribution of melanomas observed by Smith (1976). These data are not in accord with those of Adler and Gaeta (1979), who found that HMFM on head and neck represented about 50 percent of all cases rather than the 25 percent figure found here. SSM does represent about 70 percent of the lower extremities tumors in this sample, and nodular melanoma is about equally distributed between head, neck, trunk, and the lower extremities.

Although, as detailed above, the various histogenic forms of melanoma have different incidences, site, sex, and racial distributions, these tumors have in common their mode of progression (Elder et al. 1980). Each (except NM) is thought to begin in a radial growth phase and proceed to a vertical growth phase. NM develops directly as a vertical growth phase nodule. In the radial phase, tumors "form a spreading patch or plaque that expands radially with time but becomes only slightly elevated." The neoplastic melanocytes may be found in the basal layer of the epidermis and, relatively early in tumor development, also in the papillary dermis. A competent host immune response possibly limits proliferation in the dermis, at least initially. At some point, however, the tumor escapes this control and begins to develop vertical growth. At that time, the neoplastic cells--possibly a clone--have acquired the ability to grow in groups or sheets, and a nodule appears. This phase may also be initially limited to an expansion within the papillary dermis until such time as the neoplastic cells acquire additional characteristics which

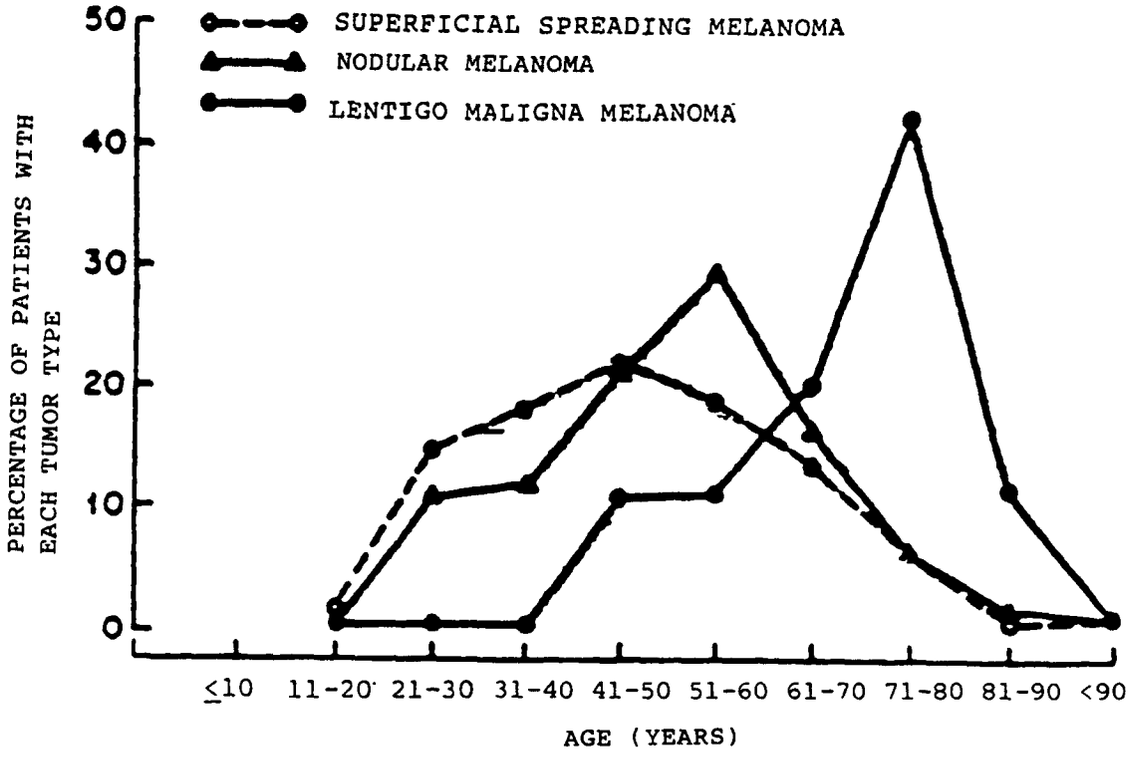

FIGURE 3-11

AGE DISTRIBUTION BY TYPE OF MELANOMA: SUPERFICIAL SPREADING (SSM), NODULAR (NM), AND LENTIGO MALIGNA (LLM) MELANOMAS.

Source: Sober et al. (1979), McGraw-Hill Book Co. Reproduced by permission.

TABLE 3-4

PRIMARY MELANOMA-DISTRIBUTION BY SITE AND SEX (SEER)

	Head and Neck	Upper Extremities	Trunk	Lower Extremities	Total
Males	573	503	1,072	11	2,402
Females	386	647	616	33	2,464

Source: Scotto and Fears (1986).

TABLE 3-5

PRIMARY MELANOMA-DISTRIBUTION BY SITE AND SEX

	Head and Neck	Upper Extremities	Trunk	Lower Extremities	Total
Males	87	46	59	61	253
Females	43	61	25	128	257

Source: Smith (1976).

TABLE 3-6

AGE, SEX AND RACIAL DISTRIBUTION OF PRIMARY MELANOMAS (M.D. ANDERSON)

		Age									
Sex	Race	00-09	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	Total
Male	White	-	6	24	47	48	43	32	29	14	-	243
	Black	-	-	-	-	-	2	1	-	-	-	3
	Latin American	-	-	-	1	-	2	3	1	-	-	7
Female	White	1	8	24	45	54	51	41	18	5	1	248
	Black	-	-	-	-	1	1	1	2	-	-	5
	Latin American	1	-	1	-	1	1	-	-	-	-	4

Source: Smith (1976).

TABLE 3-7

HISTOGENIC DISTRIBUTION OF PRIMARY MELANOMAS (M.D. ANDERSON)

Site	Flat (SSM)	Nodular on Flat (SSM)	Nodular (Pure)	HMFM	HMFM (nodular)	UCM
Head and Neck	34	35	29	17	12	3
Trunk	33	33	13	2	3	0
Upper Extremities	52	23	24	6	1	1
Lower Extremities	102	38	38	2	0	9
Total	221	129	104	27	16	13

Source: Smith (1976).

allow them to survive in the more hostile (less vascular) environment of the reticular dermis. Further changes may then occur which confer on these cells the ability to metastasize (Elder et al. 1980).

The rate at which these developments occur may vary tremendously among the various morphologic types of melanoma. The rate of development of HMFM is the slowest: between 5 and 20 years. SSM progresses somewhat faster: 1 to 7 years. Nodular melanoma is very rapid: on the order of months (Fitzpatrick and Soter 1985). Indeed, nodular melanoma may skip the radial growth phase, or so shorten it as to make it appear missing. It should be noted that once SSM and HMFM enter the vertical phase, they may be indistinguishable (prognostically though not clinically) from NM, although some believe that even in the vertical phase HMFM progresses much more slowly than SSM. This may be because HMFM and other lentigenous melanomas (e.g., ALM) are more frequently associated with spindle cells or desmoplastic vertical growth phases (Elder et al. 1980), an observation which has led to the suggestion (discussed below) that HMFM and SSM have different precursor cells.

Several theories have been suggested to explain the observed histogenic differences in malignant melanoma, particularly with regard to SSM and HMFM. Perhaps the best known is that of Mishima (1967) in which, on the basis of electron microscopic observations, he proposed that melanoma be divided into two separate histogenic lineages--one derived from melanocytes and one derived from nevus cells. In his report, Mishima suggests that HMFM develops from melanocytes and is characterized by radiosensitivity and a slower rate of growth, metastasis, and invasiveness than that observed in melanomas developing from junctional nevi. The latter type of melanoma would be equivalent to SSM or pure NM. Tumors from junctional nevi are more rapidly

growing, invasive, and metastatic. Mishima also distinguished between these two lineages on the basis of their melanosomes, their degree of spontaneous regression, and the presence of sun-damaged skin. HMFM regresses more completely, shows ellipsoid melanosomes, and appears more frequently in the presence of sun-damaged skin than does SSM, and rarely shows more than partial regression.

Mishima's theory has been accepted by some researchers (Holman et al. 1983) but not by others (Paul and Illig 1976). Holman et al. (1983) use the Mishima hypothesis as the starting point for a further hypothesis of their own which postulates that HMFM arises from sun-damaged melanocytes, whereas UCM and SSM arise from initiated nevus cells. The initiation process can be effected by a variety of agents, e.g., viruses, chemicals, or UV. Once a nevus cell is generated, however, its subsequent development can be "promoted" by UV, estrogens or other hormones, or trauma.

Paul and Illig (1976), however, do not believe that a dualistic theory of melanoma histogenesis is appropriate. In their work, they studied the presence of dendritic-branched tumor cells in all types of malignant melanoma. They found that such cells occur in all tumors, but that this is to some extent controlled by the environment. This led them to hypothesize that the difference between HMFM on the one hand, and NM and SSM on the other, was that the properties of HMFM were attributable to the sun-damaged skin in which it develops. These authors proposed, in addition, that the nevus cell is an end stage in differentiation, i.e., that it is not the precursor to SSM and UCM as proposed by Mishima. In this position, Paul and Illig are seconded by Ackerman and Mihara (1985), who challenge the contention that the dualistic hypothesis is supported by the available data. These authors view the dysplastic nevus as one of the many variants of melanocytic nevi and, in their experience "rarely see evidence of malignant melanoma in continuity or contiguity with a dysplastic nevus." They contend that those researchers who assert that 20 to 40 percent or more of all malignant melanomas begin in association with pre-existing dysplastic nevi have misinterpreted the histology of melanomas in situ to conclude that they are dysplastic nevi.

Clark et al. (1986) believe that ALM, HMFM, and SSM differ etiologically. Light is not considered to be an inducer of ALM because of its site preference (soles, palms, and subungual surfaces), racial distribution (it is virtually the only form in blacks), and "occurrence in persons who have never lived south of the Arctic Circle." In contrast, HMFM and SSM are thought by these authors to be induced by light, but in a different fashion. The favored sites for HMFM are the face, neck, and back of the hands--sites irradiated by light in a relatively continuous fashion. "If irradiation of this type is to induce melanoma, it does so as a rule on the face of a fair, freckled person who has few or no melanocytic nevi." The melanomas which develop do so via an indolent hyperplastic process which progresses to HMFM uncommonly.

SSM is thought to derive from a process which begins with the induction of melanocytic nevi by discontinuous or sporadic light exposure. The susceptible individual has "a cutaneous phenotype quite different from that of the fair-freckler--a phenotype that tans better and is darker." In some

individuals the distributions of freckles and nevi appear to be mutually exclusive, with freckles and no nevi on areas of continuous exposure such as the face, and with nevi and no freckles on areas receiving discontinuous irradiation. The nevi may progress through hyperplasia to dysplasia and thence (rarely) to SSM and (even more rarely) to NM (Clark et al. 1986).

SUMMARY AND CONCLUSIONS

The information reviewed in this chapter is drawn from a wide variety of disciplines and indicates, to some degree, the complexity of the problem addressed by this document. The chapter is designed to provide background information important to understanding the ultimate question that this document must answer: If the UV-B component of sunlight is increased, will there be an increase in the incidence, mortality, and/or morbidity of melanoma?

These are the summary points of this chapter:

3.1 Melanoma is a cutaneous neoplasm whose incidence in white Caucasian populations is increasing. It has been estimated that in the U.S. during 1987 there will be 25,800 cases of CMM, 5,800 CMM deaths and that by the year 2000 one out of every 150 individuals will develop melanoma.

3.2 Melanomas arise from transformed melanocytes. Basal cells and squamous cells are differentiation states of keratinocytes; when transformed, these cells become basal cell and squamous cell carcinomas, respectively.

3.3 Melanocytes may have two differentiation states: melanocytes and nevus cells. There is some discussion whether a nevus cell is a differentiated state of the melanocyte or a premalignant precursor cell for melanoma.

3.4 Melanocytes produce melanin and distribute it to the keratinocytes via organelles termed melanosomes. Blacks and whites differ in the amount of melanin produced by their melanocytes, the quality and quantity of melanosomes delivered to the keratinocytes, but not in the total number of melanocytes per site. Black (pigmented) skin is between five and ten times more effective at protecting the basal layer from UV-B and other wavebands of UVR than white (non-pigmented) skin.

3.5 The highest concentration (~2300/mm^3) of melanocytes is found on the cheek, while the back and the thigh have the lowest number (approximatly 900 and 1000/mm^3, respectively). This distribution pattern differs from those of all forms of melanoma except possibly HMFM.

3.6 Melanin absorbs in a broad range of UV wavelengths although evidently not much beyond 1200 nm. There are several forms of melanin; red hair melanin (pheomelanin) has a greater ability to produce superoxide (free radicals) when irradiated with UV and visible radiation light than does black hair melanin (eumelanin).

3.7 The wavelengths of sunlight that reach the earth's surface lie above 290 nm. UV-B (290-320 nm) comprises a very small amount of the total energy from sunlight reaching the earth but is considered to contain much of the biological activity.

3.8 There are five different types of melanoma: 1) melanoma in Hutchinson's melanotic freckle (HMFM) or lentigo maligna melanoma, 2) superficial spreading melanoma (SSM), 3) nodular melanoma (NM), 4) unclassified melanoma, and 5) acral lentiginous melanoma (ALM). They behave differently in site preference, in their relationship to cumulative sun exposure, and possibly in their precursor cells. These differences in behavior may be important to the question of whether sunlight is an agent for melanoma, in that the answer may have to differ qualitatively or quantitatively for each of the different types of melanoma.

3.9 Certain authorities on melanoma believe that the relatively continuous solar irradiation received on face, neck, and back of hands, when it induces melanoma does so on the face of the fair freckled individual with few or no melanocytic nevi via an indolent tumor progression pathway involving increasing degrees of atypical melanocytic hyperplasia (lentigo maligna) until HMFM occurs after years of growth.

3.10 The same authorities also believe that discontinuous or sporadic light exposure such as that received by the back induces melanocytic nevi which may progress to abnormal melanocytic dysplasia, and, on rare occasions, to SSM and, even more rarely, to NM.

3.11 UV-B radiation is known to cause DNA damage via the formation of pyrimidine dimers. The most active wavelengths are in the UV-B range; however, UV-A may also cause DNA damage. The latter damage is probably not via pyrimidine dimers, but is thought to involve reactive oxygen species.

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SECTION II

REVIEW OF EPIDEMIOLOGIC INFORMATION

CHAPTER 4

TIME-RELATED FACTORS IN THE INCIDENCE AND MORTALITY: AGE, PERIOD, AND BIRTH COHORT EFFECTS

The increasing incidence of and mortality due to cutaneous malignant melanoma (CMM) have been the subject of numerous international studies and reports over the past two decades. Most publications have been based upon tumor registry and vital statistics data from westernized countries where recordkeeping systems are generally very good. Research has primarily focused on: definition of secular trends; verification of trends; description of age-specific curves; and cohort analysis of CMM rates to determine the respective contributions of time-related effects. This chapter summarizes the literature addressing time-related factors in the incidence and mortality of CMM.

SECULAR TRENDS IN INCIDENCE AND MORTALITY

Sharp rises in incidence and mortality due to cutaneous malignant melanoma have been reported in nearly all Caucasian populations worldwide (see Table 4-1). Magnus (1982) analyzed trends in incidence in Norway, Sweden, Denmark, Finland, and Iceland for the period 1943-1976 and found that, although the absolute levels of incidence varied from country to country, an approximate annual increase of 6 percent was observed in all five countries with no sign of leveling off. Likewise, Connecticut incidence rates increased fivefold from 1935 to 1974, with an annual average increase of 5 percent (Roush et al. 1985a). Osterlind and Jensen (1986) noted that increases in Danish incidence were most pronounced since 1955, and showed no signs of leveling off as late as 1982. However, Danish mortality did not begin to increase until 1965, about 10 years after incidence rates began to rise markedly. Incidence rates in the United States increased steadily until 1983 when a 5 percent decrease was observed; however, this drop is thought to be an artifact due to the advent of DRG (disease related group) legislation, which is resulting in decreased hospitalization of individuals with melanoma in the United States (Sondik et al. 1985).

In general, increases in mortality due to CMM have been less steep than those observed for incidence. From 1943 to 1982, Danish incidence rose fivefold while corresponding mortality rates doubled, with signs of leveling off in women since 1975, but not in men (Osterlind and Jensen 1986). Leveling off of Australian mortality has been evident at least since 1965 to 1969 in both sexes, although incidence continues to increase (Armstrong 1982). In Sweden, overall incidence rose by 7 percent per year from 1959 to 1968, while only negligible changes in mortality occurred in both sexes (Malec and Eklund 1978). Similarly, data from the New Mexico Tumor Registry indicate that incidence rose considerably from 1969 to 1976, but mortality did not change over this period (Pathak et al. 1982). Lee (1982a) reported steady increases in mortality of 3 percent per year over the period 1951-1975 in England and Wales, Canada, and the United States. Lee noted that if diagnosis or treatment had improved over this time period, their influences were

TABLE 4-1

INCREASES IN INCIDENCE AND MORTALITY FROM MALIGNANT MELANOMA FROM DIFFERENT COUNTRIES

	Country	Sex	First Period of Observation		Second Period of Observation		Total Percent Increase	Number of Years	Annual Percent Increase
			Time	Rate per 10^6	Time	Rate per 10^6			
Incidence	New York State	M	1941-1943	1.2	1967	3.4	176	25	7.0
		F	1941-1943	1.8	1967	2.9	65	25	2.6
Incidence	Norway	M	1955	1.8	1970	6.3	264	15	17.6
		F	1955	2.6	1970	6.8	195	15	13.0
Mortality	Norway	M	1956-1960	1.6	1966-1970	2.7	69	10	6.9
		F	1956-1960	1.3	1966-1970	1.8	36	10	3.6
Mortality	Canada	M	1951-1955	0.7	1966-1970	1.4	93	15	6.2
		F	1951-1955	0.6	1966-1970	1.2	107	15	7.1
Mortality	United Kingdom	Both	1950	0.5	1967	1.0	100	16	6.3
Mortality	Australia	M	1931-1940	1.0	1961-1970	3.6	267	30	8.9
		F	1931-1940	0.8	1961-1970	2.5	227	30	7.6
Mortality	Denmark	M	1956-1960	1.6	1966-1969	2.4	49	10	4.9
		F	1956-1960	1.6	1966-1969	2.1	32	10	3.2
Mortality	Sweden	M	1956-1960	1.7	1966-1968	2.1	30	9	3.3
		F	1956-1960	1.1	1966-1968	1.5	40	9	4.4
Incidence	Connecticut	M	1935-1939	1.1	1975-1979	8.2	645	40	16.1
		F	1935-1939	0.9	1975-1979	6.8	656	40	16.4
Incidence	U.S.A.	WM	1974	6.7	1983	9.6	43	10	4.3
		WF	1974	6.0	1983	8.3	38	10	3.8
Mortality	U.S.A.	WM	1950	1.0	1977	2.6	160	27	5.9
		WF	1950	0.8	1977	1.6	200	27	7.4

Adapted from: Elwood and Lee (1976); NCI 198); NCI (1985a); NCI (1985b).

sufficiently constant that no change in the mortality trends was observed. More recent data from the United States (1974-1983) indicate that mortality due to CMM has continued to increase significantly both in white males and females (Sondik et al. 1985).

Secular trends in CMM mortality are less steep than those for incidence, probably due to earlier diagnosis rather than increasing diagnosis and registration of benign and semi-malignant cases in recent years (Magnus 1977; Elwood and Lee 1975). A study of cancer registries over the period 1955-1980 in Alabama and New South Wales, Australia (Balch et al. 1983) showed that melanoma skin tumors tended to be detected at progressively earlier stages of development; tumors were thinner, less invasive, and less likely to present with ulcerations. In addition, nodular tumors became less frequent while the incidence of superficial spreading melanomas, which have a better prognosis, increased over the period. Incidence rates of nodular and superficial spreading melanoma in Finland, however, increased to the same extent over the period 1963-1976 (Teppo 1982).

WORLDWIDE INCREASES IN CUTANEOUS MELANOMA: ARTIFACTUAL OR REAL?

Whenever significant changes in incidence or mortality rates are observed, it is necessary to determine whether the trends are genuine. In 1977, Ressuguie suggested that rising trends in CMM incidence were largely a result of improved diagnosis and registration (as cited in Lee 1982a). Histopathological studies, however, indicate that criteria for diagnosis of CMM have been consistent over time in Norway (Magnus 1975), and that the quality of diagnoses in well-run population-based cancer registries has been excellent (Pakkanen 1977; Malec et al. 1977). In addition, reasonable consistency in histologic diagnosis has been demonstrated between pathologists working in the same city (McCarthy et al. 1980) and in different countries (Larsen et al. 1980).

Considerable observational data have also led most investigators to conclude that actual increases in the incidence and mortality of CMM have occurred. Osterlind and Jensen (1986) point out that if substantial changes in histopathological criteria and registration efficiency have occurred, higher rates of diagnosis would most likely have resulted in stepwise increments in incidence, rather than the gradual rise observed. Furthermore, Danish mortality tends to mirror incidence rates with a lag period of 10 years, suggesting that the rise in incidence is real (Osterlind and Jensen 1986). Lee (1982a) has noted that improved diagnosis or registration is not likely to affect mortality since it would mean that the lower mortality rates observed earlier were due to the incorrect registration of large numbers of deaths in countries having very good systems of vital statistics. The fact that proportional increases in incidence have been similar in populations from both high and low incidence areas, such as Queensland and Hawaii (high rates), and Canada and the United Kingdom (low rates), further suggest that the increases are real (Elwood and Hislop 1982) and associated with a universal factor(s). Incidence rates also demonstrate distinct patterns over time by sex, age, and anatomic site, further suggesting that increases in rates are consistent with changes in sunlight exposure habits by sex and birth cohort (see Chapter 5).

There appears to be general agreement that the sharp rise in the incidence of CMM is associated with increasing exposure to ultraviolet radiation through sun exposure as a consequence of changing clothing and leisure habits (Magnus 1981). The etiologic mechanism of solar radiation in the causation of CMM, however, remains controversial (Magnus 1982).

AGE-SPECIFIC TRENDS IN INCIDENCE AND MORTALITY

The age-specific incidence and mortality curves for CMM are unlike those for most other forms of cancer, which tend to increase linearly with increasing age (Cook et al. 1969; Elwood and Lee 1975; Magnus 1982). In contrast, steep increases in CMM incidence begin in adolescence, leveling off through middle age, followed by less steep increases in the older age groups. Distinct changes in the shape of the age-specific curves occur when rates are stratified by sex and anatomical site (see Chapter 5).

Age-specific incidence curves also change in shape according to the decade of diagnosis, as shown in the Danish population for the years 1943-1982 (Figure 4-1). Among individuals diagnosed from 1943 to 1952, incidence increased gradually with increasing age. Over subsequent decades, the age-specific curves showed progressively steeper increases from ages 20 to 50, followed by a more gentle slope or plateau in the older age groups (Osterlind and Jensen 1986). These changes over time in the shape of the cross-sectional age-specific curves suggest the potential influence of birth cohort effects (Lilienfeld and Lilienfeld 1980). Based on Figure 4-1, it is not surprising that the mean age at diagnosis of CMM has tended to decrease over time in Denmark.

Using cancer registry data from Norway, Magnus (1981) compared the age-specific incidence curves for the two periods, 1955-1970 and 1971-1977, and found that the difference between the two curves was greatest for the age groups 30 to 70 (Figure 4-2). He concluded that this finding was due to birth cohort effects operating primarily on the individuals born between 1900 and 1930. This conclusion will be discussed further in the following section on cohort analyses of CMM incidence and mortality.

COHORT ANALYSES OF CMM INCIDENCE AND MORTALITY

The technique of cohort analysis involves careful study of incidence, mortality, or prevalence rates (i.e., the proportion of individuals with the disease at a specified time period) in individuals born in the same period of time, usually within the same decade. Age-specific rates in cohorts are compared, the major objective being to distinguish the three time-related effects--age, period of diagnosis (i.e., calendar time), and birth cohort--that might explain the changing trends (Kleinbaum et al. 1982). An age effect is present when the disease rate varies by age, regardless of birth cohort; a period effect is present when the disease rate varies by time, regardless of age or birth cohort; a cohort effect is present when the disease rate varies by year of birth, regardless of age (Kleinbaum et al. 1982). Cohort analyses may be conducted graphically, using statistical modelling techniques which attempt to separate the respective contributions of age, period, and birth cohort effects.

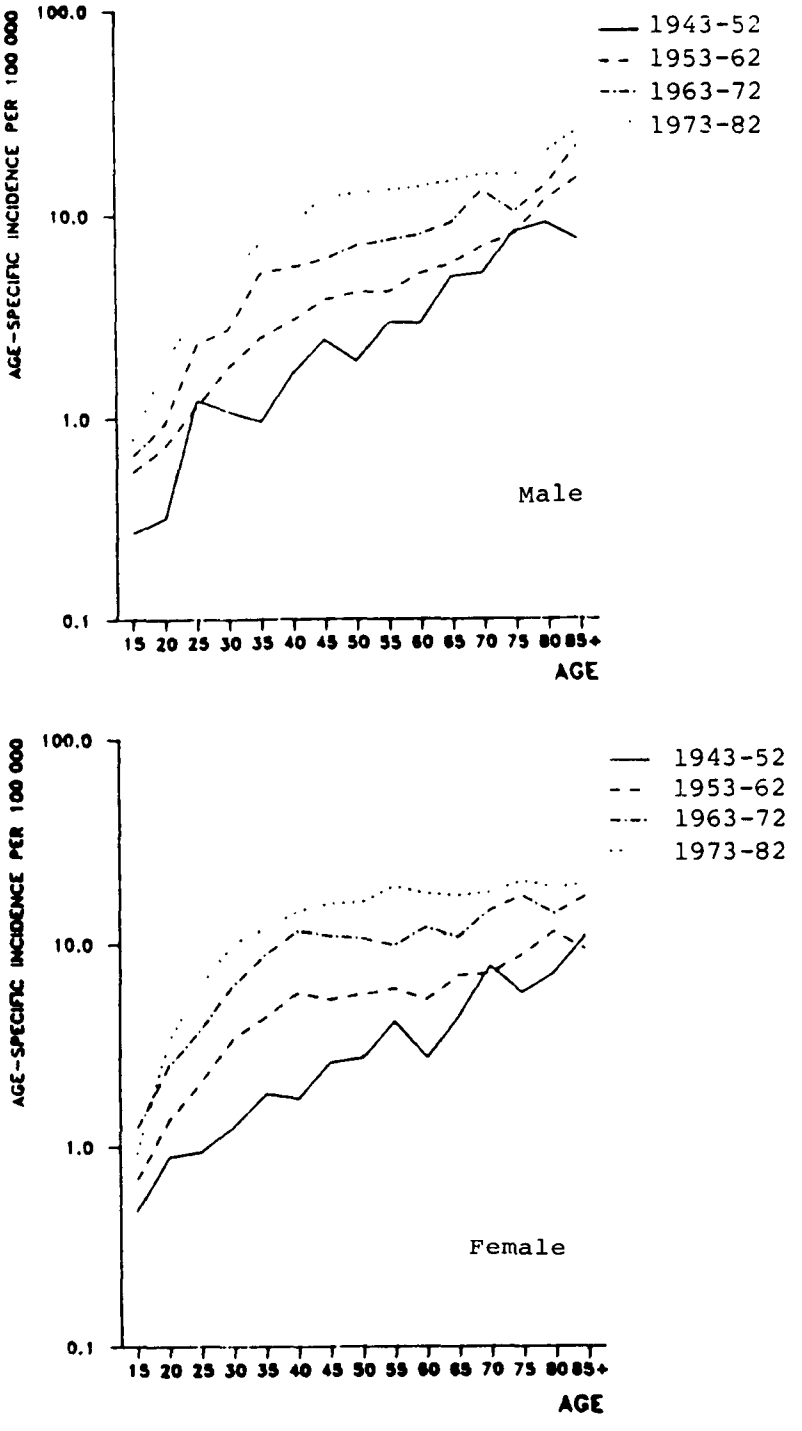

FIGURE 4-1

AGE-SPECIFIC MALE AND FEMALE INCIDENCE RATES OF MALIGNANT MELANOMA OF THE SKIN IN DENMARK, FOR ALL SITES COMBINED AND FOR SUCCESSIVE TIME PERIODS

Source: Osterlind and Jensen (1986).

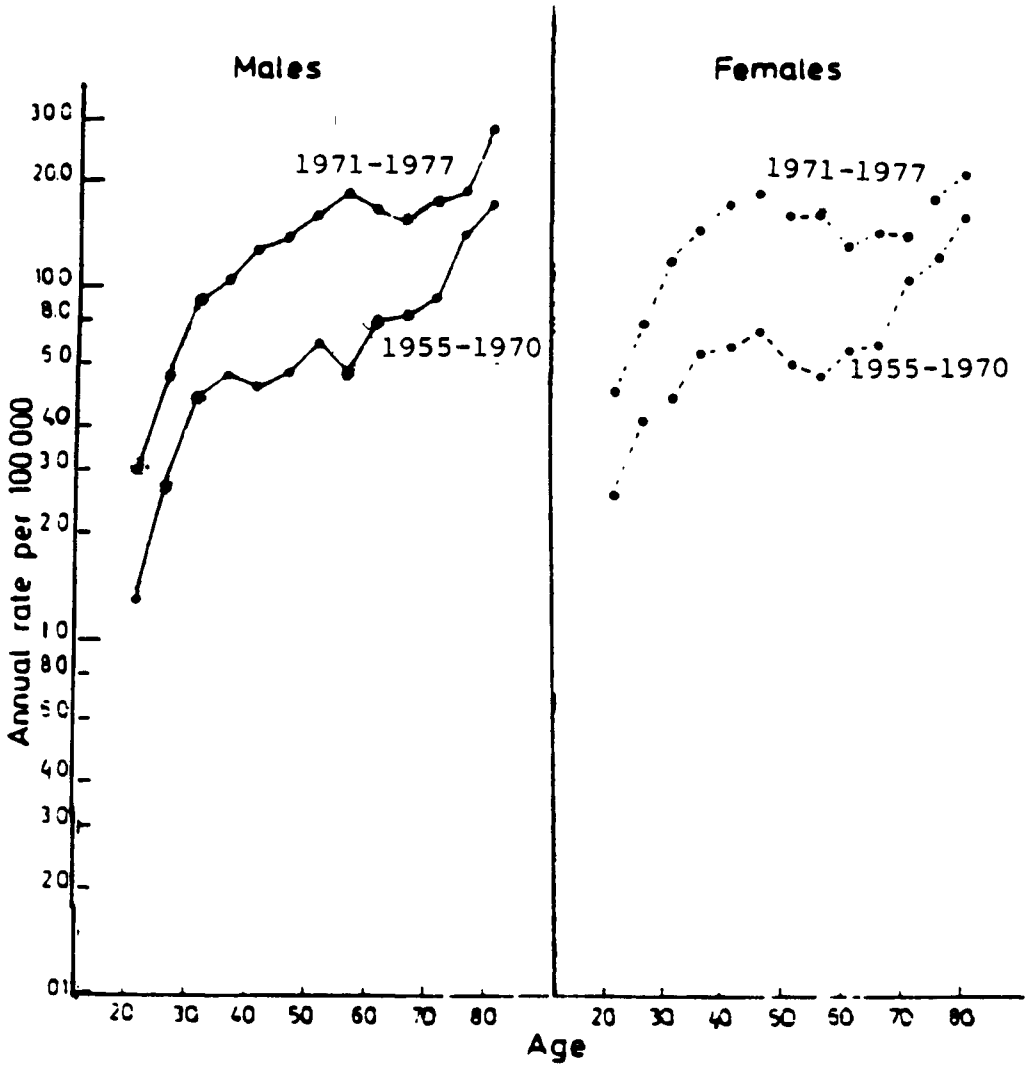

FIGURE 4-2

AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF CUTANEOUS MALIGNANT MELANOMA IN NORWAY, 1955-1970 AND 1970-1977

Source: Magnus (1981), Am. Cancer Society, Inc., J.P. Lippincott Co. Reproduced by permission.

As early as 1961, Haenszel suggested on the basis of United States data that "persons born after 1885 have been exposed with increasing intensity to some factor(s) associated with high skin cancer mortality" (Gordon et al. 1961). These increases in skin cancer mortality in successive cohorts were apparently due to malignant melanoma, although CMM was not separately classified until the sixth revision of the International Classification of Diseases in 1950. In 1970, Lee and Carter first associated the long-term trends in total skin cancer mortality with the effects of CMM, and concluded that year-of-birth effects were most likely responsible for the secular increases. Other birth cohort analyses of overall CMM trends have since been conducted by investigators using data from several different countries, all reporting similar findings.

Graphical Analyses of Birth Cohort Effects

Magnus (1981; 1982) plotted age-specific incidence rates for separate birth cohorts in Norway over the period 1955-1977, as shown in Figure 4-3. It can be seen that the risk of malignant melanoma within each cohort rises consistently throughout life, as is true for most other cancers. Graphing CMM rates by birth cohort substantially changed the age-specific curve from that observed in the cross-sectional data; the stable rates in middle age seen cross-sectionally disappeared. Shifting of the birth cohort curves to the left as seen in Figure 4-3 implies that there are consistent increases in incidence for each successive cohort. The cohort effect in Norway is most marked for individuals born from 1900 to 1930, where distance between the curves is greatest. For example, at ages 45-49, individuals born in 1920 to 1929 had incidence rates four times higher than individuals born in 1900 to 1909. Cohort curves after 1930 are closer together, suggesting that the differences in incidence rates by cohort are being reduced. One factor postulated as responsible for differences in incidence rates in successive birth cohorts is solar radiation.

Cohort effects are most evident for sites which have shown the greatest increase in incidence over time, such as the trunk in males and lower limbs in females, and are minimal for sites which increased less dramatically, such as the face and neck (Magnus 1981; Houghton et al. 1980; Boyle et al. 1983; Stevens and Moolgavkar 1984).

For CMM of the trunk in Norwegian males 50 to 54 years old, the incidence rate for the 1920-1929 birth cohort was six times that of the 1900-1909 birth cohort (Magnus 1981). As shown in Figure 4-4, among males and females born between 1890 and 1909, the incidence of CMM of the face was greater than that of the trunk among males and lower limbs among females. For cohorts born between 1930 and 1949, however, the highest incidence (per skin surface area) was of the trunk of males and the lower limbs of females. Magnus concluded that the ratio of carcinogenic exposure to the trunk/lower limbs and to the face/neck varied according to year of birth. He suggested that the shift in melanoma distribution by cohort was consistent with changes in clothing and suntanning habits during the first half of this century.

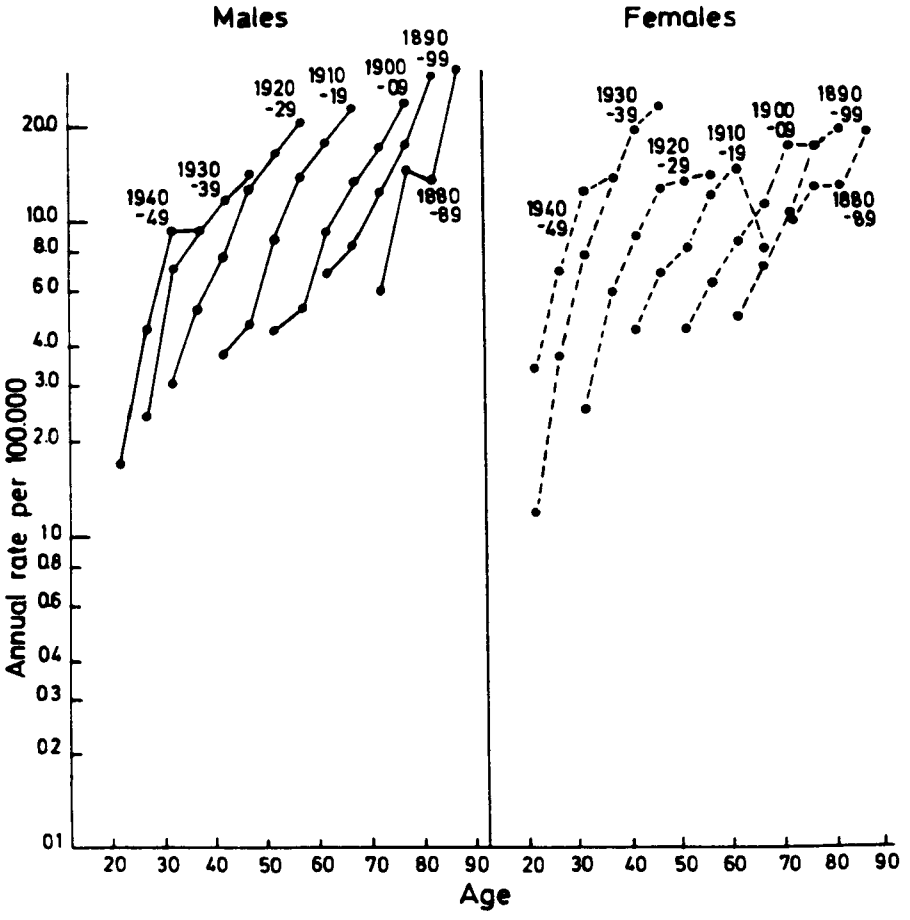

FIGURE 4-3

AGE-SPECIFIC INCIDENCE RATE OF TOTAL SKIN MELANOMA BY COHORT IN NORWAY, 1955-1977

Source: Magnus (1982), Hemisphere Publishing Corp. Repreduced by permission.

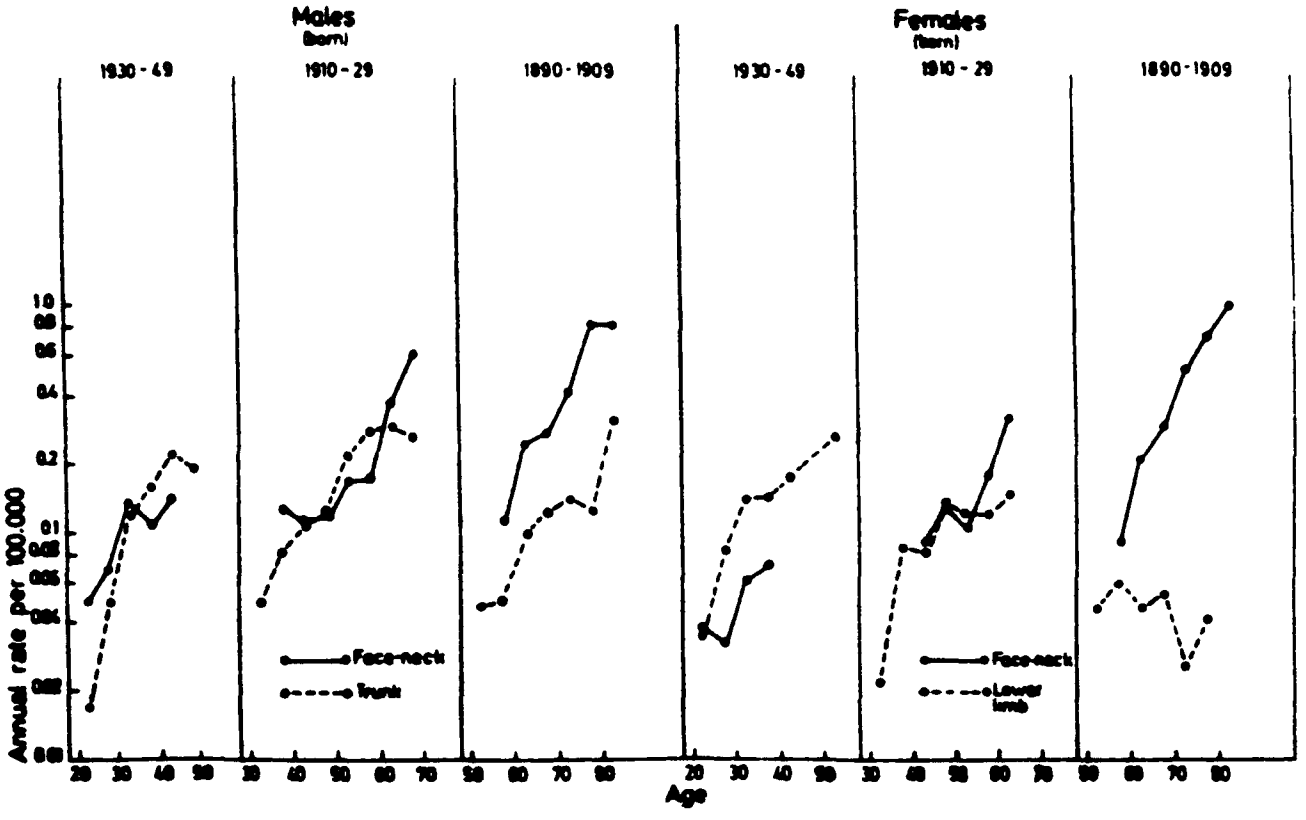

FIGURE 4-4

INCIDENCE OF MALIGNANT MELANOMA IN NORWAY, 1955-1977, PER AREA UNIT OF THE PRIMARY SITE: [a] AGE-SPECIFIC RATES FOR COHORTS

[a] The area unit corresponds to 1 percent of the total skin surface.

Source: Magnus (1981), Am. Cancer Society, Inc., J.P. Lippincott Co. Reproduced by permission.

Magnus (1982) notes a slight tendency for the cohort curves to level off with age, particularly in generations born after World War I. The leveling off of the cohort curves is best seen in incidence rates for CMM of the trunk and lower limbs, particularly among Norwegian cohorts born from 1900 to 1929. Magnus notes that this leveling off with age is "rather atypical for most types of cancer," and postulates that it may be due to decreases in sunning with increasing age. This statement implies that sunlight might have a promoting as well as an initiating role in the etiology of CMM.

Birth cohort analyses of incidence rates in Denmark (1943-1972), Connecticut (1935-1974) (Houghton et al. 1980), and Finland (1953-1973) (Teppo et al. 1978) yielded overall findings consistent with those of Magnus (1981, 1982), i.e., increasing incidence rates were observed in successive birth cohorts. The first sign of changing incidence for all sites was observed among those born in 1892 to 1895 in Connecticut and Denmark. Rising incidence began at different times for different anatomic sites in Denmark, with changes in incidence for those born as early as 1882 for the trunk-neck in males and lower limbs in females (Houghton et al. 1980). The incidence curves for facial CMM changed little in successive cohorts.

Muir and Nectoux (1982) conducted cohort analyses with CMM incidence data from Australia, Czechoslovakia, England and Wales, France, Japan, and the Netherlands. Cohort effects were apparent in all six nations, but were most discernible in individuals born from 1910 to 1930. Even in Japan, where incidence rates are 15 times lower than those in Australia, an upward trend in incidence of comparable magnitude was observed in successive cohorts. Later birth cohorts born from 1940 to 1950 did not differ with respect to incidence. This lack of increase in rates among the youngest cohorts may be due to a small number of cases, or might indicate that later cohorts had similar exposure to the carcinogenic factor(s). Muir and Nectoux concluded that the universality of a cohort effect strongly implicates an environmental factor that is widespread, and affects light-skinned people more and both sexes equally, though on somewhat different parts of the body.

Utilizing recent CMM incidence data from the Connecticut Tumor Registry, (1940-1979) Roush et al. (1985b) plotted age-specific incidence rates for seven age groups by birth cohort (Figure 4-5). The age-specific incidence curves were generally parallel on a semi-log scale, showing that rates within age groups increased similarly with each successive cohort. The slopes of the curves, however, showed a tendency to be less steep for individuals in age groups born in 1925 and later. If rates are actually leveling off in the younger cohorts, this could be interpreted to mean that sunlight exposure has peaked in these individuals, i.e., that the maximum change in behavior patterns with regard to leisure time has occurred. This finding is consistent with those of Muir and Nectoux (1982).

Birth cohort analyses of New Zealand's non-Maori population were conducted for the period 1948-1977, revealing different trends for CMM incidence and mortality (Cooke et al. 1983). While incidence rates continued to increase in recent cohorts, mortality rates stabilized in both sexes by the 1924 birth cohort. These mortality changes are similar to those observed in a number of

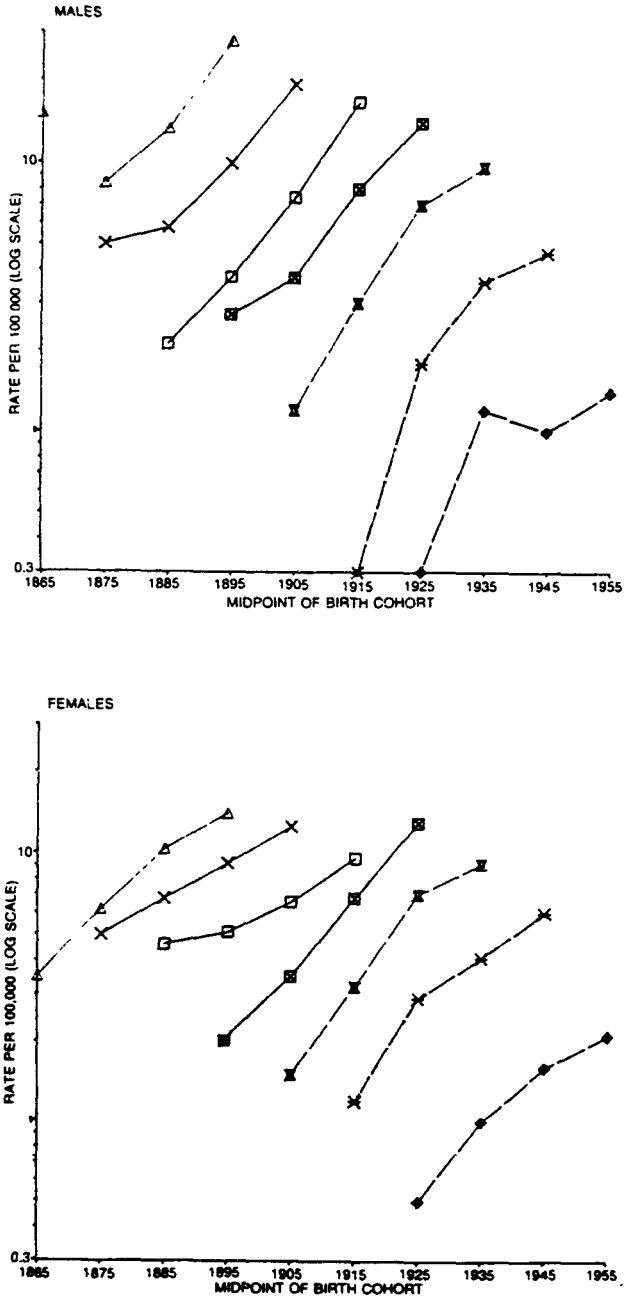

FIGURE 4-5

AGE-SPECIFIC INCIDENCE RATES IN CONNECTICUT FOR CUTANEOUS MALIGNANT MELANOMA BY SEX AND COHORT

Source: Roush et al. (1985b), Am. Public Health Assoc. Reproduced by permission.

other countries (Elwood and Lee 1974; Lee et al. 1979; Holman et al. 1980). The New Zealand incidence patterns are also similar to those described in Norway, Finland, Denmark, and Connecticut (Magnus 1981, 1982; Teppo et al. 1978, Houghton et al. 1980). Cooke et al. (1983) concluded that both the incidence and mortality data were correct, and that the stabilization of mortality rates was most likely due to improvements in prognosis.

Modelling Approaches in the Evaluation of Cohort Effects

Lee et al. (1979) studied mortality rates by cohort in the United States (white population), England and Wales, and Canada for the period 1951-1975. They calculated age-specific cohort slopes for each sex within each of the three populations, finding large and consistent differences in mortality rates with each successive cohort. These authors concluded that secular increases in mortality over this time period (approximately 3 percent per year) were caused by cohort effects. Although case-fatality (measured as the proportion of CMM cases who died among CMM cases diagnosed over a specified time period) decreased over this period, slopes of the age-specific cohort curves did not appear changed. This observation suggests that any effects of earlier diagnosis or improved treatment occurred evenly over the study period, thereby failing to alter the trend in the slopes.

Holman et al. (1980) examined Australian mortality rates due to malignant melanoma over the period 1931-1977, when rates more than quadrupled in both sexes. Estimates for the independent effects of calendar year, birth cohort, and age on mortality were determined using statistical modelling techniques. On the basis of their analysis, Holman et al. concluded that virtually all of the secular trends in mortality rates could be attributed to increases in successive cohorts, beginning with those born from 1865 to 1885. Increases by birth cohort, however, stabilized by the 1925 (women only) and 1935 (men only) birth cohorts. Slowing of mortality rates has also occurred in cohorts born around this period (1926) in England and Wales (Lee and Carter 1970) and Finland (1930-1940) (Teppo et al. 1978). Holman et al. (1980) emphasized that the stabilization of rates was probably not due to the immigration of persons with lower rates of CMM, because migrants were not overrepresented among the cohorts in which the rates leveled off (i.e., 1925 and after). Instead, cohort trends in CMM mortality were more likely associated with lifestyle changes involving more recreational exposure to the sun over the generations (Holman et al. 1980). The authors, however, were unable to state whether Australian sun exposure habits have stabilized, and if so, whether those born in 1925 and after would have been the first cohorts affected. Improvements in prognosis would probably affect all cohorts equally, and therefore, are not likely to account for the stabilization of mortality rates in the later cohorts.

The individual effects of age, birth cohort, and calendar year derived from CMM mortality rates by Holman et al. (1980) are shown on graphs in Figures 4-6, 4-7, and 4-8. The age factor (Figure 4-6) rose sharply between the age groups 10-14 and 30-34, followed by less rapid increases in the subsequent age groups. The time factor (Figure 4-7), after correction for age and birth cohort, demonstrated very little change with year of death. The

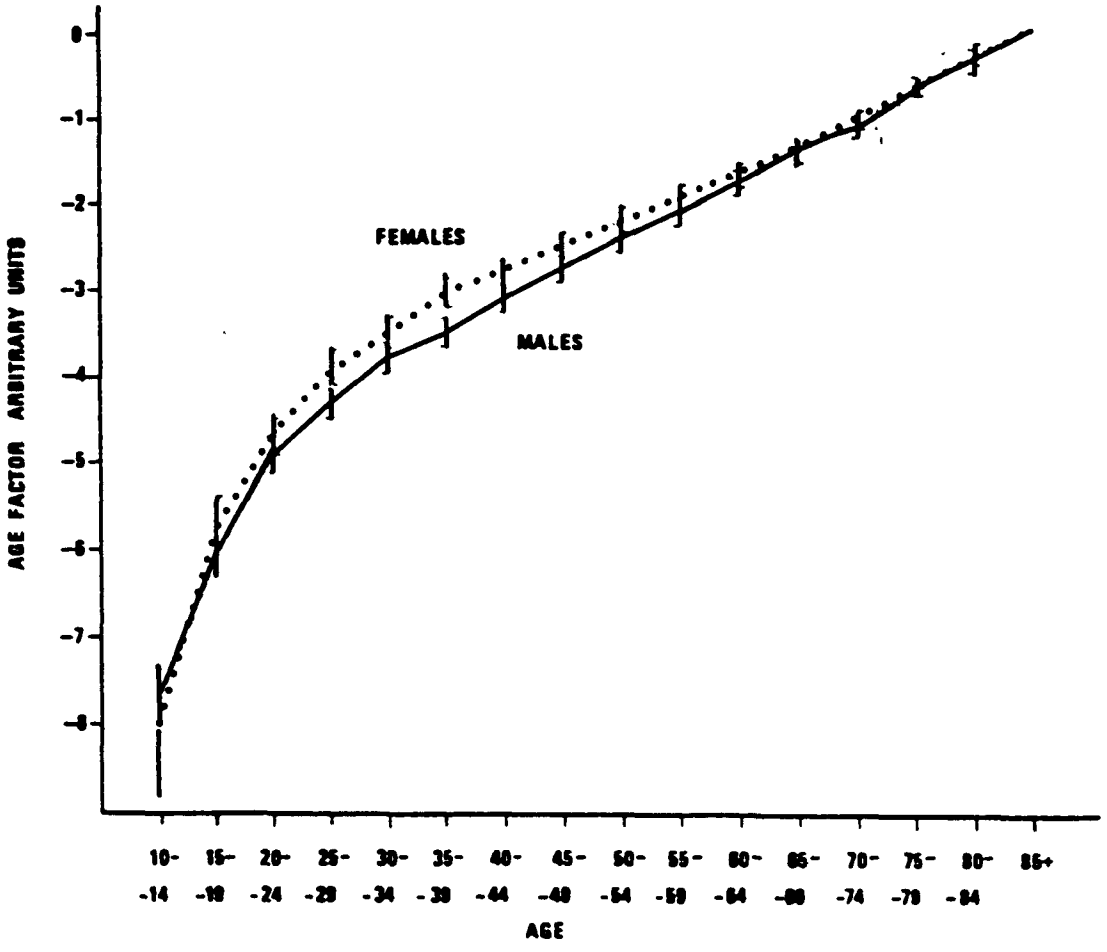

FIGURE 4-6

STATISTICAL MODELLING RESULTS FOR THE EFFECT OF AGE ON CMM MORTALITY RATES IN AUSTRALIA (1931-1977), ADJUSTING FOR EFFECTS OF CALENDAR YEAR AND BIRTH COHORTS

Standard errors associated with point estimates are indicated by ↓ for males and ↑ for females and are conditional on elimination of linear trend on the time factors.

Source: Holman et al. (1980).

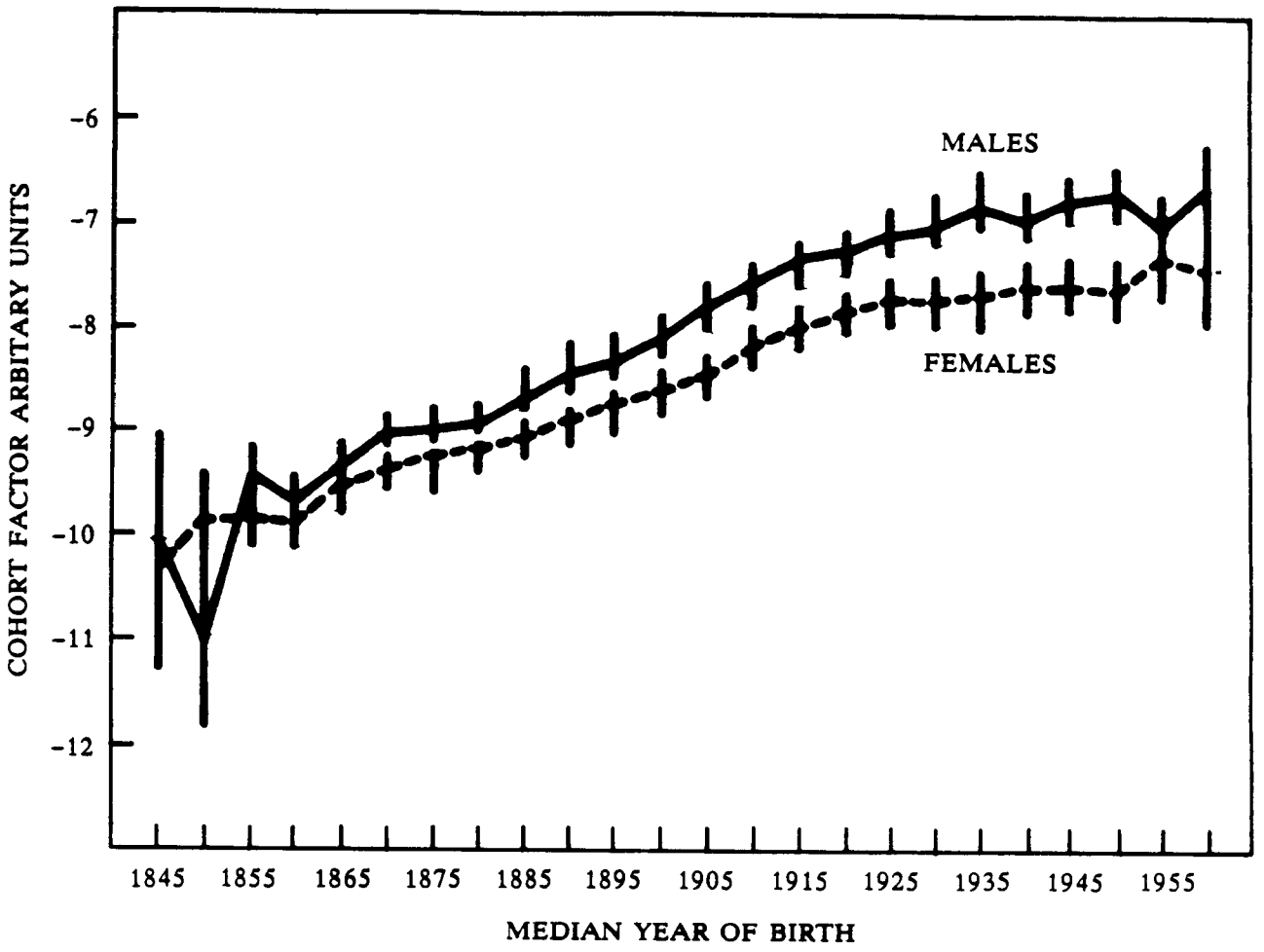

FIGURE 4-7

STATISTICAL MODELLING RESULTS FOR THE EFFECT OF BIRTH COHORT ON CMM MORTALITY RATES IN AUSTRALIA (1931-1977), ADJUSTING FOR EFFECTS OF AGE AND CALENDAR YEAR

Standard errors associated with point estimates are indicated by ↓ for males and ↑ for females and are conditional on the elimination of linear trend on the time factors.

Source: Holman et al. (1980).

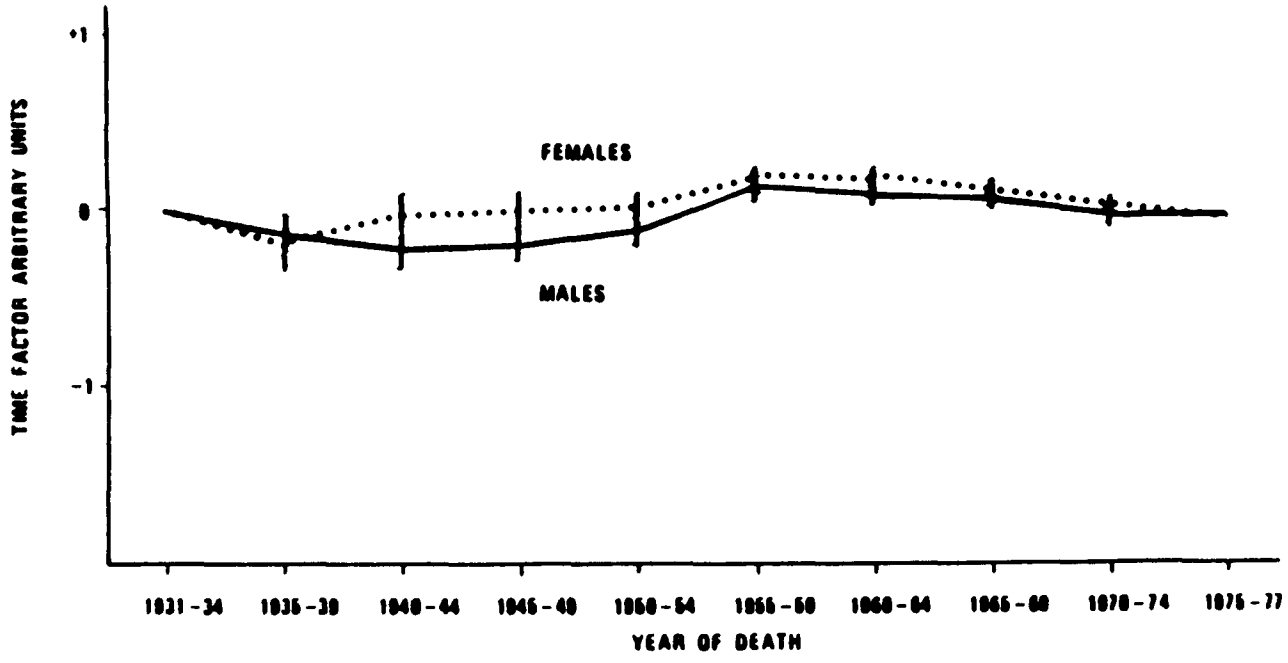

FIGURE 4-8

STATISTICAL MODELLING RESULTS FOR THE EFFECT OF CALENDAR YEAR ON CMM MORTALITY RATES IN AUSTRALIA (1931-1977), ADJUSTING FOR EFFECTS OF AGE AND BIRTH COHORT

Standard errors associated with point estimates are indicated by ↓ for males and ↑ for females and are conditional on the elimination of linear trend on the time factors.

Source: Holman et al. (1980).

birth cohort factor (Figure 4-8) increased with successive cohorts from about 1865 to 1935 in males, and 1865 to 1925 in females. Holman et al. concluded that secular increases in CMM mortality will continue for approximately 30 to 40 years, until the cohorts born before the stabilization of rates (i.e., 1925-1935 cohorts) die.

Utilizing a modelling approach similar to that of Holman et al. (1980), Venzon and Moolgavkar (1984) conducted cohort analyses of CMM mortality in five countries: Australia, New Zealand, the United States, Canada, England, and Wales. These countries were selected to represent populations with high, intermediate, and low rates of CMM in order to determine whether similar time-related effects were present in populations varying in CMM risk. Under all models tested, cohort effects were seen to "drive up mortality" within each country. In addition, the relative increases in mortality due to cohort effects were approximately the same in the five countries. Thus, Venzon and Moolgavkar were able to derive an age-specific mortality curve, corrected for birth cohort effects, using combined data from all five populations. A nearly straight-line relationship of CMM mortality and age was observed, the slope being somewhat less in women than men. The authors stated that the lower slope in females might reflect a larger proportion of female deaths in the younger age groups; it could also be interpreted as reflecting an excess of male deaths in the older age groups. Lee and Storer (1980, 1982) discuss a hormonal risk factor in premenopausal women that could be responsible for higher mortality in young women.

When cohort effects derived from statistical modelling were plotted for the five countries, they were seen to be leveling off in recent cohorts (Venzon and Moolgavkar 1984). The authors suggested that this may represent a slowing down of the increase in incidence of melanomas of the trunk and lower limbs (i.e., sites of greatest cohort effects) or possibly an improving prognosis for these sites.

Both, Stevens and Moolgavkar (1984) and Boyle et al. (1983), modelled the independent effects of age (i.e., correcting for birth cohort effects) on site-specific CMM incidence rates using data from Denmark and Connecticut, and Norway, respectively. Both studies noted rapidly increasing risk by birth cohort for all sites. Stevens and Moolgavkar concluded the fit of their model showed a similar age-dependence for all common subsites of CMM, while Boyle et al. found age-dependent relationships differed by site (see Chapter 5). Discrepancies between the findings and conclusions of Stevens and Moolgavkar (1984) and Boyle et al. (1984) may be associated with the application of different statistical models to different sets of data. In addition, these authors grouped the anatomical sites somewhat differently.

Roush et al. (1985a,b) conducted cohort analyses of CMM incidence data from Connecticut, 1940-1979, using statistical modelling techniques similar to those used by Holman et al. (1980) and Venzon and Moolgavkar (1984). As in similar studies, modelling demonstrated the importance of cohort effects on CMM incidence rates, while period effects were not detected. Roush et al. (1985a) suggested, however, that period effects (i.e., time) could theoretically be present since CMM rates by year of diagnosis show marked

fluctuations annually with sunspot activity (Houghton et al. 1978), or seasonally with changes in sunlight exposure (Swerdlow 1979; Holman and Armstrong 1981). The period effects, present as cross-sectional fluctuations in the rates, could be superimposed on the underlying cohort patterns, thus preventing their detection (Roush et al. 1986a). Holman et al. (1983) have suggested that annual or monthly fluctuations in diagnosis of CMM would be consistent with promotional effects of sun on transformed cells in the development of melanoma. Roush et al. (1985a) suggested that period effects and cohort effects may reflect different stages of neoplastic transformation (i.e., promotional and initiating, respectively) in the etiology of CMM.

The dramatically changing public health importance of CMM was emphasized in another recent analysis of Connecticut Tumor Registry data by Roush et al. (1985b). Modelled summary incidence rates (age-adjusted) for cutaneous malignant melanoma were compared with rates of colon cancer within the youngest birth cohorts. The analysis revealed that incidence rates for CMM in the 1955 cohort will rival those for colon cancer, presently the third most common cancer site in Connecticut. Thus, in the coming decades, CMM could easily become one of the most common malignancies in the absence of preventive measures (Roush et al. 1985b).

FINDINGS

The following findings can be drawn from the studies reviewed in this chapter:

4.1 Sharp increases in incidence and mortality have been reported in white but not non-white populations worldwide. Based on observational and analytical evidence, most experts agree that the trends are genuine, and not due to increases in the registration and diagnosis.

4.2 Steeper increases have been reported for incidence versus mortality rates. In addition, there are indications that mortality rates are leveling off in some areas where incidence rates continue to rise annually, such as Australia, Denmark, and New Mexico. Diagnosis at earlier stages of the disease, leading to increased survival, is thought to be a major cause for the leveling off of mortality rates.

4.3 The age-specific incidence curve for CMM is unlike that for most other forms of cancer, which tend to increase linearly with increasing age. Steep increases in CMM incidence begin in adolescence, level off in middle age, and show low rates of increase, if any, in the older age groups. This low slope of age-specific incidence is due to the high lifetime risk of melanoma in younger individuals. The slope of the age-specific incidence curve increases substantially when rates are

plotted on a semi-log scale and stratified by birth cohort.

4.4 Most authors who have conducted cohort analyses of CMM incidence and mortality rates conclude that virtually all secular increases in CMM are due to cohort effects. In most countries, the first signs of increasing rates are seen in cohorts born around 1900, although increases in cohorts born as early as 1865 are observed in Australia and New Zealand. In Norway and several other countries, there is a tendency for a slowing of the increase in incidence in cohorts born around and after 1930. Stabilization of mortality rates is also occurring in cohorts born from 1925 to 1935 and later, in countries such as Australia, New Zealand, England and Wales, and Finland.

4.5 On the basis of the Connecticut Tumor Registry data, statistical modelling indicated that the incidence rates of CMM in the 1955 birth cohort will rival those for colon cancer, currently the third most common cancer site in Connecticut.

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CHAPTER 5

VARIATIONS IN THE ANATOMICAL DISTRIBUTION OF CUTANEOUS MALIGNANT MELANOMA

The anatomical distribution of cutaneous malignant melanoma (CMM) has been the subject of numerous epidemiologic studies. Research efforts have focused on site-specific trends in CMM incidence related to sex, age, race, histogenic type, birth cohort, and season. The most pronounced differences have been associated with gender, race, and birth cohort. Some researchers have also investigated the effect of primary CMM site on patient prognosis. Several factors which could explain the observed trends in CMM site distribution have been presented in the literature, including effects of occupation, recreational activities, clothing habits, pigmentation, trauma, and exposure to sunlight. This chapter summarizes the epidemiologic information addressing the anatomical distribution of CMM.

OVERALL SITE DISTRIBUTION

The overall site distribution of melanomas among several study populations is presented in Table 5-1. The relative proportion of CMMs at each site listed in Table 5-1 varies considerably as a result of many potentially influential factors, such as the sex and racial distributions of the study populations. To gain a better understanding of CMM distribution by site, it is necessary to examine the epidemiologic data by these and other subcategories.

Gender Differences

Gender is associated with pronounced differences in CMM site distribution. Table 5-2 lists data from several studies reporting CMM site distribution among males and females. The percentage of total CMMs occurring on the head/neck, the trunk, the upper extremities, and the lower extremities for each sex is presented based on data from different countries. This table indicates that most epidemiologic studies which have examined the effect of sex on site distribution observe higher incidences of CMM on the lower extremities among females and on the trunk among males than on other parts of the body. Although these sites (the lower extremities and the trunk) are relatively less exposed than the head, neck, and upper extremities, most researchers have concluded that the observed anatomical differences by sex are not incompatible with the hypothesis that sunlight exposure is involved in the development of CMM among Caucasians (Pathak et al. 1982; Hinds and Kolonel 1980; MacDonald 1976; Movshovitz and Modan 1973).

The first 13 studies listed in Table 5-2 used data obtained primarily from Caucasians. These studies indicate that melanomas of the trunk occurred about one-and-a-half times more frequently in males than in females for the same site. Of the total CMMs among males, the percentage occurring on the trunk ranged from 25 percent (Denmark) to 53 percent (United States), in contrast to the occurrence of melanomas of the trunk among females, which ranged from 14 percent (Scotland) to 31 percent (United States).

TABLE 5-1

ANATOMIC SITE DISTRIBUTION OF CUTANEOUS MALIGNANT MELANOMA
(Percentage of Total Tumors)

Location	Years	Sample Size	Head/Neck	Trunk	Extremities		Source
					Upper	Lower	
United States[a] (caucasian)	1978-1981	4,864	20	35	23	22	Scotto 1986
Texas	1944-1966	911	22	25	19	13	MacDonald 1976
Texas	1954-1970	510	25	16	21	37	Smith 1976
Alabama	1955-1980	537	27	28	19	23	Balch et al. 1982
New Mexico	1966-1977	403	27	29	19	25	Pathak et al. 1982
New South Wales	1955-1980	1,110	14	37	14	33	Balch et al. 1982
Queensland	1977	690	21	34	20	24	Little et al. 1980
New Zealand (Maori/Polynesian)	1963-1981	24	13	13	0	54	Moss 1984
Israel	1960-1972	966	16	25	21	38	Anaise et al. 1978
Norway	1955-1970	2,541	22[b]	43[c]	8	18	Magnus 1973
Finland	1953-1973	2,501	19	37	10	26	Teppo et al. 1978
Japan	1961-1982	546	15	20	13	46	Takahashi 1983
Hong Kong	1964-1982	43	7	7	21[d]	63[e]	Collins 1984
Uganda	1963-1966	152	8	11[f]	5	72[g]	Kiryabwire et al. 1968

[a] Based on data from Seattle, Detroit, Iowa, Utah, San Francisco/Oakland, Atlanta, and New Mexico.
[b] Face.
[c] Neck/truck.
[d] 17 percent of the total on the hands.
[e] 56 percent of the total on the feet.
[f] "Skin" and genitals.
[g] Feet and legs.

TABLE 5-2

ANATOMIC SITE DISTRIBUTION OF CUTANEOUS MALIGNANT MELANOMA BY GENDER

(Percentage of total tumors by gender[a])

Location (Ethnic Group)	Years	Sample Size	Sex	Head/Neck	Trunk	Extremities		Source
						Upper	Lower	
			Predominantly Caucasian Study Populations					
United States	1980	4,545	F	15	31	19	35	Balch et al. 1984
			M	23	53	13	11	
United States[a]	1978-1981	4,864	F	16	25	26	33	Scotto 1986
			M	24	45	21	11	
North America (Caucasian)	-	-	F	16	29	18	36	Crombie 1981[c]
			M	27	44	17	12	
Europe (Caucasian)	-	-	F	16	23	13	47	Crombie 1981[c]
			M	23	42	13	23	
Texas (White)	1944-1966	1,252	F	17	18	25	28	MacDonald 1976
			M	23	25	20	11	
Hawaii (Caucasian)	1960-1977	262	F	9	28	28	35	Hinds and Kolonel 1980
			M	24	37	24	15	
New Mexico (Anglos)	1966-1977	403	F	22	20	21	37	Pathak et al. 1982
			M	33	41	16	10	
Israel	1960-1972	966	F	16	19	15	50	Anaise et al. 1978
			M	16	32	21	31	
Scotland	1961-1976	477	F	25	14	14	47	Pondes et al. 1981
			M	32	27	11	30	
Finland	1953-1973	2,501	F	18	28	11	36	Teppo et al. 1978
			M	19	48	9	17	
Denmark	1943-1957	1,204	F	24	19	14	33	Clemmesen 1965 (cited in Lee 1982)
			M	32	25	9	22	
Queensland	1977	713	F	19	21	22	35	Little et al. 1980
			M	23	45	17	13	
Texas	1954-1970	510	F	17	10	24	50	Smith 1976
			M	34	23	18	24	

TABLE 5-2 (Continued)

Location (Ethnic Group)	Years	Sample Size	Sex	Head/Neck	Trunk	Extremities		Source
						Upper	Lower	
Mixed_Study_Populations								
Israel (Mixed Race)	1961-1967	368	F	15	21	15	42	Movshovitz and Modan 1973
			M	17	35	5	25	
Japan	1961-1982	546	F	20	19	18	42[d]	Takahashi 1983
			M	13	23	11	51[e]	
Texas (Spanish surname)	1944-1966	206	F	22	16	18	30	MacDonald 1976
			M	18	22	11	30	
Texas (Non-White)	1944-1946	30	F	6	6	18	53	MacDonald 1976
			M	31	--	8	54	
New Mexico (Hispanics)	1969-1977	35	F	23	36	32	9	Pathak et al. 1982
			M	23	46	23	8	
Hawaii (Non-Caucasian)	1960-1970	66	F	26	17	13	44	Hinds and Kolonel 1980
			M	16	19	19	47	
Hawaii (Non-Caucasian)	1960-1977	64	F	26	17	13	44[f]	Hinds 1979
			M	16	20	20	44[g]	
Uganda	1963-1966	152	F	6	11[h]	4	78[i]	Lewis 1967
			M	10	11[h]	5	74[j]	

[a] Percentages may not total 100 percent because of rounding errors and exclusion of "other sites" of MM.

[b] Based on data from Seattle, Detroit, Iowa, Utah, San Francisco/Oakland, Atlanta, and New Mexico.

[c] Truck includes scrotum and "unspecified" melanomas.

[d] 29 percent of the total were on the feet.

[e] 39 percent of the total were on the feet.

[f] 22 percent of the total were on the feet.

[g] 42 percent of the total were on the feet.

[h] "Skin" and genitals.

[i] 63 percent of the total were on the feet.

[j] 64 percent of the total were on the feet.

Similarly, the occurrence of CMM of the lower extremity in females was generally two times greater than that for males. The percentage of total CMMs on the lower extremities among females (for the same 13 studies) ranged from 28 percent (Texas) to 50 percent (Israel), whereas for males the range was 11 percent (Texas) to 31 percent (Israel).

Pathak et al. (1982) concluded that the distribution of melanomas among New Mexican Anglos was compatible with the sunlight hypothesis. They observed that the most common sites, the trunk in males and the lower extremities in females, were affected by styles in dress and recreational activities, which in turn influenced site-specific levels of exposure to the sun. Based on cancer incidence data from Europe and North America, Crombie (1981) observed that the lower limbs were the major site in females, whereas the trunk was the most common among males. Crombie concluded that the sex differences in site distribution corresponded in direction and magnitude to differences in exposure associated with accepted dress styles among males and females, and that the observed melanoma pattern was not incompatible with the role of sunlight as a major etiologic factor.

Some epidemiologic studies have indicated an excess of upper extremity lesions in females and an excess of head and neck lesions in males, but the trends are not as consistent, nor are the differences as significant, as those observed for the lower extremities in females and the trunk in males. Crombie (1981) noted that head lesions were slightly more common among males than females, while there was little difference for CMMs of the upper extremities. Hinds and Kolonel (1980) observed that the incidence of head and neck melanomas among 262 Caucasian Hawaiians was seven times lower among females than among males. They concluded that the differences in site distribution by sex were consistent with the sunlight hypothesis, suggesting that the lower incidence of head and neck tumors among women was due to protection of the scalp, ears, and neck by longer hair. There was a less than twofold difference in incidence of facial lesions, which was ascribed to the potentially higher occupational exposure to the sun by males.

Race and Ethnic Background

Race and ethnic background also show pronounced effects on the distribution of melanomas. The predominant difference is the higher proportion of melanomas occurring on the feet and in some cases the hands among darker-skinned populations compared to lighter-skinned populations.

Hinds (1979) noted that the anatomical distribution among blacks differed from Caucasians, with the largest proportion of melanoma lesions occurring on the feet among blacks, while among Caucasians there was a more even distribution of CMMs over the entire body. Hinds pointed out that in two separate studies, less than 5 percent of the lesions were observed on the feet of Caucasians in Australia (both sexes) and less than 10 percent on the feet of Caucasians in Norway. In a study of 31 blacks and an unspecified number of Caucasians from the United States, Reintgen et al. (1983) observed that 60 percent of the lesions among blacks occurred on the feet, whereas the dominant site among whites was the trunk.

A similar predominance of melanoma of the feet has been observed in blacks from both Africa and America. Kiryabwire et al. (1968), in a study of 152 melanoma cases from Uganda, observed that 64 percent occurred on the feet (Table 5-1). Lewis (1967) noted that there were tribal and ethnic differences in distribution even within the Ugandan study population. He suggested that the high incidence of melanomas on the feet of Ugandans was closely related to the high incidence of discrete pigmented areas on the sole, which he characterized as genetically determined, potentially unstable melanocytes. Lewis indicated that trauma (e.g., heat and wood smoke) could have played a role in inducing malignant changes in these pigmented areas.

Collins (1984) found that among 43 cutaneous melanomas in Chinese patients, 74 percent occurred at volar (palm) and subungual (under the nail) sites. Fifty-six percent of the melanomas occurred on the foot, with 83 percent of these on the plantar surfaces (see Table 5-1). Collins observed that the preponderance of melanomas on the feet and the pigmentation of the skin among Chinese were intermediate between those for whites and blacks. He also noted that the annual incidence of melanoma occurring on plantar surfaces may be similar in all racial groups although in some groups (e.g., blacks) the percentage of lesions occurring on the feet may be higher.

In a study of 24 melanoma cases among Maoris and Polynesians, Moss (1984) observed that over half of the melanomas were on the lower limbs (13 of 24), with six of these occurring on the soles of the feet. Among 546 melanoma patients from Japan, Takahashi and Seiji (1983) observed that 45 percent of the melanomas occurred on the hands and feet, with particularly elevated incidence on the thumb and big toe (see Table 5-2).

Hinds (1982) observed that the high risk of melanoma on the sole of the foot among blacks from Africa had led to speculation that trauma may be involved. However, he noted that although incidence appeared to be higher among blacks of African, rather than American, origin, the sole of the foot remained predominant for both groups. In a review of the role of trauma in the etiology of malignant melanoma, Briggs (1984) concluded that there was no unequivocal evidence indicating that trauma played a role in the development of the vast majority of melanomas. He cited information indicating no difference in incidence on the foot between shoe-wearing and non-shoe-wearing Africans. In addition, he pointed out that although the hand was one of the most traumatized parts of the body, melanoma was not excessive on this site compared to other sites.

Hinds (1979) suggested that trauma could still be a factor among non-Caucasians other than blacks who developed melanoma on the feet due to use of open-toed shoes and sandals. In addition, he concluded that exposure to sunlight was probably not an important risk factor for any site among non-Caucasians. In support of this hypothesis, Magnus (1973) observed that the foot was the only site not showing a north-south gradient in melanoma incidence.

In a study of the anatomic site distribution of CMM among 262 Caucasians and 66 non-Caucasians from Hawaii, Hinds and Kolonel (1980) observed a higher proportion of melanomas of the lower extremities and a lower proportion of

melanoma of the trunk and upper extremities among both male and female non-Caucasians (see Table 5-2). The highly significant differences between Caucasian and non-Caucasian males were mostly due to the higher proportion of melanomas on the lower extremities among non-Caucasian males. The difference for females was not quite as large. The authors suggested that factors other than solar exposure were responsible for the anatomic distribution of melanoma among non-Caucasians and that trauma could play a role among certain ethnic groups in Hawaii.

Other differences in site distribution have been observed between Hispanics and Anglos. Based on a study of 495 melanoma cases in New Mexico, Pathak et al. (1982) concluded that site-specific incidence rates differed significantly between Anglos and Hispanics (Table 5-2). The site-specific, age-adjusted incidence rates for Anglos from New Mexico were significantly higher than for Hispanics from New Mexico at each site. Melanomas of the head and neck were 10 times more frequent among Anglos than among Hispanics, melanomas of the trunk 6.2 times more frequent, upper extremities 5.6 times more frequent, and lower extremities 24.9 times more frequent. Lower extremities and the trunk were the most common sites in Anglo females and males, respectively, whereas the trunk was the most common site for Hispanics. The authors noted that protection by skin pigmentation and cultural factors were the most obvious explanations for the observed differences.

In a study of 2,252 white, 30 non-white, and 206 Spanish-surnamed Texans with CMM, MacDonald (1976) observed a higher proportion of lower extremity melanomas among non-white males (54%), followed by Spanish-surnamed males (30%), then white males (24%) (see Table 5-2). Only among whites were there notable sex differences for the lower extremities. In contrast, melanomas on the upper extremities were more frequent among male and female whites (18 and 24%, respectively) than among the other groups (11 and 18%, respectively, among Spanish-surnamed, and 8 and 18%, respectively, among non-whites). Among non-whites, lesions on the head and neck were more frequent among males and less frequent among females compared to the other two groups.

Anatomical Distribution and Age

Age differences appear to be associated with two general patterns of melanoma incidence, one for melanomas of the face and the other for melanomas of the neck/trunk and extremities. Some researchers have cautioned, however, that such age-specific effects may be confounded by birth cohort effects. Since both age and birth cohort may affect individual risk of melanoma, analyses of changing incidence over time without consideration of potential cohort effects may obscure real trends in the data. The discussion below focuses on age-specific trends, particularly those observed after controlling for birth cohort effects.

In a study of 5,108 melanoma cases in Norway, Magnus (1981) observed an age-specific incidence pattern by 10-year birth cohorts for the face/neck, with rates increasing rather slowly up to about 50 years and more rapidly thereafter. For the trunk and lower extremities, however, age-specific

incidence rates were observed to increase steeply up to about 40 years and gradually level off or decrease thereafter. In an analysis of 2,501 melanoma patients from Finland, Teppo et al. (1978) also observed different age-specific incidence curves (by time of diagnosis) for different sites, as shown in Figure 5-1. Melanomas of the trunk in both sexes and of the lower extremities among women showed a relatively high incidence rate at 30 to 49 years and a leveling off of incidence thereafter. For head and neck lesions in both sexes and lower extremity lesions in males, rates were lower in middle age and increased continuously with age. The age-specific curve for the upper limbs was intermediate between the two other site groups. The shapes of the curves were similar in three successive time periods (1953-1959, 1961-1970, 1971-1973). Excess trunk lesions among males and lower limb lesions among females were apparent in almost all age groups.

Holman et al. (1980) showed that the incidence rate of invasive head and neck melanomas among 542 Australians progressively increased after about age 40. Melanoma incidence rates for the lower extremities increased at 20 to 29 years among females and 30 to 39 years among males, peaked at about 50 to 59 years in both sexes, and declined thereafter. The authors noted that the age-specific pattern for upper and lower extremities and trunk would be consistent with a birth cohort effect beginning with those born around 1915 even though other researchers [e.g., Magnus 1973] had observed cohort effects beginning as early as 1900.

In a study of incidence rates in Denmark, Houghton et al. (1980) also observed differing age-specific melanoma incidence rates in 10-year birth cohorts for melanomas of the face versus melanomas of the trunk/neck, and upper and lower extremities. Figures 5-2 and 5-3 present the age-specific incidence curves by anatomical location for Danish males and females, respectively. For cases of facial melanoma, incidence was relatively low for both males and females until age 60, when it rose rapidly. This age-specific pattern was not seen for melanomas of the trunk/neck, and upper and lower extremities for males and females. For these sites, incidence rose from adolescence to middle age and generally plateaued thereafter. As a result, the mean age for these sites for both sexes was lower than for melanomas of the face.

A comparison of the Danish age-specific melanoma incidence curves for the lower extremities for males and females also reveals striking differences. Not only do the curves for females indicate higher incidence rates than for males for all three 10-year birth cohorts, but they also show the rapid increase in age-specific incidence rates among the 1963-1972 birth cohort group for melanomas of the lower extremities. The authors postulated that the distinct age-specific patterns suggested two different mechanisms of carcinogenesis, with continued, prolonged effects of solar radiation implicated in a majority of facial melanomas. In contrast, melanomas of the trunk and lower extremities, including nodular and superficial types, were considered to be related to short-term noncumulative effects of solar radiation.

Lee (1982) similarly observed that the mean age at diagnosis of melanoma was lower for the trunk and limbs than for the head and neck, but cautioned

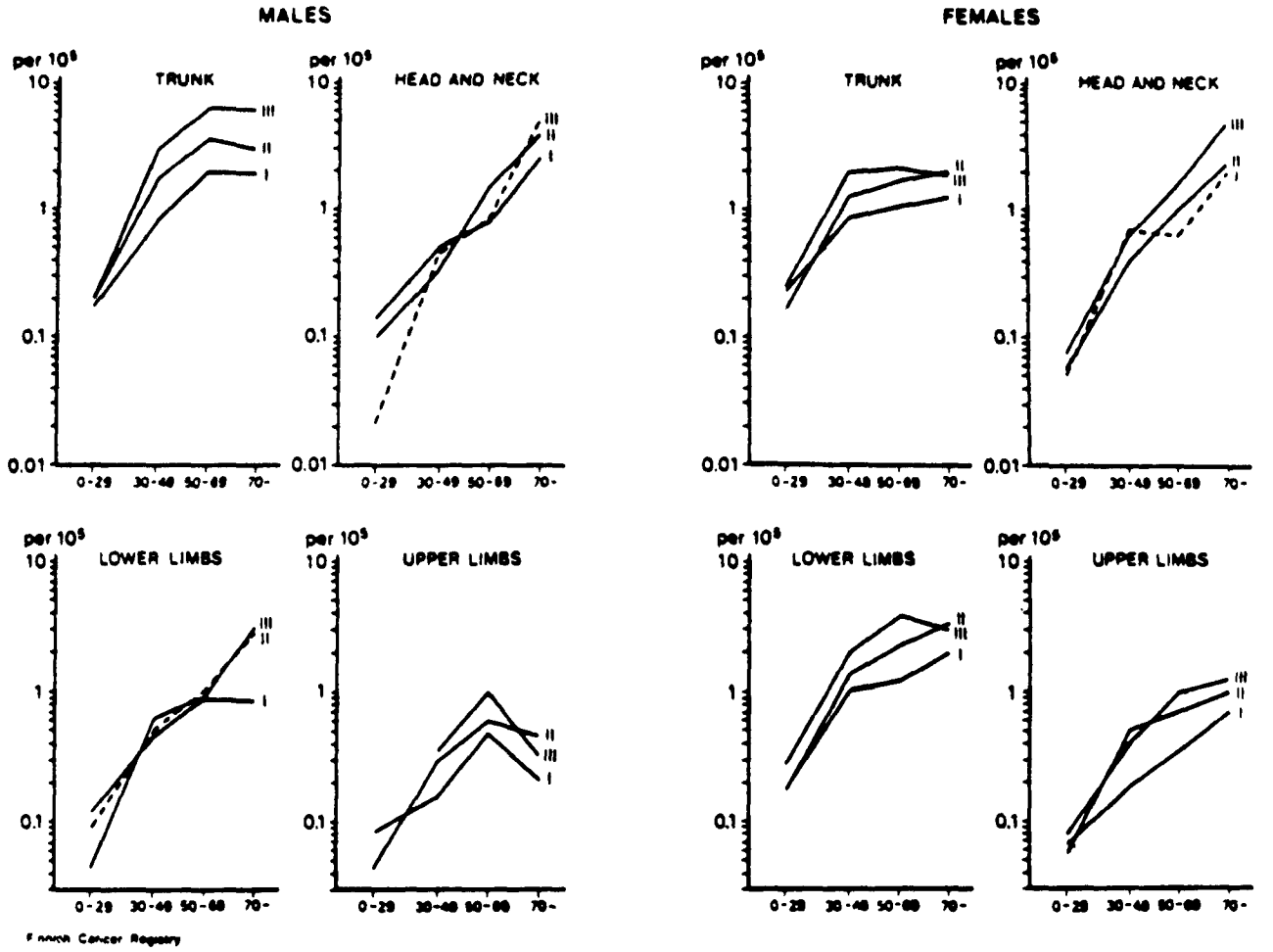

FIGURE 5-1

TRUNCATED AGE-ADJUSTED INCIDENCE RATES (per 10^6) OF CUTANEOUS MELANOMA IN FOUR AGE GROUPS IN FINLAND BY SEX, ANATOMICAL LOCATION, AND TIME OF DIAGNOSIS

NOTE: Time of diagnosis: I=1953-1959, II=1961-1970, III=1971-1973.

Source: Teppo et al. (1978).

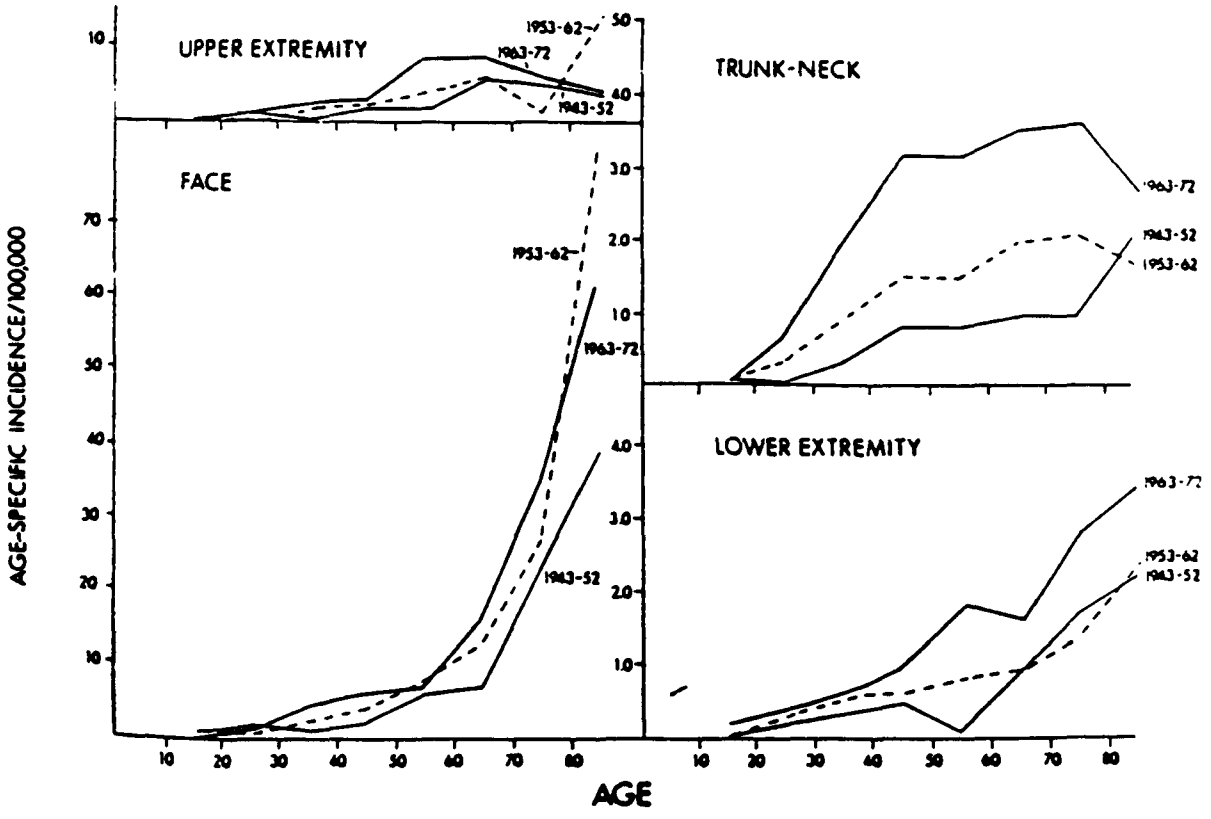

FIGURE 5-2

AGE-SPECIFIC INCIDENCE OF MELANOMA OF THE SKIN IN DANISH MALES BY SITE (GROUPED BY YEAR OF DIAGNOSIS)

Source: Houghton et al. (1980).

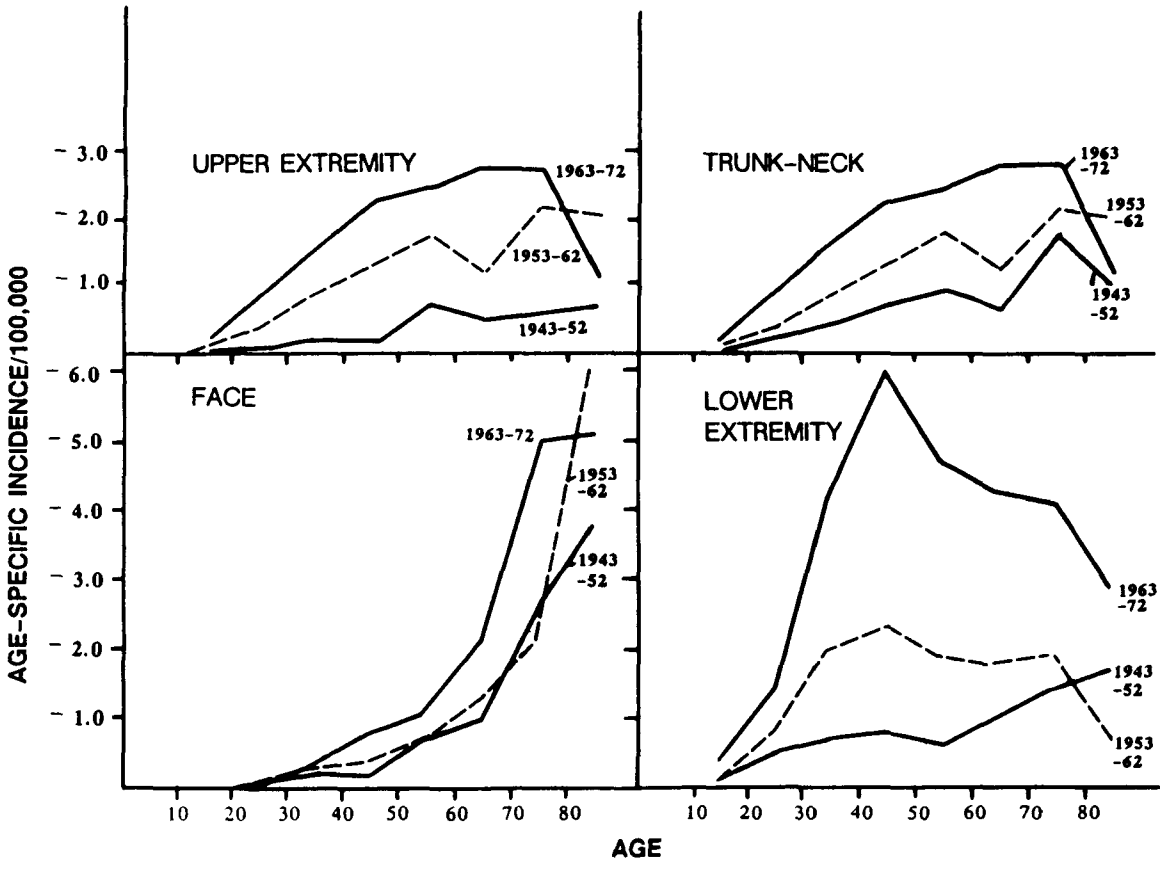

FIGURE 5-3

AGE-SPECIFIC INCIDENCE OF MELANOMA OF THE SKIN IN DANISH FEMALES BY SITE (GROUPED BY YEAR OF DIAGNOSIS)

Source: Houghton et al. (1980).

that birth cohort effects could have accounted for differences in the site-specific age distribution. Based on an analysis of incidence data from five Nordic countries, Magnus (1977) observed two sets of age-specific incidence curves by primary melanoma site. The curve for the face indicated an exponential rise with age, whereas for the neck/trunk and lower limbs, the maximum incidence was reached at middle age. Magnus (1977) noted that the neck/trunk classification was not uniform across countries. Sweden grouped CMMs of the neck with those of the face and scalp, and Finland included CMMs of the scalp in the neck classification.

In a study of 5,741 melanoma cases from Norway, Boyle et al. (1983) observed a smooth rise (approximately linear on a log-log scale) in the incidence of head and neck lesions with age for both sexes (assuming equal cohort effects for each site). In contrast, the incidence rate for the trunk and lower limbs declined in older age groups, particularly in females, for whom lower limb melanoma incidence remained virtually constant after age 40. The authors suggested that the decline in incidence may have been associated with reduced sunlight exposure with the passage of youth.

Histologic Type

Differences in the anatomical distribution of melanoma have also been observed on the basis of histologic type. In a study of 542 western Australians with pre-invasive or invasive melanoma, Holman et al. (1980) showed a predominance of Hutchinson's melanotic freckle (HMF)* among pre-invasive melanomas of the head and neck, sites which are usually exposed, and a predominance of superficial spreading (SSM) and invasive malignant melanomas (ICMM) among melanomas of the trunk in males and of the lower extremities in females (Table 5-3). These latter sites are not habitually exposed. In an analysis of 1973-1981 Surveillance Epidemiology End Results (SEER) data, Scotto (1985) also observed that HMFM occurred predominantly on the face, head, and neck, and that SSM occurred predominantly on the trunk among males and the lower extremities among females (Table 5-4). In a study of 510 melanoma patients in Texas, Smith (1976) noted that SSM was most common on the lower extremities, and HMFM was most common on the head and neck.

Adler and Gaeta (1979) noted that SSM was more common on non-exposed skin, and HMFM was more common on the face and other exposed sites. Among 477 melanoma patients from southeast Scotland, SSM and NM occurred most frequently on the lower limb; the distribution by histogenic type was similar in each sex (Pondes et al. 1981). Among 29 volar and subungual melanomas in Chinese patients, Collins (1984) observed that five of the six SSMs and the two NMs occurred on the sole, while the sixth SSM occurred on the palm.

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* HMF is the pre-invasive lesion of HMF melanoma (HMFM). It is also called lentigo maligna.

TABLE 5-3

PERCENTAGE DISTRIBUTION OF PRE-INVASIVE MELANOMA AND INVASIVE MALIGNANT MELANOMA IN WESTERN AUSTRALIA BY BODY SITE [a]

Body Site	Pre-Invasive Melanoma				Invasive Malignant Melanoma	
	[b] HMF		[c] SSM			
	Males (14) [d]	Females (14)	Males (36)	Females (54)	Males (208)	Females (210)
Head and neck	79	79	17	17	24	18
Trunk	7	7	39	26	41	18
Upper extremities	14	0	27	20	14	26
Lower extremities	0	1	17	37	17	37
Cryptogenic metastases	-	-	-	-	4	1

[a] Data on site were missing in four patients.
[b] Hutchinson's melanotic freckle.
[c] Superficial spreading melanoma, non-invasive.
[d] Numbers in parentheses refer to numbers of patients.

Source: Holman et al. (1980).

TABLE 5-4

PERCENTAGE DISTRIBUTION OF MALIGNANT MELANOMA IN UNITED STATES CAUCASIANS BY HISTOGENIC TYPE, SEX AND BODY SITE a/

	HMF[b]		SSM[c]		NM[d]		NOS[e]		Other Cell Types[f]	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Face, Head and Neck	62	58	10	17	22	15	20	14	31	34
Trunk	18	8	27	26	45	24	38	20	25	20
Upper Extremities	11	18	26	20	22	26	18	24	17	20
Lower Extremities	8	16	36	37	10	35	11	34	14	26
Other Sites	1	-	1	-	1	-	13	8	13	10

a Based on SEER data from Seattle, Detroit, Iowa, Utah, San Francisco/Okland, Atlanta, and New Mexico.

b Hutchinson's melanotic freckle.

c Superficial spreading melanoma, non-invasive.

d Nodular melanoma.

e Not otherwise specified.

f For example, spindle cell and an amelanotic melanoma.

Source: Scotto (1985).

Geographical Area

Geographical area of residence and latitude have been noted in trends of overall melanoma incidence, but only a few studies have investigated their effects on melanoma site distribution.

Magnus (1973) observed some geographic variations by site in 2,541 melanoma patients from Norway. Figures 5-4 and 5-5 show that incidence by site noticeably decreased from southern to northern parts of the country and was clearly higher in the capital and provincial towns than in rural areas for the neck/trunk and lower extremities. For facial melanomas, only the northernmost part of the country exhibited somewhat lower incidence rates compared to those in the southernmost part. The urban-rural difference for facial melanomas was less conclusive, in that the face was a relatively rare site in the capital. The foot was the only site which lacked a definite north-south gradient in melanoma incidence. It was proposed that the north-south gradient was due to the increasing amount and intensity of sunlight, as well as the increasing temperature with decreasing latitude, both of which would promote sunbathing to a greater extent in the south than the north. Since the foot would rarely be exposed to the sun, the absence of a gradient for that site also fits the sun exposure hypothesis. Magnus noted that the high incidence of melanomas of the feet indicated the possible importance of other etiological factors.

Comparison of sites among melanoma patients from Queensland living in tropical and subtropical areas (Little et al. 1980) generally showed similar site distributions in both males and females. For example, among males the proportion of back lesions did not significantly vary from the tropics to the subtropics. There were a few notable exceptions, however, as 19 percent of the lesions among males and females in tropical areas (12 patients) were of the arm in contrast to 9 percent in subtropics (26 patients). The leg was the site of 16 percent of the tumors in the tropics (10 patients) and 27 percent in the subtropics (78 patients).

Balch et al. (1982), in a comparative study of 676 melanoma patients from Alabama and 1,110 from Australia, observed that although melanomas of the trunk were the most common in both patient series, they occurred in higher proportions among Australians (37 percent vs. 28 percent) (see Table 5-1). The occurrence of melanomas on the lower extremities was also more common among Australians (33 percent vs. 23 percent), whereas head and neck lesions occurred more frequently among the Alabama patients (27 percent vs. 14 percent). In contrast, Magnus (1977) did not observe dissimilar melanoma site distributions across five Nordic countries.

Scotto and Fears (1986) analyzed National Cancer Institute age-adjusted 1978-1981 melanoma incidence data for Caucasians from seven locations in the United States (Seattle, Detroit, Iowa, Utah, San Francisco/Oakland, Atlanta, and New Mexico). As shown in Figures 5-6 and 5-7, latitudinal trends (based on UV-B measurements) were observed for the upper extremities and for the head and neck among white males and females.

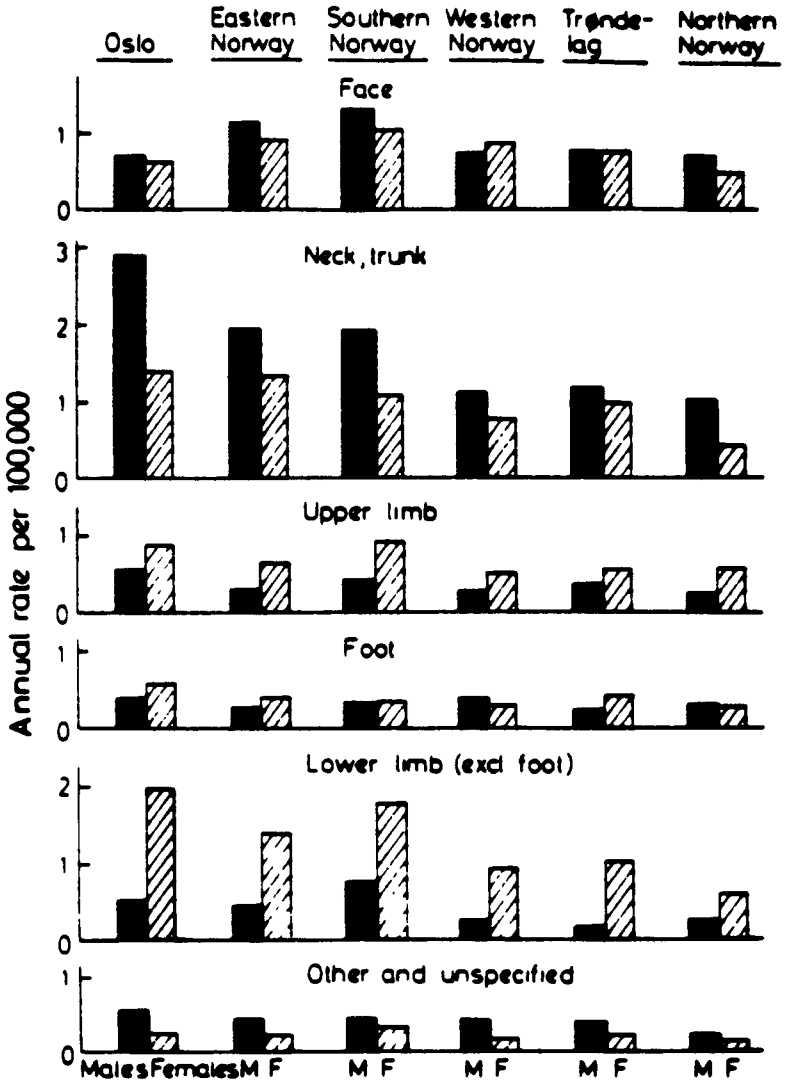


FIGURE 5-4

TOTAL AGE-ADJUSTED INCIDENCE RATE OF MALIGNANT MELANOMA OF THE SKIN IN NORWAY, 1955-1970, BY REGION AND ANATOMICAL SITE

Source: Magnus (1973), Am. Cancer Society Inc., J.P. Lippincott Co. Reproduced by permission.

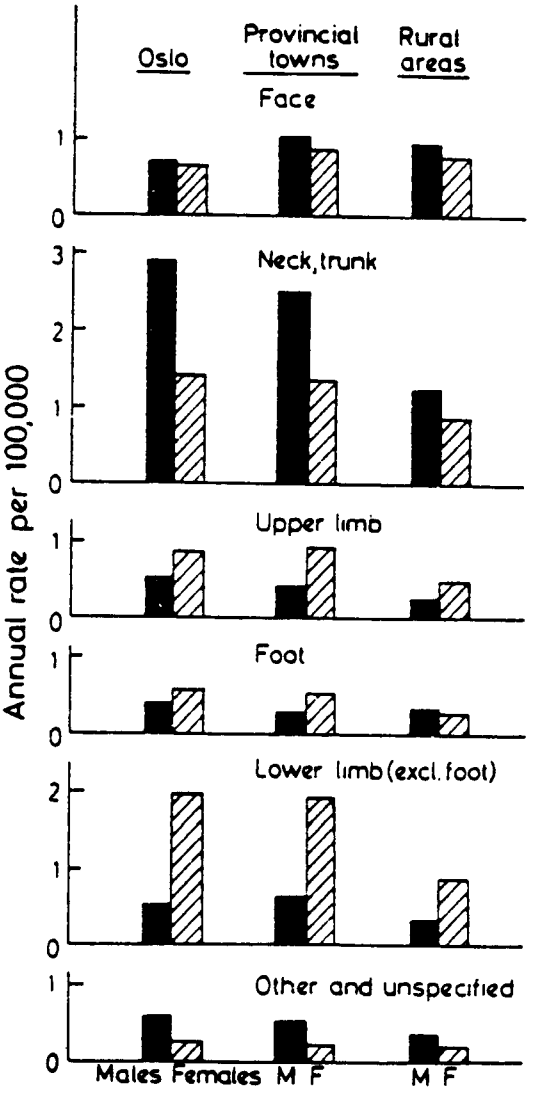
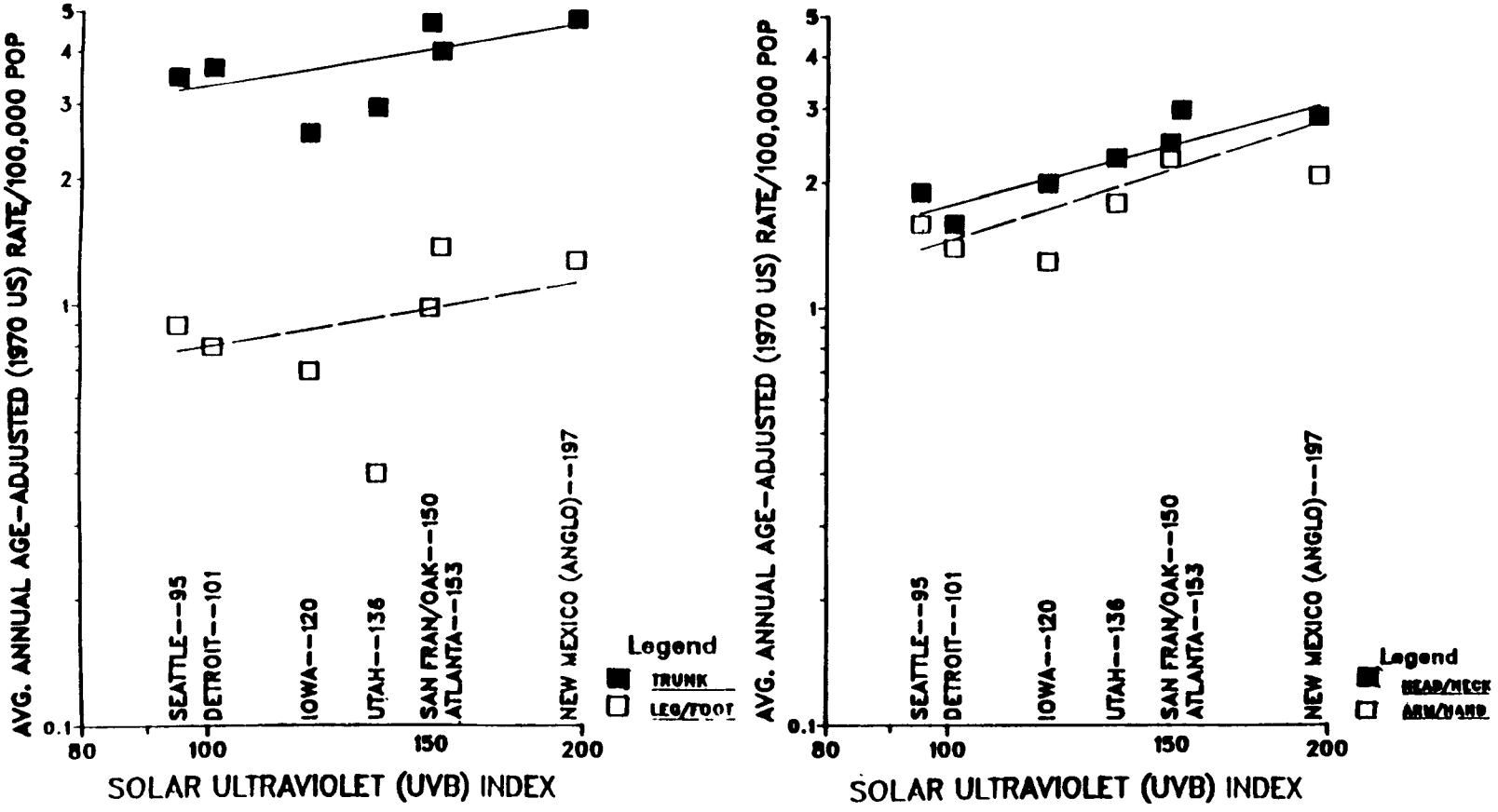


FIGURE 5-5

TOTAL AGE-ADJUSTED INCIDENCE RATE OF MALIGNANT MELANOMA OF THE SKIN IN NORWAY, 1955-1970, IN THE CAPITAL, PROVINCIAL TOWNS, a AND RURAL AREAS BY ANATOMICAL SITE

a
Areas administratively classified as urban, excluding the capital.

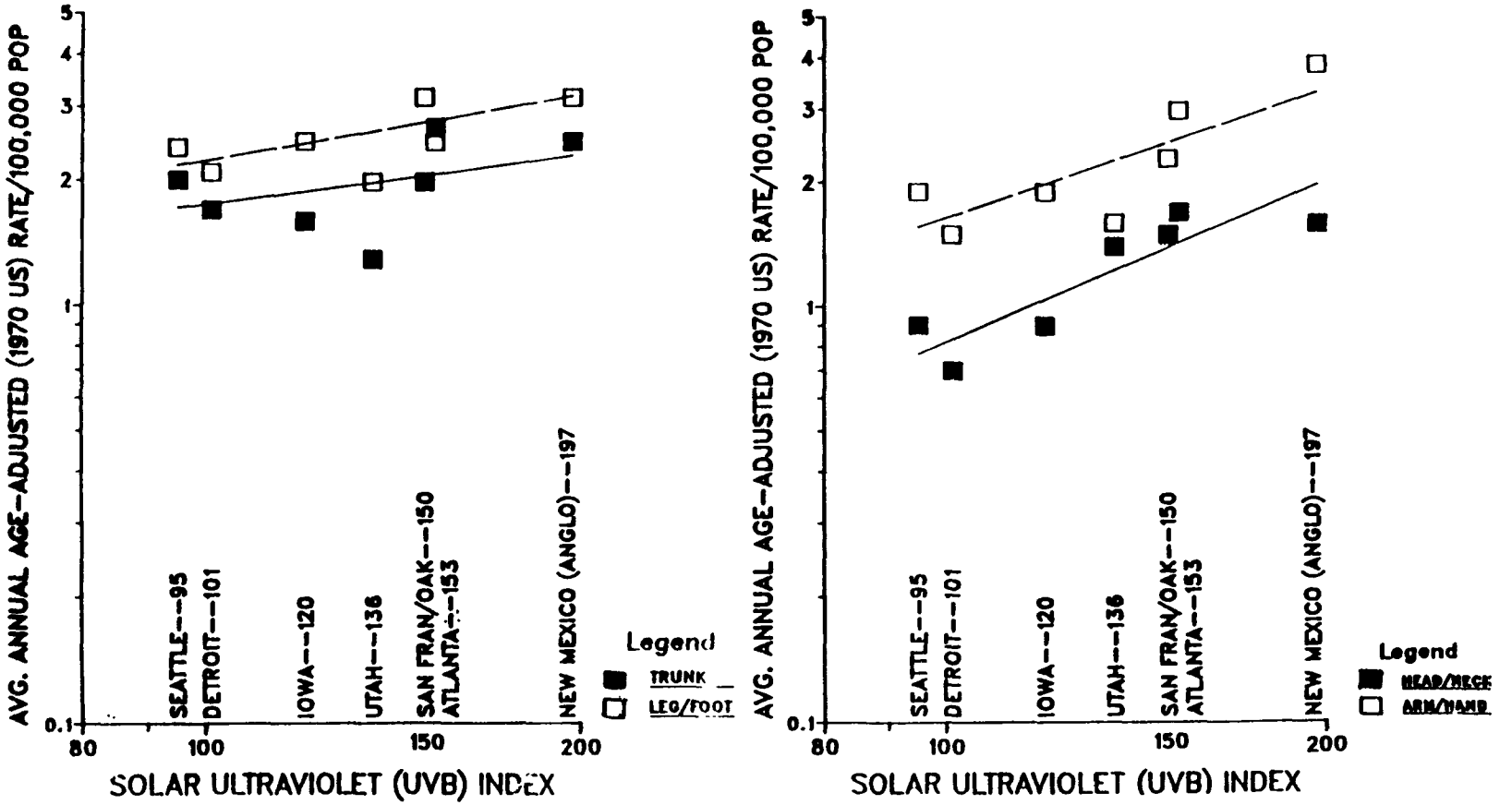
Source: Magnus (1973), Am. Cancer Society Inc., J.P. Lippincott Co. Reproduced by permission.



Source: Scotto and Fears (1986).

FIGURE 5-6

SKIN MELANOMA INCIDENCE BY UV RADIATION INDEX AMONG WHITE MALES IN THE UNITED STATES ACCORDING TO ANATOMICAL SITE (1978-1981)



Source: Scotto and Fears (1986).

FIGURE 5-7

SKIN MELANOMA INCIDENCE BY UV RADIATION INDEX AMONG WHITE FEMALES IN THE UNITED STATES ACCORDING TO ANATOMICAL SITE (1978-1981)

A common hypothesis put forth by many researchers to explain the observed trends in anatomical location suggests that differential exposure to sunlight due to patterns of attire and recreational activities may play a role in determining the predominant sites of melanoma in both males and females. This hypothesis has been cited to explain the higher proportion of melanomas on the lower extremities among females and the trunk among males. In addition, significant increases in melanoma incidence on the trunk of males, and often on the trunk and lower extremities of females, have been observed for cohorts born between 1900 and 1935 (see Chapter 4). These trends have been attributed to the sunlight hypothesis.

The high proportion of melanomas on the feet of blacks and other dark-skinned ethnic groups represents the only major deviation from this postulated explanation. The potential damaging effect of trauma has been cited as a possible explanation for this occurrence, although many have noted that a predominance of melanomas on the feet has also been observed among shoe-wearing blacks, and an excess has not been noted on the hands, one of the most traumatized parts of the body. Nevertheless, most agree that exposure to sunlight is not involved in the development of melanomas on the feet.

TEMPORAL TRENDS IN SITE DISTRIBUTION

In a review of epidemiologic evidence, Elwood and Hislop (1982) noted that incidence rates in Connecticut from 1935 to 1970 increased the most for the lower limb among females, the trunk among males, and the upper limbs in both sexes, a pattern which was consistent with changes in general clothing habits during that time.

In a study of melanoma incidence data from New South Wales, Australia, from 1970 to 1976, McCarthy et al. (1980) observed that melanomas of the trunk among males and of the lower limbs among females more than doubled from 1971 to 1976 (Figures 5-8 and 5-9). Melanoma incidence rates of the upper limbs increased from 1971 to 1972, but from 1972 to 1976 no marked increases above the 1972 rates were observed. Incidence of melanoma of the face and ear increased markedly in males but only a slight increase was observed for these sites in females. The authors argued that the trends in incidence supported the hypothesis that sunlight exposure is the dominant cause of melanoma. They cited trends in attire among the male and female populations as causes of increased melanomas of the trunk among men and melanomas of the leg among women. The presence of more hair and use of cosmetics among females were cited as causes of lower incidence increases of lesions of the head and neck. The authors also proposed that the steeper incidence rise from 1971 to 1972 than for later years could have been related to major sunspot activity in 1970. This hypothesis may be questionable, since the latency period of melanoma is generally considered to be longer than 2 years. However, it is possible that sunlight, acting via a promotional mechanism, could show such a short lag period.

A comparison of site-specific incidence among 3,289 melanoma patients from Sweden between 1959 and 1968 indicated an overall annual increase of about 7 percent, with increases greater for females than for males (Malec and Eklund

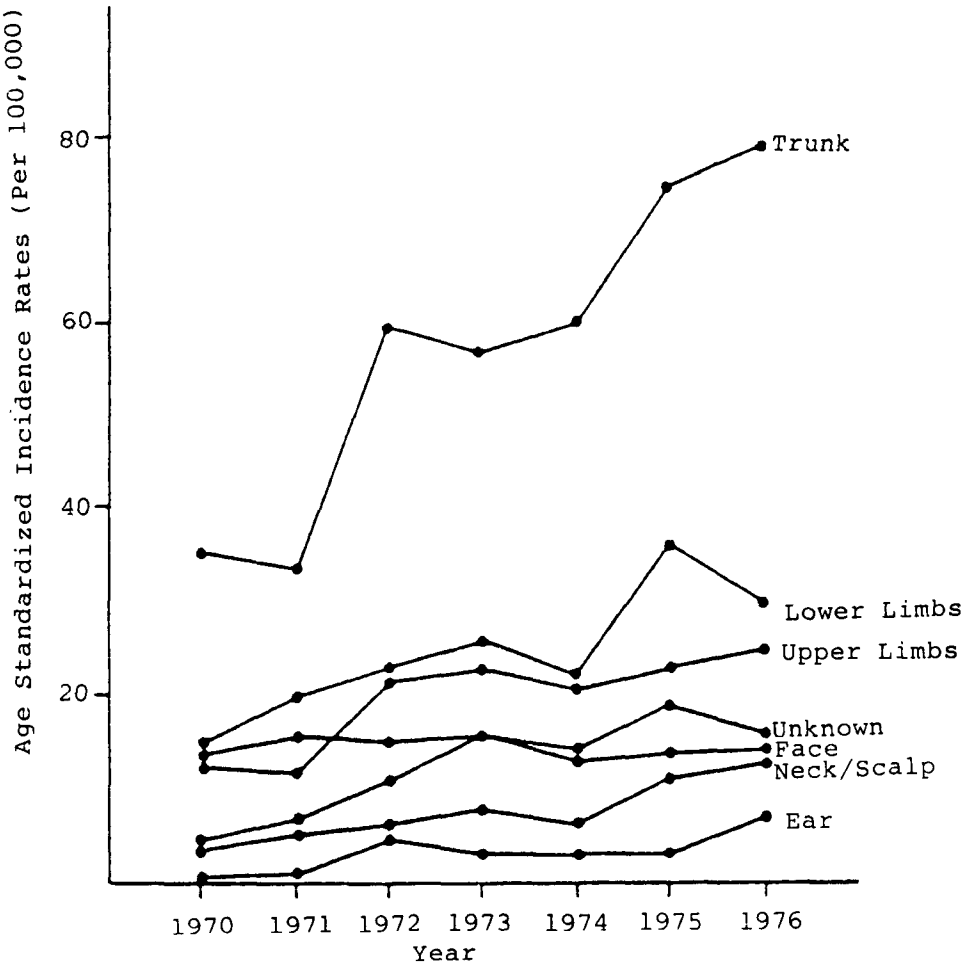


FIGURE 5-8

ANNUAL MELANOMA INCIDENCE RATES FOR MALES BY ANATOMICAL SITE (New South Wales, Australia: 1970-1976)

Source: McCarthy et al. (1980).

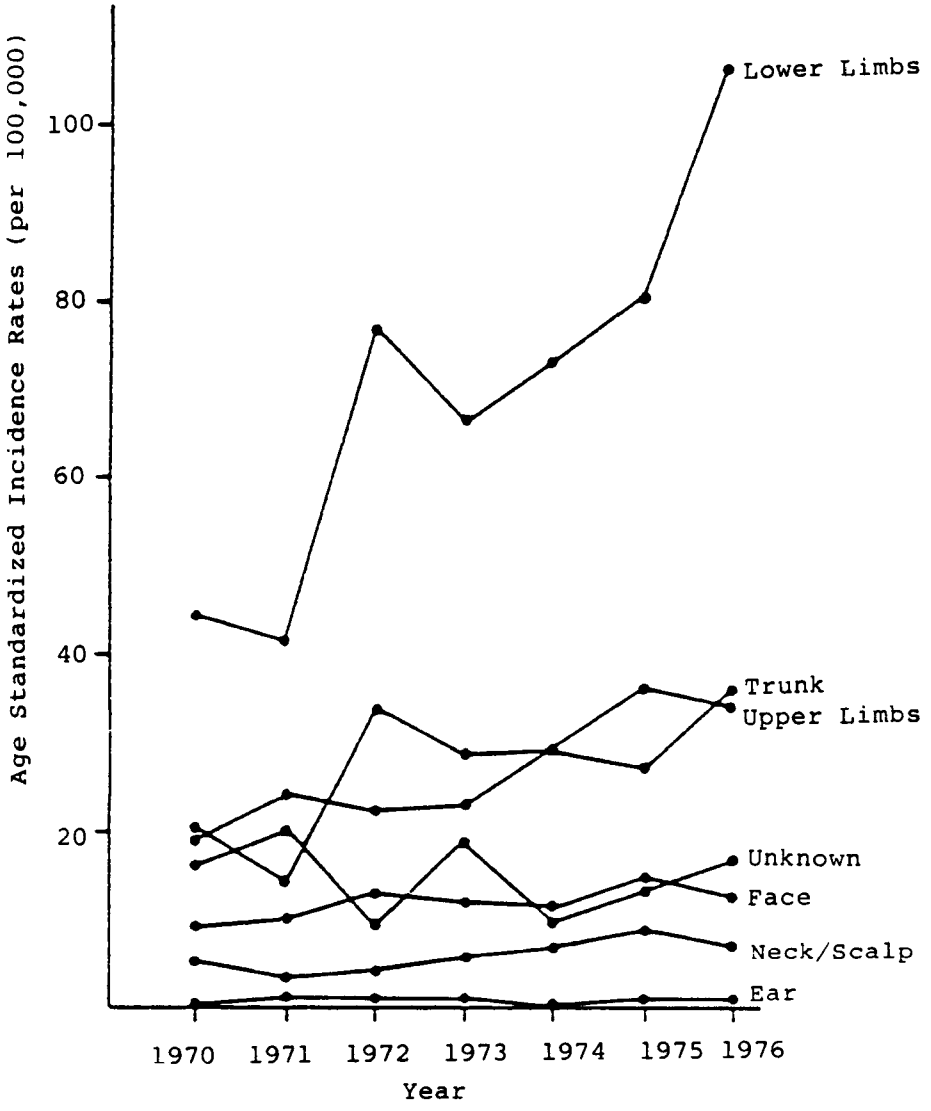


FIGURE 5-9

ANNUAL MELANOMA INCIDENCE RATES FOR FEMALES BY ANATOMICAL SITE (New South Wales, Australia: 1970-1976)

Source: McCarthy et al. (1980).

1978). The greatest annual increase in percentages for both sexes was for melanomas of the trunk (i.e., 11 percent for males), whereas the smallest was for the arm in males (4 percent) and the head/neck in females (4 percent). The correlation between annual incidence rate and year (from 1959-1968) was highly significant ($p \leq 0.001$) for the trunk and head/neck in males and the trunk in females, and moderately significant ($p \leq 0.05$) for the lower limbs in females.

Balch et al. (1983) observed a significant increase in melanomas of the trunk and a significant decrease in melanomas of the head and neck among males between 1955 and 1980 for 1,647 Stage I patients from Alabama and New South Wales. No significant changes in site distribution were observed for the extremities in males or any site in females.

Hinds and Kolonel (1980) conducted a study on 333 melanoma cases from Hawaii from 1960 to 1977. Among the 262 Hawaiian whites, site-specific age-adjusted incidence rates increased in both sexes, except for fairly stable rates for lower extremities in females. By 1972-1977, as compared to 1960-1971, the incidence rate for lower extremities in males had increased to equal that in females. For CMM of the head/neck and the trunk, incidence rates for males were consistently higher than rates for females. The authors concluded that the apparently stable incidence rate of lower extremity lesions among females from 1960 to 1977 could not be ascribed to the lack of a trend toward more revealing clothing. They postulated that the stable rate in females suggested that a maximum rate of melanoma induced by sunlight had been reached and that the similar rates between the sexes by 1977 was due to attainment of a similar maximum in males.

Magnus (1981) investigated trends in 5,108 melanoma cases from Norway between 1955 and 1977. Overall incidence increased by about 7 percent annually for both sexes, with a doubling of melanomas of the face/neck and a fivefold increase of melanomas of the trunk and lower limbs. An anlysis of the data in two time periods (1955-1970 and 1970-1977) indicated a reduction in annual percentage incidence increases for melanomas of the trunk among males (from 13.5 percent to 8.4 percent) and an increase in annual percentage incidence increases for females (4.5 percent to 12.5 percent). This resulted in a more similar pattern of annual incidence trends for the two sexes during 1970-1977 than during 1955-1970. Magnus suggested that this equalizing trend between the sexes may have reflected the increased similiarity of sunlight exposure to various parts of the body.

Teppo et al. (1978) analyzed 2,501 melanoma cases in Finland between 1953 and 1973, and observed that the incidence of melanomas of the trunk in both sexes and melanomas of the lower limbs in females increased markedly over this period. Over 80 percent of the total incidence increase in males was attributed to lesions of the trunk, while 44 percent and 28 percent of the total increase in females was attributed to the lower limbs and the trunk, respectively. Only minor incidence changes were observed for the head and neck from 1953 to 1973. The authors concluded that the site-specific incidence increases could be interpreted as a cohort effect and accounted for by changes in clothing habits, which would have increased sunlight exposure to these sites.

SEASONAL VARIATIONS

Seasonal variations in site-specific CMM have also been investigated. Some seasonal trends have been observed for melanomas of the extremities, particularly among females, but the scarcity of available epidemiologic evidence limits the ability to draw broad conclusions from these data.

Malec and Eklund (1978) examined the association between site-specific melanoma incidence and season (summer vs. winter) for 3,289 melanoma cases from Sweden. They observed a highly significant increase ($p \leq 0.001$) of melanomas on the lower extremities of females during summer months (June-August) compared to winter months (December-February). No corresponding seasonal increase was observed for males. Given the apparent predominance of SSM of the leg among females, and the possibility that the vertical growth phase may become clinically apparent in a few weeks or months, the authors suggested that the seasonal rise in melanoma of the lower extremities among females could have been due to an increase in SSM and a result of short-term ultraviolet radiation exposure.

Scotto and Nam (1980) tested for monthly patterns of melanoma incidence among 2,168 melanoma cases from nine locations in the United States from 1969 to 1971. They applied a first-order sine-wave model to the data that estimated the frequency of cases diagnosed in 1-month intervals. As shown in Table 5-5, they observed a strong seasonal pattern of incidence, with summertime peak for upper and lower extremities among females ($p=0.0001$ and 0.0007 for lower and upper extremities, respectively) and a nonsignificant summertime peak for upper extremities among males ($p=0.11$). When incidence trends for melanomas of the upper extremities were analyzed by 2-month periods, statistical significance was greater for females ($p=0.003$) than for males ($p=0.07$). The lower significance for males was possibly due to the small number of cases. Analysis of seasonal pattern by age (≤ 55, ≥ 55 years) indicated significant trends among females less than 55 years of age for lower extremities, and upper and lower extremities pooled, but not for the trunk or face and head lesions. The authors concluded that it was difficult to determine if seasonal melanoma patterns resulted from the potential promoting effects of UV-B exposure or from enhanced recognition during summer months.

Hinds et al. (1981) analyzed the seasonal pattern of site-specific melanoma in 351 Hawaiians from 1960 to 1978, also using a sine-wave model. Since significant differences were not observed between male and female site-specific diagnosis of melanoma (divided into 2-month periods), the authors applied the model to male and female cases combined. The sine-wave model was consistent with (i.e., not rejected by) a peak in summer months for all sites and for the four site subgroups (head/neck, upper extremities, lower extremities, and trunk). The amplitude of the sine-wave model was, however, significantly different from zero ($p \leq 0.02$) only for all cutaneous melanomas and melanoma of the lower extremities. The authors concluded that their findings supported the hypothesis that solar radiation may have been a factor in promoting the short-term growth of cutaneous malignant melanoma.

TABLE 5-5

SEASONAL PATTERNS OF SKIN MELANOMAS AND EDWARDS' TEST RESULTS,
THIRD NATIONAL CANCER SURVEY, 1969-1971

Sex and Anatomic Site	Number of Cases by Month of Diagnosis												Edwards' test X^2 (2.d.f) (p-value)
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	
Males													* *
Face, Head and Neck	39	19	20	27	31	18	12	18	23	23	21	16	--- ---
Upper Extremities	17	11	24	14	20	22	23	19	22	16	14	15	4.50 (p = 0.11)
Trunk	32	27	37	32	27	35	34	34	32	27	34	32	0.12 (p = 0.94)
Lower Extremities	9	14	11	16	8	12	15	9	9	8	9	11	2.06 (p = 0.36)
Females													
Face, Head and Neck	15	13	18	20	23	20	13	16	18	19	13	12	3.02 (p = 0.22)
Upper Extremities	18	20	13	22	31	33	39	34	21	19	32	22	14.42 (p = 0.0007)
Trunk	20	17	22	18	20	23	26	18	26	26	17	22	1.53 (p = 0.47)
Lower Extremities	26	29	49	37	37	46	40	40	33	25	27	21	18.19 (p = 0.0001)

* The data for male face, head and neck depart significantly from the sine curve model by chi-square goodness-of-fit test ($p<0.05$) thus Edwards' method for testing amplitude is considered inappropriate.

Source: Scotto and Nam (1980).

The anatomical distribution of melanomas among lighter-skinned populations appears to be influenced by variations in exposure to sunlight. Furthermore, interpretation of epidemiologic evidence from ecological studies indicates to a certain extent that two mechanisms of carcinogenesis may be involved, in which prolonged cumulative exposure to the sun may be associated with facial melanomas, and short-term acute exposure may be associated with melanomas of the trunk and lower extremities.

RELATION OF SITE DISTRIBUTION TO PROGNOSIS

The results of several epidemiologic studies indicate that the primary melanoma site may be related to prognosis. Significantly poorer survival rates were observed among those melanoma patients from southeast Scotland (both sexes combined) with lesions of the trunk, with 5-year survival rates (based on deaths due to melanoma) of 75 percent for upper extremities, 74 percent for the head and neck, 72 percent for lower extremities, and only 49 percent for the trunk (Pondes et al. 1981). Among females, 5-year survival rates were 86 percent for melanoma of the head and neck, 76 percent for lower extremities, 79 percent for upper extremities, and only 45 percent for the trunk. Among males, site-specific prognosis was not as favorable, with 5-year survival rates of 67 percent for the upper extremities, 59 percent for the lower extremities, 54 percent for the head and neck, and 54 percent for the trunk. The sex difference in survival was due mainly to the poorer survival of males older than 50 years.

Lemish et al. (1983) also observed that 5-year survival rates among 401 Australians with invasive malignant melanoma from 1975 to 1976 were affected by the primary site of melanoma. However, lower survival rates were not associated with melanomas of the trunk among these patients. Table 5-6 indicates that 5-year relative survival rates for both sexes combined were 80 percent for the head and neck, 88 percent for upper extremities, 90 percent for the trunk, and 91 percent for lower extremities. Among females, the lowest survival rates were for the head and neck (77 percent), followed by upper extremities (86 percent), the trunk (88 percent), and lower extremities (97 percent). Among males, 5-year survival rates were the lowest for the lower extremities (77 percent) and highest for the upper extremities and trunk (93 percent and 90 percent, respectively).

In an investigation of the influence of 11 clinical and prognostic factors on survival rates among 776 melanoma patients from Australia and 293 melanoma patients from Alabama, Balch et al. (1982) observed in a multivariate analysis (stage of disease and other tumor characteristics were controlled for) that anatomic location of the lesion was a significant factor associated with survival ($p \leq 0.00001$) among the Australian patients ($p \leq 0.09$ for Alabama patients). Survival rates for the patients from Australia and from Alabama were, however, not significantly different. The distribution of melanomas differed between the two patient series, with melanomas of the lower extremities and the trunk present in higher proportions among the Australians and melanomas of the head and neck higher among the Alabama patients. Cascinelli et al. (1985) also observed that primary lesion site was significantly related to prognosis ($p \leq 0.05$), based on 686 melanoma patients in the World Health Organization melanoma register from 1967 to 1974.

TABLE 5-6

CRUDE AND RELATIVE 5-YEAR SURVIVAL RATES BY PRIMARY SITE OF INVASIVE MALIGNANT MELANOMA IN WESTERN AUSTRALIA, 1975-1976

Site (number of cases)	Five-Year Survival Rate (%)					
	Crude			Relative*		
	Men	Women	Total	Men	Women	Total
Head and neck (87)	66[a]	72	69	79	77	80
Trunk (120)	83	83	83	90	88	90
Upper extremities (83)	86	81	83	93	86	88
Lower extremities (111)	72	93	87	77	97	91

* Relative to the survival rate expected on the basis on sex- and age-specific mortality rates in the normal Western Australian population.

Source: Lemish et al. (1983).

FINDINGS

The most pronounced differences in site distribution of melanomas are associated with sex, race, and birth cohort. Other potentially influential factors include age, histogenic tumor type, geographical location, and season of diagnosis. The following major findings can be drawn from the epidemiologic data presented in this chapter:

5.1 Cutaneous malignant melanomas of the lower extremities occur about twice as frequently among females than among males. Melanomas of the trunk occur about 1.5 times more frequently among males than among females. Although these sites (the lower extremities and the trunk) are relatively less exposed than the head, face, and neck, and the upper extremities, most researchers have concluded that the observed differences by sex are still compatible with the hypothesis that sunlight exposure is involved in the development of CMM among Caucasians.

5.2 The major difference in melanoma site distribution between different racial and ethnic groups is the higher proportion of melanomas occurring on the feet and in some cases the hands among darker-skinned populations (blacks and orientals) compared to lighter-skinned populations (whites). The available epidemiologic evidence suggests that factors other than sunlight exposure are associated with the anatomic distribution of melanomas among dark-skinned populations. The annual incidence of melanoma occurring on plantar surfaces may, however, be similar in many racial and ethnic groups (Collins 1984).

5.3 The anatomical distribution of CMM has been observed to vary according to histologic type, with Hutchinson's melanotic freckle melanoma (HMFM) more commonly recurring on regularly exposed sites such as the head and neck, and superficial spreading melanoma (SSM) occurring more frequently on regularly unexposed sites such as the trunk and the lower extremities.

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CHAPTER 6

GEOGRAPHIC DISTRIBUTION

The hypothesis that ultraviolet radiation is causally associated with the development of cutaneous malignant melanoma (CMM) has been explored by examining potential exposure to sunlight. Most of the studies are ecological studies which sought to find correlations between incidence or mortality rates of CMM and the potential for sun exposure estimated by proximity to the equator (latitude) or by other surrogates for average exposures to sunlight or UV radiation, such as number of sunlight hours at residence.

This chapter presents results from analyses of the geographic distribution of CMM and includes both incidence and mortality studies. These ecological or geographic correlation studies are subject to many assumptions, and thus the results must be interpreted in light of the many limitations inherent in the study design. For example, the failure to measure individual exposure to sunlight in the study population makes it impossible to establish a causal association between CMM and solar radiation; yet significant associations between surrogate estimates of UV exposure and CMM have provided indications of causal associations which in turn led to studies in which individual exposure has been assessed (these studies are discussed in Chapter 9).

The earliest epidemiologic evidence that solar radiation might play a role in the etiology of CMM resulted from ecological studies which showed a negative correlation between latitude of residence and incidence and mortality rates for CMM in white populations. Using Australian mortality data, Lancaster (1957) showed that the distribution of CMM among "relatively fair-skinned types" was associated with proximity to the equator. Among the states of Australia, he found a north-to-south decreasing gradient in death rates (1951-1953) due to melanoma, with the crude death rates from melanoma in Queensland almost three times higher than those in Tasmania and Victoria, and a decreasing gradient of rates in the intervening states with increasing latitude.

In the same study, Lancaster (1957) examined melanoma mortality rates in other predominantly Caucasian populations and found that rates tended to be higher in populations living closer to the equator. Mortality from melanoma was higher on the northern island of New Zealand than on the southern; rates in the British Isles and Europe were generally lower than those in Australia and New Zealand; and rates in Canada were below those in the United States. Within Europe, however, no latitude gradient was found when CMM mortality rates from the same years were compared. In fact, Norway and Sweden reported higher rates than any other European countries. Lancaster (1956) attributed this absence of a gradient to probable differences in medical certification of death, differences in statistical coding practices between countries, and the fact that melanoma had only recently been separated from carcinomas of the skin. However, studies cited in Chapters 10 and 11 indicate that this lack of gradient may be due to other factors such as differences in ethnicity or

pigmentation characteristics. Within the United States (grouped into eight areas), mortality from CMM (1949-1952) was somewhat higher in southern than in northern areas and the coastal areas had higher CMM mortality rates than the mountain or central areas. Lancaster (1956) linked the general latitude association to CMM mortality with the variations in sunlight and UVR, and concluded that the distribution of melanoma among fair-skinned populations was consistent with a hypothesis of excess sunlight as an important predisposing cause of CMM.

Holman et al. (1980a) examined Australian mortality rates from cutaneous malignant melanoma by state in successive 5-year periods from 1931-1934 through 1975-1977 and determined that melanoma mortality rates were highest in Queensland (the northern part of Australia) and diminished on a gradient from north to south, with the lowest rates in Victoria and Tasmania. This relationship of increasing melanoma mortality with decreasing latitude was generally maintained for the six states of Australia over roughly 45 years, even though CMM mortality rates increased steadily over this time period.

An analysis of melanoma incidence rates (1975-1976) in Western Australia (Holman et al. 1980b) showed that the highest rates of CMM occurred in areas which received the fewest hours of bright sunlight per day, although each area received a considerable amount of sunlight each day. Stratifying on the five statistical divisions in the state of Western Australia, the highest rates were found in Perth and the southwestern region, which tend to be coastal and more urbanized. Although tropical, the northern areas are less populated and residents may be more likely to avoid sun exposure in the middle of the day and wear protective clothing than in the more urbanized southwestern coastal areas, where residents are more likely to sunbathe and engage in outdoor recreational activities.

Herron (1969) analyzed data on 1,100 melanoma patients in Queensland, Australia (1963-1969) to investigate the geographical distribution of CMM in this state and found little difference between northern, central, and southern Queensland (rates per 1,000 = 0.63, 0.51, and 0.71, respectively). There were, however, higher rates in residents of coastal areas than in those from inland areas; the author hypothesized that this distribution may be related to sun exposure.

CMM incidence rates in Queensland, Australia, were also examined for geographical differences by Green and Siskind (1983). All incident CMM cases over a 12-month period (July 1979 to June 1980) were analyzed by statistical division, and no association with latitude was found. Like Herron (1969) and Holman et al. (1980b), they found a significantly increased incidence of melanoma in the coastal areas compared to the inland regions. Green and Siskind (1983) stated that a latitudinal relationship with CMM incidence may have been absent due to increased summer cloud cover in North Queensland. In addition, the mapped contours of erythemal UV doses during the summer months deviate substantially from latitude circles, and in summer, the critical recreational portion of the year, there is no association of UV radiation with latitude.

Fears et al. (1976) plotted U.S. melanoma and non-melanoma skin cancer incidence rates (Third National Cancer Survey 1969-1971) and U.S. CMM mortality rates (1950-1969 by county) for white males and females against latitude and found that incidence, and mortality rates due to melanoma and non-melanoma skin cancers, increased with decreasing latitude. Regression analyses produced strong negative correlation coefficients for each parameter (see Table 6-1).

Haenszel (1963) found a similar increasing north-south gradient in the incidence of malignant melanoma in four northern and four southern U.S. cities based on a 1947 survey of hospitals and physicians' offices. The ratio of north/south incidence rates showed higher risks of CMM in the southern cities than in the northern cities, although the ratio was somewhat lower for CMM of the trunk or lower extremities in males. The north-to-south incidence ratios were generally similar to those presented in a report for basal cell carcinomas and squamous cell carcinomas.

When the 1973-1976 incidence data from the National Cancer Institute's (NCI) Surveillance Epidemiology and End-Results (SEER) program were plotted against the 1977-1978 NCI R-B meter measurements of accumulated dose in eight locations in the United States, a strong positive association was noted (Scotto et al. 1982), as shown in Figure 6-1.

Elwood and Lee (1974) examined age-standardized (1960 U.S. population) mortality rates of CMM and other (non-melanoma) skin tumors separately over the period 1950-1967 for each Canadian province and U.S. state. In both analyses (melanoma and other skin tumors), the mortality rates showed a strong negative correlation with geographic latitude based on the latitude of the largest city in each province or state. Estimates of annual ultraviolet radiation in the erythema-producing wavelengths were made for each province and state. These estimates showed a strong negative association with latitude and with CMM mortality rates. The results were similar for analyses of melanoma mortality and for other skin cancer mortality; in addition, the estimates of UV flux in the erythema-producing wavelengths showed a similar association with CMM mortality as with latitude alone. The authors concluded that the similar relationships of mortality rates due to CMM and other skin cancers to estimates of annual UVR suggest the involvement of ultraviolet radiation as the causal agent in both diseases, and that latitude is a major factor affecting CMM mortality rates.

Baker-Blocker (1980) failed to find a significant correlation between CMM mortality in U.S. white males and females and amount of ultraviolet radiation received in the area. Correlation of average annual UV radiation estimates from 18 counties with CMM mortality rates by county for 1950-1969 (Mason and McKay 1974) showed no association, although the estimates of ultraviolet radiation were significantly correlated with latitude ($p=0.01$). El Paso County (Texas) had the lowest melanoma mortality rates (1.2 and 1.1. per 100,000 for white males and females, respectively) even though it received the highest amount of ultraviolet radiation. The counties with the highest melanoma mortality rates (Leon County, Florida--2.9/100,000 for females; Tarrant County, Texas--1.9/100,000 for females and 2.5/100,000 for males; and

TABLE 6-1

SUMMARY STATISTICS FOR REGRESSIONS OF U.S. SKIN CANCER INCIDENCE AND MORTALITY ON LATITUDE: 1969-1971 INCIDENCE RATES (THIRD NATIONAL CANCER SURVEY) AND 1950-1969 MORTALITY RATES (MASON AND McKAY, 1974)

	Males		Females	
	Correlation Coefficient*	Regression Slope + SD	Correlation Coefficient a/	Regression Slope + SD
Non-melanoma incidence	-0.89	-0.037+0.013	-0.83	-0.033+0.016
Melanoma incidence	-0.86	-0.031+0.007	-0.83	-0.028+0.007
Melanoma mortality	-0.81	-0.017+0.002	-0.71	-0.014+0.002

a Simple correlation coefficient of log rate and latitude.

Source: Fears et al. (1976).

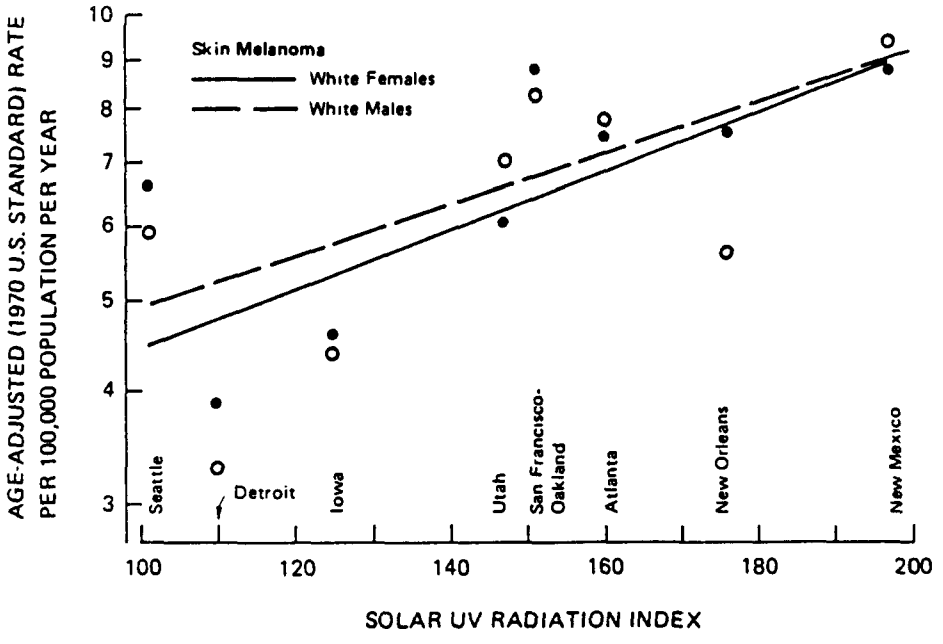

FIGURE 6-1

ANNUAL AGE-ADJUSTED INCIDENCE RATES FOR CMM (SEER DATA 1973-1976) AMONG WHITE FEMALES (OPEN SYMBOLS) AND MALES (CLOSED SYMBOLS), ACCORDING TO 1 YEAR'S UV MEASUREMENTS IN SELECTED AREAS OF U.S. a/

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a/ The UV radiation index is the total R-B meter counts over a 1 year period multiplied by 0.0001. The meters read UV-B between 290 nm and 320 nm, as well as some UV-A.

Source: NRC 1982.

Nassau County, New York--2.3/100,000 for males) received considerably less UV radiation than El Paso County. Bernalillo County (New Mexico) also had low CMM mortality (1.2/100,000 for both sexes) but received more ultraviolet radiation than those counties with the highest melanoma mortality rates. These results were interpreted as evidence that CMM mortality may be due to factors other than ultraviolet radiation, and that the high rates in Nassau and Ulster Counties (New York) and Montgomery County (Maryland) suggest that urbanization may play a role. However, the ethnicity and pigmentation characteristics of the populations were not considered in this analysis. The counties with the lowest rates have high proportions of Hispanics and Indians among their white populations in contrast to counties such as Nassau, Ulster, and Montgomery; in addition, the differences in CMM rates could reflect the varying susceptibility of the populations.

Anaise et al. (1978) found similar results of high CMM incidence in coastal versus inland areas in Israel. An analysis of all incident CMM cases in the total Israeli Jewish population from 1960 to 1972 showed higher age-adjusted rates of melanoma (3.5 and 3.2 per 100,000) for two coastal cities (Haifa and Tel Aviv) than for Jerusalem (2.0 per 100,000), which is situated inland in the mountains. This difference may be consistent with the sunlight exposure hypothesis of etiology, since those in the coastal regions are likely to spend more leisure time in outdoor activities and on the beach, and wear clothes which expose more skin. No analysis of latitude was done in this study.

Melanoma incidence data from 14 health regions in England and Wales (1962-1970) showed a significant negative correlation with latitude for both males ($p<0.0001$) and females ($p<0.05$) (Swerdlow 1979). In addition, Swerdlow (1979) analyzed mean daily hours of sunshine (1960-1968) for each region and found a positive correlation between melanoma incidence and mean hours of sunshine, although the correlation was statistically significant ($p<0.05$) in women only. The author concluded that these findings suggest that exposure to sunshine is an important causal factor for CMM. He also postulated that the higher melanoma incidence rates and stronger correlation with sunshine for females may be due to greater skin exposure to sunlight or sunburn due to sunbathing and style of clothing.

An examination of geographical variation in Norwegian CMM incidence rates from 1955 to 1970 (Magnus 1973) also showed a marked north-south increasing gradient; the age-adjusted incidence in southern Norway was two to three times higher than the rate in the northern part of the country.

An analysis of melanoma incidence from 1953 to 1973 in Finland (Teppo et al. 1978) also showed a distinct north-south increasing gradient, with the age-adjusted (1950 world population) rates being higher in the south. However, when the rates were adjusted for the urban/rural differences in population residence, the north-south gradient almost disappeared because of the high rates of melanoma in the urban areas of southern Finland. While this observation suggests that factors other than latitude may be causally associated with malignant melanoma, this finding does not negate a sunlight hypothesis because people in urban areas in Finland are thought to experience

more exposure to the sun through leisure activities and holidays than those living in rural areas, where skin has traditionally been more protected from direct sunlight by clothing (Teppo et al. 1978).

Eklund and Malec (1978) used data from the Swedish Cancer Registry during the period 1959 to 1968 to investigate association of latitude with CMM incidence in Sweden. They found a negative correlation between incidence rates and latitude ($R=-0.74$) signifying decreasing incidence with increasing latitude. A similar relationship was found when CMM incidence was correlated with annual estimates of ultraviolet radiation (in the erythema-producing wavelengths), supporting the hypothesis that melanoma is influenced by environmental factors such as ultraviolet radiation. These analyses, however, showed considerable variations, with some counties falling well above the regression line. Population density was also associated with melanoma incidence rates, with higher rates in urban areas regardless of latitude. Further analyses tested the hypothesis that these variations were related to frequency of foreign travel to sunny locations (see Chapter 8).

The International Agency for Research on Cancer (IARC 1976) collected and published data on cancer incidence on five continents, including both age-specific and age-standardized incidence rates from 59 population-based cancer registries in 27 countries. Crombie (1979) analyzed the IARC data on malignant melanoma from the 27 cancer registries in Europe and 16 in North America to investigate the relationship between melanoma incidence and latitude in areas with predominantly Caucasian populations. Melanoma incidence in North America showed significantly increasing trends with decreasing latitude for both males ($p<0.01$) and females ($p<0.05$). A similar trend of increasing incidence with decreasing latitude was also found for both males ($p<0.001$) and females ($p<0.05$) in England. Analyses of data for the European cancer registries showed significant trends in the opposite direction, i.e., increasing melanoma incidence with increasing latitude. The analyses showed particularly high melanoma incidence and mortality rates in Sweden and Norway. These European results contradict findings of ecological studies in North American and England, but are consistent with those of Lee and Issenberg (1972), who found higher incidence and mortality rates due to CMM in Swedish versus English populations, as shown in Table 6-2. IARC (1976) and Armstrong (1984) have attributed the lack of a latitude gradient in Europe to differences in complexion between Mediterranean and Scandinavian populations. Lee and Isenberg (1972) postulated that differences between English and Swedish rates could be due to genetic or occupational factors.

Armstrong (1984) also considered the inconsistencies seen in the relationship between geographic area and melanoma, mainly in Europe, and concluded that in Europe the south-to-north gradient associated with melanoma risk may be explained by a gradient in the opposite direction for skin pigmentation (i.e., more highly pigmented populations reside in southern Europe), and by a more intermittent pattern of sun exposure for populations living in northern Europe.

TABLE 6-2

AGE-ADJUSTED* INCIDENCE AND DEATH RATES PER 100,000 FOR MALIGNANT MELANOMA BY SEX: ENGLAND AND WALES (1962-1967) AND SWEDEN (1962-1965)

	England and Wales	Sweden
Incidence per 100,000		
Male	1.43	3.94
Female	2.40	4.23
Deaths per 100,000		
Male	0.92	1.92
Female	1.01	1.41

* Adjusted to UICC standard European population distribution.

Source: Lee and Issenberg (1972).

FINDINGS

From the information reviewed above, the following findings are evident:

6.1 Within nations with predominantly White populations, most ecological studies of melanoma and latitude show increasing melanoma incidence and/or melanoma mortality with decreasing latitude, leading to the hypothesis that melanoma is associated with sunlight, particularly its UV-B component, because of UV's strong correlation with latitude. The ecological studies which failed to show this association may not have accounted adequately for pigmentation differences.

6.2 Although further north, Sweden has higher incidence of and mortality rates due to CMM than England and Wales. As discussed in Chapter 7, pigmentation differences may be responsible, since the Swedish are a more homogeneous fair-skinned population than the English, who are a mixture of several European races.

6.3 In general, CMM incidence and mortality rates tended to be higher in populations living closer to the equator, in coastal compared with inland areas, and in urban versus rural areas within various nations.

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CHAPTER 7

MIGRANT STUDIES

Several epidemiologic studies have compared cutaneous malignant melanoma (CMM) incidence and mortality rates among migrants, among natives of the country adopted by these migrants, and among natives in the countries from which the migrants originated. These investigations have generally indicated that CMM risks among migrants who have moved to sunnier climates are lower than those among the native-born population from the adopted country (Houghton and Viola 1981; Lee 1982). All of the epidemiologic results showed that increasing duration of residence and earlier age at arrival were associated with higher risks of CMM among European-born immigrants to Israel, Australia, and New Zealand (Movshovitz and Modan 1973; Anaise et al. 1978; Katz et al. 1982; Holman et al. 1980; Dobson and Leeder 1982; Holman and Armstrong 1984; Cooke and Fraser 1985). There are no published data on the CMM risk of migrants to less sunny locales. This chapter reviews the available epidemiologic information about the risk of CMM among immigrants.

The earliest studies which identified migrants as a unique population with respect to CMM were conducted in Israel. The Israeli population has largely developed over the last century as a result of substantial immigration from Europe, Asia, and Africa, and thus provided a valuable population for various studies. Three studies using data from Israel's Central Cancer Registry have been conducted (Movshovitz and Modan 1973; Anaise et al. 1978; Katz et al. 1982), with cases overlapping among the studies; therefore, only the most recent study is described.

This most recent Israeli study examined 1,050 CMM cases diagnosed from 1960 to 1974 and reported in the Central Cancer Registry (Katz et al. 1982). The authors analyzed incidence rates (based on Central Bureau of Statistics data) by place of birth and length of stay. As shown in Table 7-1, incidence rates among the Israeli-born or the European- and American-born Jews were higher than the rates among Asian- or African-born Jews for all age groups and each average length of residence. The age-categorized incidence rates (see Table 7-1) among the European- and American-born were generally lower than the rates among the Israeli-born except for those immigrants residing in Israel for at least 17 years and in the 15-29 or 65+ age groups, and those living in Israel for an average of 4 years and who were 65+ years of age. The incidence rates among European- and American-born Jews who had lived in Israel for 17+ years consistently exceeded the rates for those who lived in Israel for an average of 13 years but not those in Israel for an average of 4 years. A clearer difference was observed when incidence rates were compared for the period of immigration (before 1947 and after 1948) for European- and American-born Jews. For those diagnosed between 1965 and 1974, the range of average annual incidence rates within 15-year age groups for those immigrating before 1947 was 10.28-12.36/10^5 compared with the range for those immigrating after 1948 (1.09-4.05/10^5). For cases diagnosed between 1960 and 1964, the differences between those arriving in Israel before 1947 and

TABLE 7-1

INCIDENCE OF MALIGNANT MELANOMA IN ISRAEL (1965-1974) AMONG JEWS BY PLACE OF BIRTH, AGE, AND AVERAGE LENGTH OF RESIDENCE IN ISRAEL [a]

Place of Birth	Average Length of Residence (yr.)	Number of Cases	Age 0-14	15-29	30-44	45-64	65+	All Ages
Israel		248	0.18	2.82	11.72	13.02	7.84	2.16
Asia or Africa	17+	25	- [b]	- [c]	0.68	2.12	3.12	1.24
	13	30	- [c]	0.38	1.04	1.64	1.84	0.88
	4	10	- [c]	0.50	- [c]	2.22	6.44	0.86
Europe or America	17+	334	- [b]	5.70	8.36	9.42	10.52	9.26
	13	121	3.08	1.68	4.14	6.20	7.26	4.72
	4	66	- [c]	2.08	6.06	8.44	17.38	5.96

[a] Average annual incidence rate per 100,000.

[b] No population.

[c] No cases.

Source: Katz et al. (1982).

after 1948 were not nearly as large. Katz et al. (1982) concluded that the higher incidence rates among European- and American-born immigrants compared to the more pigmented immigrants from Middle Eastern countries, and the increasing incidence with length of exposure among the European- and American-born, were "consistent with the cumulative effect of solar radiation as a causative factor."

Beginning in 1980, four detailed studies based on CMM data from Australia and New Zealand were published. Holman et al. (1980) analyzed data on 120 pre-invasive malignant melanoma (PIM) and 422 invasive malignant melanoma (CMM) cases identified in Western Australia from hospital discharge records and pathology lab reports for 1975 and 1976. As shown in Table 7-2, incidence rates (age-standardized to the total population of Western Australia in 1976) were greater among native-born Australian males with PIM and CMM and females with CMM than among British immigrants. Table 7-2 also indicates that rates of CMM among male and female British-born immigrants were about two times greater than all other immigrants combined. The differences in incidence rates were unchanged after adjustment for social class and age. Although their data sources did not provide information on duration of residence, the authors noted that the observed differences in incidence rates would be expected if CMM risks "were proportional to duration of residence in an area of high sun exposure."

Dobson and Leeder (1982) examined data on 2,243 CMM deaths obtained from the Australia Bureau of Statistics for 1968 to 1977. Standardized mortality ratios adjusted for age and country of birth were about two times higher among native-born Australians (124.3 and 118.6 for males and females, respectively) than among immigrants (except immigrants from New Zealand). The standardized mortality ratios among male immigrants ranged from 30.1 for the Netherlands to 71.0 for "elsewhere" (i.e., non-European). Among female immigrants the standardized mortality ratios ranged from 28.4 for Germany to 85.2 for Poland. Among immigrants from England and Ireland, those living in Australia for 24 years or longer had higher mortality rates than those living in Australia for less than 24 years. This finding was consistent in all sex and age groups considered, except for females in age group 20-39. The CMM mortality rates among these immigrants by age, sex, and duration of residence were all less than the comparable mortality rates among native-born Australians. The mortality rates among Australian immigrants of at least 24 years exceeded those rates shown for England and Wales (Lee and Yongchaiyudha 1971, as cited in Dobson and Leeder 1982).

Dobson and Leeder (1982) also compared CMM deaths for English and Irish immigrants (for 1968 to 1977) with deaths from all causes (for 1971) in Australia according to age at arrival, age at death, and sex. For CMM deaths occurring after age 40, the ratio of CMM deaths to deaths from all causes among immigrants generally had an inverse relationship with age (i.e., the earlier the age of arrival, the higher the ratio). For example, males arriving before 10 years of age were about three times more likely to die from melanoma than those who arrived after age 40 and about two times more likely to die from CMM than those arriving between 20 and 39 years of age. Dobson and Leeder (1982) concluded that the higher CMM mortality among immigrants

TABLE 7-2

AGE-STANDARDIZED INCIDENCE RATES OF PRE-INVASIVE AND INVASIVE MELANOMA IN WESTERN AUSTRALIA BY PLACE OF BIRTH

	Males		Females	
Place of Birth	Number	Incidence Rate[a]	Number	Incidence Rate[a]
		Pre-invasive Melanoma		
Australia	38	5.6	49	6.7
British Isles	7	2.8	11	4.8
Elsewhere	5	3.0	6	3.3
		Invasive Malignant Melanoma		
Australia	170	26.1	170	23.7
British Isles	23	10.0	29	12.7
Elsewhere	13	6.1	8	4.3

[a] Rate per 100,000 standardized to the age-distribution of the total population of Western Australia in 1976.

Source: Holman et al. (1980).

arriving during childhood and adolescence suggested that young people may be especially susceptible to a melanoma-initiating agent, such as sunlight, which is more prevalent in Australia than in their countries of birth.

Holman and Armstrong (1984) examined incident melanoma patterns among Western Australians in a case-control study. The 511 cases (23 percent migrants), were classified according to histologic type. The controls were matched by sex, 5-year birth period, and area of residence from the Australian Commonwealth Electoral Roll or, for 10 cases younger than 18 years, from public school student rolls. Sixty-five percent of all immigrants in the study were born in the U.K. The authors did not, however, provide a numerical breakdown of the places of birth of the cases and controls. As shown in Table 7-3, the odds ratios calculated for each histogenic type increased with increasing duration of residence (0-24, 25-39, 40-59, and ≥60 years), especially for nodular melanomas (NM) and Hutchinson's melanomic freckle (HMF). The trend of increasing melanoma incidence with increasing duration of residence was statistically significant ($P \leq 0.003$) for all melanomas combined and each histogenic type except for unclassified melanoma (UCM).

Holman and Armstrong (1984) also evaluated the CMM risk associated with age at arrival and discovered that age at arrival was a better predictor than duration of residence for risk of all melanomas combined and superficial spreading melanoma (SSM). For NM and HMFM, the variables age at arrival and duration of residences were too highly interrelated to permit separation of their effects. The data on 267 SSM case-control pairs were further analyzed by age at arrival after controlling for ethnicity (i.e., numbers of European, African, and Asian grandparents). The results are presented in Table 7-4. The risk of SSM in immigrants arriving between 0-4 and 5-9 years were somewhat though not significantly greater than that for native-born Australians. The odds ratios were less than one, however, for those immigrants arriving between 10-14 and 15-19 years of age and then generally stabilized around 0.25 for subsequent ages of arrival. The trend in odds ratios by age at arrival was significant ($p=0.0001$). Holman and Armstrong (1984) concluded that the results for SSM suggested a crucial age at arrival somewhere between 10 and 15 years of age, before which exposure to sunlight in early childhood may play a role in the production of benign nevi. They hypothesized that the benign nevi in turn may act as precursor lesions for SSM.

Holman and Armstrong (1984) also observed an increased proportion of palpable nevi on the arms of controls of English, Celtic, or Australian heritage who were born or arrived in Australia before 10 years of age compared with those who were 10 years or older at arrival. They hypothesized that if the production of "initiated nevus cells" was a step in the pathogenesis of SSM, then the potential to develop SSM would be determined by the number of initiated nevus cells induced in childhood or young adulthood. This, they concluded, could explain the overriding effect of age at arrival versus duration of residence in Australian immigrants with SSM, and the uniformly low rate of SSM in immigrants arriving after 10-14 years of age. They further concluded that it would be difficult to propose a factor other than sun exposure that could account for the lower CMM incidence rate in British migrants compared with native-born Australians, the majority of whom were of British descent.

TABLE 7-3

RELATIONSHIP OF HISTOGENIC TYPES OF MALIGNANT MELANOMA TO DURATION OF RESIDENCE IN AUSTRALIA

Parameter[a]	Duration of Residence, yr.[b] 0-24 (215)	25-39 (293)	40-59 (275)	≥60 (231)	P-value of Trend
All melanomas (507)					
Odds ratio	1.00	1.47	3.24	4.87	0.000001
95% CI		0.92-2.35	1.93-5.44	2.41-9.85	
Histogenic type					
HMFM (86)					
Odds ratio	1.00	0.90	3.12	6.35	0.003
95% CI		0.21-3.87	0.65-15.03	1.11-36.45	
SSM (267)					
Odds ratio	1.00	2.30	4.13	3.46	0.00008
95% CI		1.21-4.39	1.98-8.63	1.30-9.20	
UCM (89)					
Odds ratio	1.00	0.71	1.18	3.91	0.545
95% CI		0.24-2.08	0.39-.358	0.36-42.02	
NM (51)					
Odds ratio	1.00	1.05	4.85	14.72	0.009
95% CI		0.20-5.44	0.85-27.55	1.16-186.16	

[a] Numbers in parentheses are number of case-control pairs.

[b] Numbers in parentheses are total number of subjects in each exposure category.

Source: Holman and Armstrong (1984).

TABLE 7-4

RELATIONSHIP OF RISK OF SSM TO AGE AT ARRIVAL IN AUSTRALIA WITH CONTROL FOR NUMBERS OF EUROPEAN, AFRICAN, AND ASIAN GRANDPARENTS

(Based on 267 case-control pairs)

Age at Arrival (yr.)	Odds Ratio	95% CI	P-value of Trend
Birth	1.00		
0-4	1.17	0.25-5.45	
5-9	1.65	0.34-7.97	
10-14	0.74	0.17-3.28	
15-19	0.25	0.05-1.43	
20-24	0.25	0.08-0.83	
25-29	0.23	0.07-0.73	
≥30	0.38	0.19-0.78	0.0001

Source: Holman and Armstrong (1984).

A recent migrant study (Cooke and Fraser 1985) focused on 893 melanoma cases who died between 1972 and 1980 in New Zealand. The data were obtained from the National Health Statistics Center and, for immigrant cases, were restricted to those with at least 5 years' residence in New Zealand. Mortality rates for the New Zealand-born were calculated using 1976 census data, while for immigrants an unpublished census table of "usually resident" populations was used. Cooke and Fraser (1985) observed that CMM mortality rates were consistently lower for European immigrants than for those born in New Zealand although the number of deaths in some immigrant groups (e.g., the Netherlands) was small. The authors compared mortality rates by age and sex for New Zealand-born cases from 1972 to 1980, for U.K. immigrants from 1972 to 1980, and for CMM cases in England and Wales in 1976. The immigrant mortality rates were intermediate between rates for England and Wales and rates for New Zealanders (except for 15- to 54-year-old female immigrants, with only four CMM deaths from 1972 to 1980). The age-standardized mortality rate for 35- to 64-year-olds was higher for those arriving in New Zealand before 30 years of age ($7.1/10^5$; 95% CI 4.6-10.5) than at 30 years or older ($2.8/10^5$). Alternatively, the age-standardized mortality rate for 35 to 64-year-olds was higher for those living in New Zealand for at least 20 years ($3.9/10^5$) than for those residing in New Zealand for 5 to 19 years ($2.9/10^5$). The authors concluded that an early age at migration appeared to be associated with increased risk of CMM death among immigrants, a risk similar to that in their adopted country. The authors postulated that some factor acting in the first few decades of life, possibly patterns of sun exposure, was important in determining CMM risk.

A Hawaiian study (Hinds and Kolonel 1980) provided results which contradicted those from most other studies. The investigators found that among 265 Caucasian CMM cases, age-adjusted incidence rates among immigrants to Hawaii were much greater than rates among Hawaiian-born Caucasians. The study did not include information on country of birth, ethnic background, duration of residence, or age at arrival. Without more detailed data on these variables, the differences in incidence rates cannot be meaningfully explained. The authors indicated, however, that the immigrating Caucasian population may have been more susceptible to melanoma than the primarily Portuguese, native Caucasian population.

FINDINGS

Evidence from the studies reviewed in this chapter supports the following findings:

7.1 Immigrants moving to sunnier climates in which the native CMM incidence rates exceed those of the immigrant's country of origin tend to have lower CMM risks than the native population. These risks increase, however, with increasing duration of residence or earlier age of arrival in the adopted homeland.

7.2 In an Australian study, age at arrival in Australia was more important than duration of residence with respect to the risk of SSM. Arrival before age 10 was associated with a risk near to or greater than the estimated risk of SSM for those born in Australia. Risks decreased in association with age at arrival at 10-14 years relative to those born in Australia; risks stablized at a significantly lower level for those who arrived at or after age 15.

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CHAPTER 8

CORRELATIONS WITH INDICATORS OF INTERMITTENT OR SEVERE SUN EXPOSURE

Results from epidemiologic studies of cutaneous malignant melanoma (CMM) have led to conclusions that ranged from those which implicate sunlight as a causal factor, (e.g., most of the latitude studies [Chapter 6], migration studies [Chapter 7]), to those which do not support sunlight as a causal factor (e.g., no overall elevated risk of melanoma observed among outdoor workers compared to office workers [Chapter 11]). In attempts to reconcile these differences, it has been suggested that the risk of CMM on sites not usually exposed to sun is increased by intermittent exposure to more intense sunlight, while chronic sun exposure at a relatively constant dose may have little effect or may be protective, due to preventive tanning of the skin. This hypothesis can be examined using different measures of intermittent exposure as surrogates for actual exposure. This chapter reviews studies of CMM which investigated intermittent exposures to sunlight as estimated by a history of sunny vacations, recreational activities, and history of severe sunburn (particularly in early life). Also included is a section which reviews studies of sunspots and seasonal differences in the incidence of CMM. Sunspots result in higher levels of UV radiation which reach the earth's surface in a cyclical pattern and may result in more severe UV exposures.

HISTORY OF SUNNY VACATIONS OR RECREATIONAL ACTIVITIES

A vacation in a sunny location may result in intermittent exposure to UV-B radiation at higher than usual levels. The levels of exposure can be variable but, in general, sunny vacations are chosen simply because of the increased sunlight in the vacation spot. Several studies have examined past history of sunny vacations using various methods to explore the role of sun exposure in the etiology of CMM.

Using data from the Swedish Cancer Registry for 1959 to 1968, Eklund and Malec (1978) found that CMM incidence increased with population density. In an attempt to explain this finding, the authors hypothesized that an increase in foreign travel as estimated by passport issuance, might explain the over-representation of CMM in the large cities because "foreign travel in Sweden generally means sunshine trips." A 3.7 percent increase in the mean frequency of annual passport issue between 1959 and 1968 corresponded to an increase in CMM incidence over the same time period. Both increases were especially high in the densely populated cities and counties. Regression analysis was performed using an exposure index based on annual UV radiation in the erythema-producing wavelengths and latitude. Results showed variations in CMM incidence between Sweden's major cities and some counties, but these differences were reduced when frequency of passport issuance was considered in the analysis. Thus, foreign travel as represented by passport issuance was seen as a possible explanation for the higher CMM incidence in the most populated areas of Sweden.

A Norwegian study (Klepp and Magnus 1979) investigated sunny vacations through self-administered questionnaires from 78 CMM cases and 131 unmatched controls who were other cancer patients. The study showed no differences between cases and controls in pigmentation characteristics (hair and eye color), in estimated time spent outdoors during leisure activities, or in degree of exposure to sunshine during occupational or leisure activities. There was, however, a borderline significant difference ($p=0.05$) between the proportion of cases (19.2 percent) and controls (9.2 percent) who had traveled to Southern Europe for sunbathing during the previous 5 years (estimated relative risk of 2.4). This study did not account, however, for socio-economic status, a variable often related to CMM and the tendency to go on vacations.

A study of oral contraceptive use and CMM in England (Adam et al. 1981) included sun exposure factors to explore potential confounding of study results. The study included 169 women aged 15-49 with CMM registered during 1971 to 1976 at the Oxford and South Western cancer registries, and 507 female controls (three controls per case) matched by 5-year age group and marital status, drawn from the physicians' practice lists. The authors found no significant differences between cases and controls who "tanned themselves while on holiday abroad" (for legs, 78 percent cases and 73 percent controls, and for trunk, 70 percent cases and 67 percent controls). A higher proportion of cases than controls spent outdoor leisure time deliberately tanning their legs (77 percent vs. 69 percent) and trunk (64 percent vs. 53 percent), although these differences were not statistically significant.

A study of 595 melanoma case-control pairs in Western Canada by Elwood et al. (1985a) showed that substantial intermittent sun exposure (as assessed by vacation and recreation histories) was strongly associated with CMM. There was a significant ($p<0.001$) trend of increasing risk of CMM occurrence with the number of "sunny vacations" (defined as severe or more intense sun exposure than normal) per decade. A relative risk of 1.8 for CMM was also associated with a history of four or more sunny vacations per decade. This relative risk remained significant (RR=1.7, 95% C.I. 1.2-2.3) even after adjustment for pigmentation factors (hair color, skin color, history of freckles) and ethnic origin. Further analyses were conducted on the risk associated with certain activities and practices on sunny vacations. Sun exposure through beach and other light-clothing activities during sunny vacations was associated with a relative risk of 1.9 (95% C.I. 1.3-3.0) for 20 to 39 exposure hours per summer season compared with no summer vacation sun exposure after adjustment for pigmentary factors and ethnic origin. This risk level could be reached by 4 to 8 hours per day of sun exposure during a 1-week vacation. The relative risk for 40 or more hours of vacation sun exposure per summer season decreased slightly to 1.5 (95% C.I. 1.0-2.3), and was of borderline statistical significance. Socioeconomic factors were not controlled for in the above analyses, and may have led to biased results.

Holman et al. (1986) analyzed data from their matched case-control study of CMM in Western Australia to investigate the relationship of different histologic types of CMM with intermittent sun exposure, as measured by history of summer sun exposure (both recreational and total, which includes

occupational) and clothing habits. Analyses were also performed to investigate variations in relationships of sun exposure and CMM by primary tumor site.

With the exception of HMFM, all histologic types of CMM appeared to be inversely associated with total summer outdoor exposure (none of the associations were statistically significant). Further analysis measured recreational exposure as a proportion of total outdoor time in summer to evaluate the concentration of sun exposure during days off work. This variable--recreational outdoor exposure proportion in summer (ROEP)--provided an index in which the range from 30 percent to 100 percent indicated an increasing concentration of outdoor (sun exposure) time during leisure days. The higher proportions in this index imply a "burst" of exposure over a relatively short part of the week as contrasted with low proportions (ROEP near 0 percent) for farmers who worked outdoors 7 days a week. The effects of ROEP were examined separately by age group (10-24 years, 25-39 years, 40 years and over) and by different time intervals prior to diagnosis of the case (0-4, 5-9, 10-19 and >20 years pre-diagnosis). Results showed little evidence of any association of CMM with ROEP after control for potential confounders (pigmentation characteristics, ethnic origin, and age at arrival in Australia). For SSM and NM, there was a suggestion of a dose-response gradient in ROEP at ages 10-24 years, but the trends were not statistically significant ($p=0.148$ for SSM and $p=0.258$ for NM). Additional analyses using the absolute average number of hours exposed per week or using the difference between average hours of recreational and work exposure as measurements of recreational exposure to summer sun showed no stronger evidence of an association between incidence of CMM and recreational sun exposure than that mentioned previously.

Analyses of specific outdoor recreational pastimes were conducted based on the 276 SSM case-control pairs. Both boating and fishing at least once per week during summer showed significantly increased risks for SSM when compared with those who never participated (boating: OR=2.43, 95% C.I. 1.10-5.39; fishing: OR=2.72, 95% C.I. 1.15-6.43). There was little evidence, however, for a relationship of SSM with swimming. Frequency of summer sunbathing at ages 15-24 years showed only a weak association with SSM (OR=1.26, 95% C.I. 0.78-2.05 for "less than one/week" and OR=1.32, 0.80-2.17 for "once or more per week"); however, when the analysis was confined to SSM occurring on the trunk, with "never sunbathing" as the reference group, the odds ratio for the higher frequency sunbathing group attained statistical significance with a p-value for trend 0.044, OR=1.20, 0.51-2.81 for less than once per week and OR of 2.55 (95% C.I. 1.05-6.19) for once or more per week. Again, socioeconomic factors were not controlled for in the analysis and may have led to biased results.

The types of bathing suit worn by women at ages 15-24 years (usually the period of most frequent sunbathing) and in the 10 years prior to case diagnosis were also examined. Results for the type of bathing suit worn showed a strong increase in risk of melanoma of the trunk with decreasing bathing suit coverage, even after control for potential confounders. Not all results reached statistically significant levels, as shown in Table 8-1, but

increased ORs were associated with type of bathing suit style for CMM of the trunk (p-value for trend = 0.005 for women at ages 15-24 years and 0.006 for 0-9 years per diagnosis).

SUNBURN IN EARLY LIFE

Elwood et al. (1984, 1985b), in a Canadian case-control study (595 matched pairs), assessed both the tendency to sunburn and history of sunburn. A specific question was asked about sunburn in childhood using gradations of 1, 2, and 3 for "rare, very mild, or no burn," "moderate or infrequent," and "severe or frequent burn", respectively. The authors found a significantly increased risk for sunburn in childhood (RR=1.9) although the risk became smaller and statistically nonsignificant after adjustment for pigmentation factors (hair, skin, and eye color). A history of frequent sunburn in childhood remained a significant risk factor along with pigmentation even after control for ethnic origin, but the authors concluded that "the risk is due to characteristics of pigmentation associated with poor sun tolerance" (Elwood et al. 1984).

Lew et al. (1983) found similar results in a Massachusetts case-control study (111 melanoma cases and 107 unmatched controls): risk factors with elevated ORs included "blistering from sunburns in adolescence" (OR=2.05, 95% C.I. 1.18-3.56) and "painful sunburn as a child" for both those who tanned well (OR=2.8, 1.3-6.3) and those who tanned poorly (OR=3.0, 0.9-9.8). A history of extended sunny vacations (30 days or more as a child) was also found to elevate CMM odds significantly (OR=2.5, 1.1-5.8). The authors concluded that the same etiology underlies each of these risk factors, i.e., "the degree of response to sun exposure," and that the nature of these traumatic exposures and sunny vacations in early life suggests that traumatic doses of sun may outweigh lifetime cumulative doses as a risk factor for melanoma. These findings should be interpreted with caution because there was no control for pigmentation factors or socioeconomic status, and the control selection was flawed (see Chapter 10). In addition, the potential for recall bias, whereby cases are more likely to remember early sunburn episodes than controls, should be considered.

Holman et al. (1986) analyzed sunburn histories of CMM cases and controls in Western Australia (507 pairs matched on age, sex, and area of residence) for age groups under 10 years and 15-24 years. No relationship between sunburn in childhood or early adulthood and any histologic type of melanoma was found after control for potential confounders such as chronic and acute skin reaction to sunlight, hair color, ethnic origin, and age at arrival in Australia. Compared with persons who reported no painful sunburns in childhood (under 10 years of age), the odds ratios for SSM were 1.06 (95% C.I. 0.65-1.75) for those who experienced painful sunburn up to four times and 1.11 (0.51-2.41) for those who reported five or more painful sunburns. For sunburn during ages 15-24 years, the corresponding odds ratios for SSM were 1.04 (0.66-1.66) for four or fewer sunburns and 0.98 (0.53-1.82) for five or more sunburns.

TABLE 8-1

RELATIONSHIP OF CUTANEOUS MALIGNANT MELANOMA IN WOMEN TO TYPE OF BATHING SUIT WORN IN SUMMER, CONTROLLED FOR POTENTIAL CONFOUNDERS a/

Melanoma Site and Period of Life	Type of Bathing Suit Worn in Summer			Null p-value of Trend
	One Piece, High Back	One Piece, Low Back	Bikini or Nude	
Trunk (60 case-control pairs)				
Ages 15-24 years	1.0	4.04 (0.65-25.23)	12.97 (1.95-83.94)	0.005
0-9 years prediagnosis	1.0	1.12 (0.23-5.47)	8.94 (1.45-55.07)	0.006
SSM trunk (30 pairs)				
Ages 15-24 years	1.0	0.19 (0.01-7.19)	4.06 (0.14-117.09)	0.054
0-9 years prediagnosis	1.0	0.61 (0.03-10.50)	2.52 (0.18-34.58)	0.175
Non-SSM trunk (30 pairs)				
Ages 15-24 years	1.0	3.22 (0.10-103.48)	374.14 (0.36-389.40)	0.119
0-9 years prediagnosis b/	-	-	-	-

a/ Chronic and acute skin reaction to sunlight, hair color, ethnic origin, and age at arrival in Australia.

b/ Too few exposed for analysis.

Source: Holman et al. (1986).

LIFETIME HISTORY OF SEVERE SUNBURN

The following section includes only those studies which reported sunburn history, i.e., remembered severe sunburn, whether in childhood, adolescence, or adulthood. The possibility of recall bias among CMM cases with respect to sunburn exposures should be considered in the interpretation of these studies.

MacKie and Aitchison (1982) conducted a case-control study of 113 age/sex-matched pairs (hospital-based controls) in the west of Scotland which also considered social class and skin type in the analysis. There was a significant difference ($p<0.05$) between the cases and controls in the history of severe or prolonged sunburn 5 years before diagnosis of CMM (i.e., blistering sunburn or erythema persisting 7 or more days after sun exposure). Overall, 56 percent of the melanoma patients had a history of severe sunburn compared with 22 percent of the controls (RR=2.8, 95% C.I. 1.1-7.4 referent group not specified by authors). When separated by sex, there were still significant differences ($p<0.05$) between the cases and controls with respect to history of severe or prolonged sunburn. The presence of recall bias among the melanoma cases could have biased the findings if cases were more likely to remember or overstate their history of sunburns.

More extensive analyses of Western Canada study data on 595 age-, sex-, and residence-matched case-control pairs, by Elwood et al. (1985b), evaluated the relationship of CMM incidence to sunburn history at any age and vacation sunburn history for those with recorded vacations. There was an increasing trend for risk of CMM with increasing number and severity of sunburn episodes ($p\leq0.01$) using a vacation sunburn score, and significantly raised odds ratios of CMM ($p\leq0.05$) for each of the sunburn history categories considered separately (sunburn on vacations, sunburn in childhood, and history of severe sunburn causing pain or blistering for over 2 days) relative to those with no or mild sunburn. Vacation sunburn scores were analyzed with the variable "usual degree of suntan" in order to consider the separate effects of these variables, but each remained statistically significant after adjustment for the other, indicating that these two factors acted independently.

As in their earlier analysis of the sunburn in childhood data (Elwood et al. 1984), the authors evaluated whether the tendency to sunburn and sunburn history, as measured by vacation sunburn score, were independent risk factors for melanoma. The results of this analysis showed a weak association between CMM risk and vacation sunburn score after adjustment for the usual reaction to sun, i.e., ranging from "tan to burn" to "burn only." Multivariate analyses controlling for usual reaction to sun and other pigmentary factors (hair color, skin color, and freckles in adolescence) further weakened the association between CMM and vacation sunburns. The authors concluded that, while history of severe or frequent sunburn was associated with an increased risk of CMM, the tendency to burn easily and tan poorly was more strongly associated with CMM risk; thus, it appeared that it was factors associated with the tendency to burn rather than a positive history of sunburn which determined CMM risk. The authors concluded, however, that in contrast to sunburn history and vacation sunburn score, melanoma risk was increased by heavy vacation or recreational exposure to sunlight and that the increased

CMM risk from these substantial intermittent sun exposures was independent of constitutional factors (pigmentation characteristics, reaction to sun, and number of nevi). This association is probably not due to the trauma of sunburn itself but to another characteristic of individual skin reaction, "related presumably to variations in melanocyte function, distribution or prevalence."

A case-control study (183 pairs matched by age, sex, and place of residence) in Queensland, Australia (Green et al. 1985) showed a positive trend of increasing CMM risk with an increasing number of severe sunburns ($p<0.001$). When the number of sunburns was grouped (0-1, 2-5, 6+) and an adjustment was made for the presence of pigmented nevi on the arms (the strongest risk factor determined in this study), and for age, the positive trend for CMM risk with number of sunburns remained significant ($p\leq0.05$); the adjusted relative risk of melanoma for six or more severe sunburns was 2.4 (95% C.I. 1.0-6.1). The risk estimates were essentially unchanged by further control for other risk factors such as presence of other skin cancers, migrant status, and social class. The authors did not control for pigmentation variables such as hair or skin color or the tendency to sunburn; therefore, the results should be cautiously interpreted. Green et al. (1985) stated that "an experience of painful erythema indicates that acute high-dose UV has been delivered to the level of the melanocyte" and, because of this, the above-mentioned variables should not confound an association between CMM and severe sunburn (defined as sunburn with pain persisting longer than 48 hours, with or without blistering). The authors also concluded that the dose-response relationship obtained from their analysis supports a causal interpretation of an observed sunburn-cutaneous melanoma association. The authors believe that their results support an "intermittent episodes of acute UV exposure" theory, but may also fit a "cumulative" or dose-related theory in which the high UV dose has accumulated from multiple severe sunburn episodes.

Holman et al. (1986) analyzed sunburn histories from 507 CMM matched cases and controls (matched on sex, age, and residence) from Western Australia, ranking them according to increasing sunburn severity: "peeling sunburn," "painful sunburn (pain for 2 days or more)," and "blistering sunburn." After control for potential confounding factors (chronic and acute skin reaction to sunlight, hair color, ethnic origin, and age at arrival in Australia), only HMFM showed some association with the occurrence of severe sunburn (p-value for trend = 0.059). For nodular melanoma (NM), there was a significant trend in the opposite direction ($p=0.010$), giving the appearance of a protective effect. This result was based on small numbers (51 NM cases) and attributed to chance. For SSM and UCM, there was no association with past sunburn severity after control for confounding variables. Using data from the same study population, this group (Armstrong et al. 1986) was able to show that the prevalence odds ratio for nevi increased more or less linearly with increasing numbers of childhood sunburns up to the age of 10. The authors note that the relationship between nevi and sun exposure is a complex one and that their data are consistent with both total exposure and total outdoor exposure time in summmer being important. In addition, the pattern of exposure may play a role.

SUNSPOTS AND SEASONAL INCIDENCE DIFFERENCES

Scotto and Nam (1980) analyzed monthly incidence of CMM from the Third National Cancer Survey (1969-1971) to test for seasonal patterns in incidence. There are monthly patterns in the amounts of solar radiation reaching the earth's surface, with the highest intensity UV-B radiation occurring during the summer months. The authors examined seasonal patterns of CMM incidence for 2,167 white patients (998 males, 1,169 females) by sex, age, geographic region, and tumor site.

A highly significant seasonal pattern ($p=0.00003$) with a summertime peak was found for the total female CMM cases: over 20 percent of all cases were diagnosed during June and July, while less than 14 percent were diagnosed during the winter months of December and January. For males, no seasonal pattern of sustained peak or dip was found. Among males, the trunk was the most common tumor site (38 percent), while among females, it was the lower extremities (35 percent). Analysis of seasonal patterns of solar radiation by anatomic site showed two highly significant sites for females--upper extremities and lower extremities ($p=0.0007$ and $p=0.0001$, respectively), but none for males; upper extremities showed a tendency toward the seasonal pattern with summertime peak but this was not statistically significant ($p=0.11$). An attempt to reduce single-month disturbances in the patterns by grouping into 2-month periods still showed a significant pattern for females ($p=0.003$) but not for males ($p=0.07$).

The observations of seasonal patterns with summertime peaks in CMM incidence for females with tumors on upper or lower extremities may be due to the promotional effects of UV-B exposure, or it may be a result of greater awareness of skin changes and/or problems during the summer months when less clothing is worn.

Hinds et al. (1981) conducted similar analyses using 1960-1978 CMM incidence data for Caucasians in Hawaii. Based on 353 incident cases (males and females combined), the authors found significant seasonal patterns with summertime peaks for melanomas of all sites ($p=0.018$), and for those of the lower extremities ($n=79$, $p=0.017$). For head and neck melanomas, there seemed to be a similar seasonal pattern but it was of borderline statistical significance ($p=0.069$). Hinds et al. (1981) stated that, because there is little variation in the types of clothing worn throughout the year in Hawaii, it is unlikely that a seasonal pattern would be due to increased observation of the skin during the summer months. These authors concluded instead that their findings supported the hypothesis that solar (UV) radiation may be a short-term promoter of some malignant melanomas of the skin.

Houghton et al. (1978) used Connecticut Tumor Registry data on 2,983 CMM cases diagnosed during 1935 to 1974 to analyze CMM incidence rates. The rate per 100,000 rose from 1.1 to 6.2 over this 40-year period with evidence of cyclical patterns with 3 to 5 year peaks in incidence every 8 to 11 years. The secular increase in melanoma incidence was highly correlated (correlation

coefficient = 0.9327, $p<0.01$) with three sunspot cycles of 8 to 11 years over a 33-year period. CMM incidence rose sharply at the peak of each sunspot cycle and the high rates persisted for 3 to 5 years before returning to a stable but increased rate. Controlling for the time effect on increasing rates did not alter the significant association between annual sunspot activity and CMM incidence rates in each of the subsequent 3 years.

Analyses of melanoma incidence from New York State and Finland also showed significant correlation with sunspot activity although data from Norway showed no significant results. Analysis of data from New York State (1950-1971) showed significant association between sunspots and CMM incidence in the 1 to 2 years subsequent to sunspot activity. In Finland, however, incidence rates were significantly correlated only with the years of sunspot activity and the first subsequent year; this decrease in lag period is postulated to be a result of Finland's higher latitude. Wigle (1978) reported similar cyclical variations in CMM incidence in Saskatchewan and Alberta, Canada; when CMM incidence rates were correlated with periods of sunspot activity, incidence rates were found to increase 0 to 2 years after the peak sunspot activity (0. to 1 in Saskatchewan and 2 in Alberta). After a review of these data, Houghton and Viola (1981) concluded that "rises in CMM incidence occur 0 to 3 years after sunspot peaks, suggesting that heavier exposures to UV radiation trigger the clinical appearance of melanoma."

FINDINGS

The following findings can be drawn from the review presented above:

8.1 A case-control study in Western Canada found evidence of increasing CMM risk with increasing number of "sunny vacations" taken, even after adjustment for pigmentation factors and ethnic origin. This study did not, however, control for socioeconomic factors which are likely to be associated both with CMM incidence and number of sunny vacations.

8.2 Using a variable for recreational sun exposure, defined as the ratio of summer recreational sun exposure to total summer sun exposure, a Western Australia study found no significant association of this factor in any of the age groups examined. However, an increased SSM risk for some summer sun activities at early ages was observed for boating, fishing, and female sunbathing (on trunk only). For CMM of the trunk in women, particularly for SSM, risks increased with decrease in coverage by the bathing suit style worn at 15-24 years of age.

8.3 CMM risk is associated with a history of childhood sunburn and/or lifetime history of sunburn but this appears only to reflect an individual's pigmentary characteristics, particularly as they relate to poor sun tolerance.

8.4 A seasonal pattern with a summertime peak was found for CMM (female in U.S., both sexes in Hawaii); this may be related to a greater awareness of skin changes in the summer months.

8.5 Most studies which examined the relationship between CMM incidence rates and sunspot cycles found high correlations. Different studies have observed slightly different lag periods between peak sunspot activity and increased CMM rates.

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CHAPTER 9

CORRELATIONS WITH INDICATORS OF CUMULATIVE SUN EXPOSURE

The results from the ecological studies of melanoma and latitude led to case-control studies which further investigated the hypothesis that exposure to UV radiation is causally associated with cutaneous malignant melanoma (CMM) using estimates of cumulative sun exposure. The estimates of sun exposure were defined somewhat differently from study to study, but all were based on individual interviews or questionnaires and, as such, provided an assessment of individual exposure. Two early studies (Lancaster and Nelson 1957; Gellin et al. 1969) might be considered crude by current epidemiologic standards, but they are historically important to the development and exploration of the hypothesis. Three other case-control studies of CMM investigated total or cumulative sun exposure in Western Australia (Holman and Armstrong 1984a, b; Holman et al. 1986), in Queensland, Australia (Green 1984), and in Western Canada (Elwood et al. 1985). The Western Australia and Western Canada studies are the largest case-control studies of CMM to date, and unlike most other studies, they controlled for important confounding variables, such as pigmentary factors.

An early case-control study of melanoma in Sydney, Australia (Lancaster and Nelson 1957) estimated total sun exposure by means of a scoring index based on: length of life in Australia, occupational exposure, industrial hazards, war service, and outdoor sports. This study is of historical importance because it was the first epidemiologic study of CMM to measure sun exposure in individuals. Interview results from 173 CMM cases, 173 non-melanoma skin cancer controls (age- and sex-matched to the cases), and 173 non-skin cancer controls (also age- and sex-matched to the melanoma cases) showed a higher proportion of melanoma cases with "excessive" sun exposure (26.6 percent) as compared with the other skin-cancer controls (21.4 percent) and the non-skin cancer controls (16.2 percent). The authors concluded that this finding, in addition to others, supported the hypothesis that sun exposure is an important factor in the occurrence of CMM.

Gellin et al. (1969) analyzed data from interviews of 79 cutaneous melanoma cases and 1,037 unmatched controls (non-tumor skin conditions) from 1955 to 1967 in New York. Results showed that 68 percent of the melanoma patients reported spending three or more hours per day outdoors as compared with only 37 percent of the controls ($p<0.01$), a finding which the authors stated "raises the question anew of the role of sunlight in the pathogenesis of this form of cutaneous malignancy."

Green (1984) analyzed interview data from 183 melanoma patients and 183 matched population controls (age $\pm$ 5 years, sex, residence) in Queensland, Australia, to investigate the "relationship between cumulative hours of solar ultraviolet B (UV-B) radiation and melanoma (excluding lentigo maligna melanoma)." Total hours of sun exposure (as a surrogate for UV-B) were

estimated by summation of reported occupational and recreational sun hours from 10 years of age onward. Results showed the cases to be more heavily exposed to the sun than controls: the relative risks increased from 3.2 (95% C.I., 0.9-12.4) for intermediate exposure (2,000-49,999 hours) to 5.3 (95% C.I., 0.9-30.8) for 50,000 or more hours of sun exposure when compared with less than 2,000 hours after adjustment for exact age, presence of nevi on arms, hair color, and sunburn propensity. The intermediate exposure category was, however, extremely broad, and it is not known how this may have affected the results or how many cases and controls were in the highest group. Eliminating exposures before 10 years of age could also have affected the results if, in fact, early sun exposures are important to the development of melanoma (see Chapter 8). Further analyses using actinic skin damage (keratoses or other skin cancers) as indicators of heavy lifetime exposure to solar UV radiation showed that the CMM patients had significantly more actinic lesions on their faces in comparison with controls ($p<0.0001$), resulting in an increased CMM relative risk of 2.8 (95% C.I. 1.1-7.2) after adjustment for exact age and presence of nevi on the arms. Socioeconomic factors were not controlled for and may have biased study findings.

Holman and Armstrong (1984a) analyzed data on cumulative sun exposure at residence from 511 melanoma cases and 511 matched (age, sex, residence) controls in Western Australia during 1980 and 1981. The measure of cumulative sun exposure was based on location and duration at each residence and mean annual hours of bright sunshine at each location, resulting in an estimate for lifetime exposure at home rather than an actual estimate of time spent in the sun. Analysis showed a significantly decreased odds ratio for migrants to Australia relative to native Australians; therefore, most analyses were restricted to native-born Australians. Results (Table 9-1) show significant positive trends for all CMM ($p=0.003$) and for SSM ($p=0.020$). A strong positive gradient with increasing sun exposure was seen for HMFM with an odds ratio of 3.78 for the highest exposure group; however, the p-value for trend (0.101) failed to reach statistical significance, probably due to the small number of pairs with HMFM in the analysis.

Data from this study on sun exposure were also examined by age for high levels (>2,800 mean annual hours of bright sunlight) of exposure during any age period (0-9, 10-24, 25-39, >40 years). The greatest risks for SSM were observed for high levels of sunlight in the 10-24 year age group (OR = 11.31, 95% C.I. 1.40-91.11) and in the 25-39 year age groups (OR = 3.40, 1.41-8.20). Elevated risks were seen for HMFM in each of the age groups but were not significant, probably due to small numbers.

While the measure of sun exposure in these analyses was basically ecological in nature, i.e., annual hours of bright sunlight at residence, an analysis of actinic skin damage by cutaneous microtopography showed an increasing risk for all CMMs with worsening actinic skin damage (Table 9-2). Analysis by histogenetic type showed significantly increased risks with increasing grade of actinic damage for both HMFM and SSM. History of non-melanotic skin cancer also resulted in an increased risk of melanoma, as shown in Table 9-3. The increased risk of melanoma with history of non-melanoma skin cancer remained even after control for pigmentary factors

TABLE 9-1

ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR CMM BY MEAN ANNUAL HOURS OF BRIGHT SUNLIGHT AT RESIDENCE, RESTRICTED TO NATIVE-BORN AUSTRALIANS

Histogenetic Type[a]	Mean Annual Hours of Bright Sunlight at Residence			P-Value of Trend
	<2,600	2,600-2,799	>2,800	
All melanomas (494)	1.00	1.34 (0.96-1.86)	1.92 (1.16-3.18)	0.003
HMFM (82)	1.00	1.54 (0.57-4.15)	3.78 (0.54-26.35)	0.101
SSM (259)	1.00	1.17 (0.68-2.00)	2.12 (0.90-4.98)	0.020
UCM (89)	1.00	0.75 (0.31-1.83)	1.41 (0.46-4.33)	0.922
NM (50)	1.00	0.32 (0.04-2.93)	0.32 (0.04-2.59)	0.193

[a] Number in parentheses is number of case-control pairs.

Source: Holman and Armstrong (1984a).

TABLE 9-2

ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR HISTOGENETIC TYPES OF CMM BY SKIN CONDITION, GRADED BY CUTANEOUS MICROTOPOGRAPHY

Histogenetic Type[a]	CMT Grade				P-Value of Trend
	1-3	4	5	6	
All melanomas (389)	1.00	1.64 (0.97-2.78)	1.76 (0.97-3.19)	2.68 (1.44-4.98)	0.003
HMF (72)		1.00[b]	4.05 (0.93-17.67)	4.37 (1.21-15.74)	0.048
SSM (198)	1.00	1.53 (0.81-2.91)	2.25 (1.04-4.88)	2.63 (1.14-6.06)	0.021
UCM (71)	1.00	2.69 (0.70-10.41)	0.62 (0.17-2.20)	1.19 (0.32-4.45)	0.652
NM (34)	1.00	0.64 (0.07-5.55)	0.94 (0.06-14.10)	5.17 (0.27-98.69)	0.092

[a] Number in parentheses is number of case-control pairs.

[b] Grades 1-4 combined for baseline because no case of HMF had CMT graded less than 4.

Source: Holman and Armstrong (1984b).

TABLE 9-3

RELATIONSHIP OF HISTOGENETIC TYPES OF MALIGNANT MELANOMA TO A HISTORY OF NON-MELANOTIC SKIN CANCER

Melanoma Type	Odds Ratio	95% C.I.	P-Value
All melanomas (507 case-control pairs)	3.71	2.11-6.57	0.000001
HMFM (86 pairs)	5.25	1.71-18.03	0.001
SSM (267 pairs)	3.33	1.27-9.26	0.011
UCM (89 pairs)	3.00	1.02-9.42	0.044
NM (51 pairs)	5.00	0.57-113.13	0.221

Source: Holman and Armstrong (1984a).

(OR = 2.87, 95% C.I. 1.64-5.04, p=0.0002). The finding of increased CMM risk with increasing actinic skin damage and with previous non-melanoma skin cancer was seen to support an association between cutaneous melanoma and sun exposure, with the strongest associations for SSM and HMFM (Holman and Armstrong 1984b).

In contrast with these results, a more recent analysis of total outdoor exposure from the same study population (Holman et al. 1986) showed that, with the exception of HMFM, all histologic types of melanoma appear to be inversely associated with total outdoor exposure (estimated by mean weekly total occupational and recreational outdoor sun exposure averaged over a working life) after control pigmentation factors. HMFM showed slightly elevated risks in the two highest exposure categories (OR = 1.40 for 16-22 hours/week; OR = 1.32 for >23 hours/week) but neither odds ratio was statistically significant, nor was there a significant trend. The inverse associations for the remaining histogenetic types (SSM, UCM, and NM) were also not significantly different from the baseline exposure group (0-10 hours/week). Analysis of the recreational sun exposure variable in this study (Holman et al. 1986) is discussed in Chapter 8 as a measure of intermittent sun exposure.

A case-control study of CMM in Western Canada (Elwood et al. 1985) examined histories of sun exposure from occupational, recreational, and vacation activities for 595 melanoma patients and 595 matched population controls (matched on age, sex, and province of residence). A significant increase in risk with increasing sun exposure from recreational and vacation activities was found even after adjusting for hair color, skin color, history of freckles, and ethnic origin ($p<0.01$). For occupational exposure, no trend was observed, and the only elevated risk was in the mild exposure group (approximately 8 hours per week) (RR = 1.8, 95% C.I. 1.2, 2.5). Analysis of sun exposure from all sources combined showed some elevated risks in the higher groups when compared with the lowest, but none were statistically significant, nor was there a significant trend of increase.

FINDINGS

Results of case-control studies of CMM and total sun exposure seem to vary by the measure used to estimate the exposure, and may be affected by adjustment for pigmentation factors such as hair and skin color, propensity to sunburn, and ethnic origin; adjustment for these factors tends to lower the risk estimates. Two early studies showed significantly higher proportions of melanoma cases than controls with high sun exposure, although pigmentary factors were not considered in the analyses.

Findings based on the information from the three most recent case-control studies are presented below:

9.1 A study from Western Australia which controlled for the potentially confounding effects of pigmentary factors found significantly elevated odds ratios for total CMM, SSM, and HMFM associated with increased annual hours of bright sunlight at residence, increasing actinic skin damage, and previous

non-melanoma skin cancer. The same study found no increased risk for CMM or any histogenetic type of CMM with increasing total outdoor exposure in summer, as measured by mean weekly total occupational or recreational sun exposure averaged over working life.

9.2 In Queensland, Australia, elevated CMM risks were associated with increasing estimated total hours of sun exposure after 10 years of age, while controlling for exact age, presence of nevi on arms, hair color, and sunburn propensity. The confidence intervals for intermediate and higher levels of exposure included unity.

9.3 In Western Canada, an analysis of total sun exposure showed some increased risks in higher exposure groups compared with the lowest exposure group, but none were statistically significant nor was there a significant trend of increasing risk.

9.4 Studies which have evaluted the association of CMM with a measure of delivered dose of UVR (presumably modified by an individual's susceptibility to solar radiation) have shown an increased CMM risk associated with increased sun damage to the skin, even when a consistent association with cumulative exposure (as assessed by questionnaire) was not found.

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CHAPTER 10

SKIN PIGMENTATION AS A RISK FACTOR

Skin color plays an important role in the determination of ultraviolet radiation (UVR) effects such as erythema or sunburn. Resistance to these effects is conferred by racially determined pigmentation of the skin or by temporary pigmentation from preventive tanning, which increases melanin and thickens the stratum corneum and epidermis in areas of sun-exposed skin. Fair-skinned people require three to five times less UVR to induce erythema than do those with moderately pigmented skin, and up to 30 times less than darkly pigmented people (Parrish et al. 1983). Melanin also plays a protective role in the development of basal and squamous cell carcinomas of the skin. This is seen in the consistent negative association between these effects and skin pigmentation, although the precise mechanisms of protection are not known.

There are also marked differences in cutaneous malignant melanoma (CMM) incidence by skin color, with the disease rates varying by the degree of pigmentation. Epidemiologic evidence from several countries is consistent and shows a clear-cut difference between white and non-white races in the incidence of melanoma. The study of pigmentation differences and melanoma incidence within the Caucasian race provides an opportunity to investigate whether the protective effects of increased pigmentation also moderate the risk of malignant melanoma. Increased pigmentation is known to protect individuals from acute effects on skin exposed to UVR, and results showing similar protective effects against melanoma may provide indirect evidence about the role of sunlight or UVR in the etiology of melanoma.

This chapter reviews studies of racial differences in melanoma incidence from many countries as well as investigations of differences within the Caucasian or white population. The latter studies go beyond the basic white/non-white differences in pigmentation and do not assume that all white skin has the same amount (or lack) of protective melanin. Several epidemiologic measures have been used to define skin differences within Caucasian populations which may alter the susceptibility to melanoma in the presence of a causal factor such as sunlight or UVR exposure. These measures include skin color, hair color, eye color, freckling or a tendency to freckle upon sun exposure, skin reaction to sun (tendency to sunburn, ability to tan), and ethnicity (used to estimate skin color because of the genetic dominance of certain pigmentation characteristics).

RACIAL DIFFERENCES

The International Agency for Research on Cancer (IARC 1976) collected and published data on cancer incidence on five continents, including both age-specific and age-standardized incidence rates from 59 population-based cancer registries in 27 countries. Crombie (1979a) analyzed the IARC data on malignant melanoma using incidence rates standardized to the 1950 world population (Segi 1960) and found a statistically significant three-fold

increase in the mean CMM incidence in whites over that of non-whites (Table 10-1). Crombie's analysis assigns populations from the IARC data into white and non-white categories in two ways: seven of the registries are separated by racial group (Crombie treats each of these as an independent population) and the other registries are assigned the white/non-white status presumably by using the information on racial and ethnic background provided to IARC by each registry (IARC 1976). Crombie recognized that the category "non-white" is not completely satisfactory because of the heterogeneous nature of the racial groups included, but the small numbers of melanoma cases for some of the non-white populations made it impossible to analyze them as separate racial entities. For further analysis by race, the registries were treated as samples from the same population and were grouped to obtain age-specific incidence rates for the composite population. The lowest melanoma incidence rates were found among Asian populations, while rates among blacks showed much variation (lower in North America, higher in Africa) (Crombie 1979a). Malignant melanoma in Africans was mostly on the lower limb, frequently on the foot (Crombie 1979a; Kiryabwire et al. 1968; Malik et al. 1974), and may account for the excess incidence in Africans over the Asian groups (see Chapters 5 and 13 for more detail on CMM variation by site).

A study of hospital records in South Africa (Rippey and Rippey 1984) for the years 1959 to 1970 found that CMM was almost six times more common in whites than in blacks. For both sexes combined, the incidence per 100,000 was 6.2 for whites and 1.1 for blacks. By sex, the difference between races remained, but the ratio of white to black was about 13 to 1 for males (5.3/0.4), whereas for females it was only about 4 to 1 (7.0/1.7). These racial differences are consistent with patterns elsewhere in the world, but the incidence rates may not be representative of the true South African rates, particularly for blacks, since there are no reliable population estimates for this racial group.

In 1968, Kiryabwire et al. reported an incidence rate of 1.5/100,000 for melanoma in Uganda based on 152 cases diagnosed during 1963 to 1966. These cases were likely to be black because the author stated in the introduction that CMM is not just "a condition of the white races" and that he would refute this "impression on world-wide statistical analysis."

Another African study reported on a population of mixed races in Sudan (Malik et al. 1974) based on a review of records from two laboratories providing histopathology services for the country. The population was reported to be Arabic, Hamitic, and Semitic, with a variable admixture of Negroid blood. The southern Sudan, where the population is almost exclusively Negroid, had a lower proportion of CMM diagnoses than in other parts of the Sudan. Fifty-two percent of the melanomas occurred in patients from two provinces in the western part of northern Sudan, an area which ethnically is "a mixture of Arabs and Negroids with some preponderance of the latter." CMM incidence rates were not calculated due to factors prevalent in many third world countries, e.g., disparity in availability of medical services and diagnostic facilities in different parts of the country, inadequate health certification, and failure to seek medical attention due to ignorance or shyness in segments of the population.

TABLE 10-1

INCIDENCE OF MALIGNANT MELANOMA FROM 59 POPULATION-BASED CANCER REGISTRIES ON FIVE CONTINENTS BY WHITE/NON-WHITE STATUS* STANDARDIZED TO 1950 WORLD POPULATION

	White	Non-White
	Incidence per 100,000	
Both sexes	2.9	0.8
Male	2.6	0.8
Female	3.2	0.8
Number of registry populations	48	26

* The years of reporting varied by registry but were within the range 1960-1973, with the most common reporting period being 5 years.

Source: Segi (1960).

In each of the three previously mentioned studies in Africa, i.e., those in South Africa (Rippey and Rippey 1984), Uganda (Kiryabwire et al. 1968), and Sudan (Malik et al. 1984), over 60 percent of all malignant melanomas were on the foot, usually on the sole, a less pigmented area of the body in blacks. This factor is discussed in more detail in Chapter 5, but the high occurrence of CMM on the foot in blacks (including American blacks) may indicate the presence of other risk factors in blacks, which may or may not be UV-R- or pigment-related.

Data from the U.S. National Cancer Institute (NCI) on incidence of malignant melanoma by white/non-white racial groups show more striking differences than results from the IARC analyses. The NCI's Surveillance, Epidemiology, and End Results (SEER) Program reported cancer incidence for 1973 to 1983 from 10 cancer registries (5 entire states and 28 counties representing 5 major metropolitan areas within 5 other states) (Sondik et al. 1985). In 1983, the age-adjusted incidence rates (1970 U.S. standard population) were 9.6/100,000 in white males and 0.5/100,000 in black males, with a white:black ratio of 19; in white women, the age-adjusted incidence rate was 8.0/100,000 compared to 0.81/100,000 in black women, with a white:black ratio of 10. Over the period 1974 to 1983, incidence remained stable in blacks, while rates increased by 40.5 percent in white males, and by 27.9 percent in white females.

Other U.S. data also show a much higher proportion of malignant melanoma in whites than in other racial groups. A 1980 survey of 614 hospitals studied 4,545 melanoma patients (representing one-third of the total estimated 14,100 cases diagnosed in 1980) and found that 98 percent of the patients were white and less than 1 percent (37 patients) were black (Balch et al. 1984). A retrospective review of melanoma cases at the Duke University Comprehensive Cancer Center during 1972 to 1981 showed similar results. Of the 2,612 patients with melanoma during this period, only 31 (1 percent) were black (Reintgen et al. 1982, 1983). This does not represent a true proportion of black melanoma cases in this geographic area since the Duke Center receives many referral patients from various geographic areas. However, the authors adjusted the melanoma case ratio (83 whites:1 black) by the white-to-black patient ratio at Duke (4:1) and found that the estimated ratio of white-to-black melanoma cases remained high: 20 to 1.

Both New Mexico and Hawaii have particularly high CMM incidence rates in their white populations, showing a significant excess of cases in whites over other races. A study of malignant melanoma from the New Mexico Tumor Registry during 1969 to 1977 showed incidence rates for non-Hispanic whites of 8.7 and 9.0/100,000 in non-Hispanic white males and females, respectively (Pathak et al. 1982). These rates exceeded the total U.S. white rates from comparable years based on data from the Third National Cancer Survey (TNCS) and SEER, and were approximately six times higher than the rates for other ethnic groups in New Mexico (Hispanic, American Indian, and black). The TNCS and SEER results are not fully comparable to the New Mexico results because of the inclusion of Hispanics in the "white" racial group.

Hawaiian Caucasians also have a high incidence of malignant melanoma. For 1968 to 1972, IARC (1976) shows age-adjusted (1950 world standard) incidence

of 6.8 per 100,000 for Caucasian males and 5.7 for Caucasian females, while the rates for the remaining population of Hawaii were less than 1.0. Hinds and Kolonel (1980, 1983) analyzed data on malignant melanoma from the Hawaii Tumor Registry and showed an excess of cases in the Caucasian population relative to other Hawaiians as well as a steady increase in the rate of melanoma diagnosed among whites during the study period, 1960 to 1980. Over this time period, 80 percent of the diagnosed malignant melanoma patients were white, even though the white population constituted only 34 percent of the state's population in 1970. Also during this time period, the incidence rates for whites more than tripled (for 1978 to 1980, 24.0 and 19.5/100,00 for males and females, respectively), while the incidence among non-whites remained fairly stable.

A similar situation exists in New Zealand, the country with the second highest incidence of melanoma in the world. Moss (1984) reviewed records from the National Cancer Registry of New Zealand for the years 1963-1981. During this time, the non-Caucasian population of New Zealand (Maoris and Polynesians) had a CMM incidence rate of 2.9/100,000, while the incidence rate in the Caucasian population was 16.9/100,000, a nearly sixfold difference.

Israel has maintained a central cancer registry since 1960 and reports differences in CMM incidence between European-born (including American-born) immigrants and African- or Asian-born immigrants. Movshovitz and Modan (1973) reported that among all foreign-born residents of Israel, CMM incidence was much higher for European-born than for Asian/African-born, based on data from 1961 to 1967. Anaise et al. (1978) analyzed all melanoma cases in the total Israeli Jewish population during 1960 to 1972 and found incidence rates of 3.4 among European-born, 0.44 among Asian-born, and 0.27 among African-born (rates per 100,000). These differences by country of origin may relate more to ethnicity and skin color variation within Caucasians than to actual racial (Caucasian/Negroid) differences, due to the racially heterogeneous population immigrating from Africa.

DIFFERENCES WITHIN CAUCASIANS

While it has been shown that malignant melanoma is more prevalent in the white or Caucasian population than in non-white populations, there are differences in melanoma incidence within the white population which have led researchers to search for more definitive constitutional risk factors than white race. The assumption that all white populations have the same risk of melanoma may lead to errors in the extrapolation of study results to other white populations. For example, Lee and Issenberg (1972) compared CMM incidence and mortality rates from England and Wales with those from Sweden to determine whether the different latitudes of two countries (and indirectly, the intensity of solar radiation) might be associated with differences in melanoma as found in earlier studies (e.g., Lancaster 1956). The authors assumed that two white populations with similar latitude might be expected to have similar skin cancer incidence rates if latitude was related to skin cancer, and that a lower latitude would result in an increased incidence rate. In fact, Sweden's rates were higher than those for England and Wales, although Sweden is situated at a higher latitude. This might occur, however,

if the white populations were not comparable with respect to CMM risk factors, such as tanning ability or sun exposure habits. The authors stated that their results suggested genetic or occupational effects. This genetic contribution to CMM risk may be further investigated by studying skin color differences within the Caucasian population.

Many epidemiologic studies have been conducted to further identify risk factors associated with increased incidence of CMM in Caucasian populations. The following are the variables most frequently investigated for pigmentation differences which may alter susceptibility to CMM within white populations:

- Skin color--self-assessed or assessed by an interviewer, either by observation or by comparison with a color chart
- Hair color--in childhood or adolescence, or at study time
- Eye color
- Freckles or tendency to freckle upon sun exposure
- Reaction to sun--tendency to sunburn, ability to tan
- Ethnicity

Most of the above risk factors are interrelated, requiring controlled analyses to evaluate their independent effects on risk of CMM. Table 10-2 summarizes these measures of skin pigmentation according to the studies which investigated each of them. The study findings associated with these pigmentation variables are discussed in the following sections.

Skin Color

As seen in Table 10-2, skin color was a significant risk factor in all of the studies that considered it. Using all major hospitals in Sydney, Australia, Lancaster and Nelson (1957) age- and sex- matched each of 173 melanoma patients with two control patients (one non-melanoma skin cancer and one non-skin cancer). All patients were of European descent. Skin color was determined "subjectively" by the researchers and classified as fair, medium, or olive. The authors reported a larger proportion of fair-skinned persons in the melanoma and non-melanoma skin cancer groups than in the other cancer controls (77, 72, and 63 percent, respectively).

Gellin et al. (1969), in an age- and sex-matched case-control study of 79 cases and 1,037 controls at the New York University Medical Center, determined that a significantly higher proportion of cases than controls (50 percent vs. 37 percent) had a fair complexion ($p \leq 0.05$) based on self-assessment. When analyzed by sex, the greatest difference in the proportion of those with fair complexions was between female cases and controls (61 percent vs. 41 percent, $p \leq 0.05$). Although slightly more male cases than controls had fair

TABLE 10-2

MALIGNANT MELANOMA RISK FACTORS BY MEASURES OF SKIN PIGMENTATION WITHIN THE CAUCASIAN POPULATION

Study Reference	Measures of Skin Pigmentation Within Caucasian Population					
	Skin Color	Hair Color	Eye Color	Freckling	Reaction to Sun (Tanning/ Sunburn)	Ethnicity
Lancaster and Nelson 1957	+	+	+		+	
Gellin et al. 1969	+	+	+		+/-	
Lane-Brown et al. 1971						+
IARC 1976						+
MacDonald 1976						+
Klepp and Magnus 1979		-	-	+	+	
MacKie and Aitchison 1982					-	
Beral et al. 1983	+	+	-	+	+	
Hinds and Kolonel 1983						+
Lew et al. 1983		-	-		+	
Elwood et al. 1984	+	+		+	+	+
Holman and Armstrong 1984b	+	+	+	+	+	+
Graham et al. 1985	+	+	+		+	+

Legend:

+ = Significant risk factor
- = Not significant risk factor
Blank = Not included in study

complexions (36 percent vs. 32 percent), the difference was not statistically significant.

Beral et-al. (1983) age-matched 287 white female melanoma cases (18-54 years old) treated in Sydney's Melanoma Clinic during 1975 to 1980 with 574 white female controls and found fair skin to be associated with a twofold increase in relative risk (RR) of CMM (RR=1.9, 95% C.I. 1.38-2.50) as compared to medium or olive skin, after adjusting for hair color. Fair skin was a risk factor independent of hair and eye color, although its importance depended to a certain extent on the associated hair color. For those with red hair, fair skin had only a small additional effect, increasing the risk by 39 percent; for those with blonde hair, the risk was increased by 80 percent; but for those with black or brown hair, the risk was increased by 108 percent.

A case-control study by Elwood et al. (1984) in Western Canada found a relative risk of 2.4 ($p \leq 0.05$) for light inner arm skin color as opposed to dark, based on data from 595 melanoma cases and 595 population-based controls (matched on age, sex, and province of residence).

A threefold greater melanoma risk (as indicated by an elevated odds ratio [OR]) was observed for those with the lightest skin relative to those with darkest pigmentation (OR=3.07, 95% C.I. 1.47-6.39), as well as a significant ($p \leq 0.1$) linear trend in odds ratios among the four skin pigmentation groups.

In a study based on 499 case-control pairs (matched on sex, 5-year birth period, and area of residence) in Western Australia, Holman and Armstrong (1984b) measured skin color reflectance of the left upper inner arm as an indicator of skin color. For each histogenetic type (HMF, SSM, UCM, or NM), elevated odds ratios were associated with fair skin color of the upper inner arm relative to dark skin.

A case-control study (404 cases, 521 unmatched controls) of CMM patients at Roswell Park Institute (NY) during 1974 to 1980 (Graham et al. 1985) consistently found increased risk with increasing fairness in skin, hair, and eye color. Using self-assessment of fair, medium, and dark, both male and female cases had elevated risks for fair as opposed to those with dark or medium complexions, and there were significantly elevated odds ratios for fair complexions in both males and females ($p \leq 0.01$).

Hair and Eye Color

Six of eight studies found hair and eye color to be significant risk factors for melanoma within Caucasian populations. Regardless of eye color, Beral et al. (1983) found that red hair was associated with a three- or fourfold increase in melanoma risk in women. Individuals with fair skin and red hair had a slightly higher risk (RR=4.4) than those with dark skin and red hair (RR=3.2). All risk analyses were conducted with reference to women with brown or black hair and medium or olive complexions. Blonde hair was associated with a relative risk of 2.7 in fair-skinned women and 1.5 in dark-skinned women. Significantly elevated risks for red hair in childhood (RR=3.0, 95% CI 1.95-4.73) and for blonde hair in childhood (RR=1.6, 95% CI

TABLE 10-3

REPORTED HAIR COLOR (AT AGE 5), SKIN COLOR, AND EYE COLOR IN CASES AND CONTROLS, AND RELATIVE RISK ASSOCIATED WITH EACH COMBINATION

(Data missing for three cases and six controls)

Hair color	Skin color	Eye color	Cases	Controls	Relative risk a
Red	Fair	Green or brown	22	18	4.5 b
Red	Fair	Blue	17	15	4.2 b
Red	Medium or olive	Green or brown	10	11	3.4 b
Red	Medium or olive	Blue	2	3	2.5
Blonde	Fair	Green or brown	33	48	2.6 b
Blonde	Fair	Blue	48	63	2.8 b
Blonde	Medium or olive	Green or brown	23	72	1.2 b
Blonde	Medium or olive	Blue	27	51	2.0 c
Brown or black	Fair	Green or brown	23	56	1.9 c
Brown or black	Fair	Blue	20	30	2.5 b
Brown or black	Medium or olive	Green or brown	41	151	1.0
Brown or black	Medium or olive	Blue	13	50	1.0

a Relative to those with brown or black hair and medium or olive skin.

b $p \leq 0.01$.

c Differs significantly from 1.0, $p \leq 0.05$.

Source: Beral et al. (1983).

1.15-2.14) were also noted. Results from analyses of combinations of hair, eye, and skin color show significant relative risks for all women with red or blonde hair or fair skin (Table 10-3). Eye color had no independent effect on risk.

Klepp and Magnus (1979) studied 78 Norwegian CMM cases and 131 unmatched "other" cancer controls in 1974 and 1975 and found no difference between cases and controls with respect to hair and eye color. As mentioned by the authors, these results may be explained by Norway's very homogeneous population of fair-skinned individuals; what may be recorded in other more mixed populations as fair skin or light brown hair may be assessed as "dark" by the predominantly blue-eyed and blonde-haired Norwegians. It is also unlikely that there was sufficient power to detect small differences in a homogeneous population based on the small numbers of cases and controls.

Lew et al. (1983) also found no difference in hair and eye color between 111 CMM cases and 107 controls in Massachusetts. This may have resulted from a bias in the method of control selection. Each patient was to provide two to three friends of the same age (+5 years) and sex for interview; however, 46 cases provided 0 controls, 30 provided 1 each, 28 provided 2 each, and 7 provided 3 each. With no more information on these populations (the authors state that sex and median age were comparable between cases and controls), it is impossible to know what biases may have been introduced.

Lancaster and Nelson (1957), in their study of 173 melanoma cases with age- and sex-matched non-melanoma skin cancer controls and other cancer controls (173 of each), found an excess of red-haired and fair-haired melanoma patients (42 percent) when compared with the non-melanoma skin cancer (36 percent) and other cancer (29 percent) patients. They also found more light-eyed (blue or green-gray) patients among the melanoma and non-melanoma skin cancer patients than among the other cancer controls (61, 66, and 46 percent, respectively).

Gellin et al. (1969) found similar significant differences between their 79 melanoma cases and 1,037 unmatched controls in eye color (55 percent of cases vs. 35 percent of controls had blue or green/gray eyes) and in hair color (26 percent of cases vs. 9 percent of controls had white, blonde, or red hair.

In a Canadian population of 595 white melanoma cases and 595 matched (age, sex, and province of residence) controls, Elwood et al. (1984) found the highest relative risks associated with hair color: 7.1 (95% C.I. 2.6-19.2) for blonde hair in childhood and 3.7 (95% C.I. 1.8-7.7) for red hair as compared with black hair in childhood, adjusting for skin and eye color. Eye color was not independently associated with risk of CMM (adjusting for hair and skin color); this finding is consistent with that of Beral et al. (1983) and Klepp and Magnus (1979). The authors stated that of all the pigmentation variables examined (hair color, skin color of upper inner arm, eye color, and freckles in adolescence), hair color showed the strongest association with an increased risk of malignant melanoma.

Results in an Australian study of 511 melanoma patients and 511 controls matched on sex, 5-year birth period, and area of residence (Holman and Armstrong 1984b) also showed positive results for hair color, while eye color did not contribute to CMM risk after controlling for other pigmentary characteristics. Persons with red hair had nearly twice the risk of those with dark hair (OR=1.89, 95% C.I. 0.99-3.59), while persons with blonde or light brown hair showed intermediate, but significant, levels of risk (OR=1.56 and 1.24, respectively); these findings were of borderline significance. When risk factors were examined by histogenetic type of melanoma, hair color was found to be related to each of the four types (HMFM, SSM, UCM, or NM), while eye color was related to only SSM and NM.

The results of Graham et al. (1985), who used data on 404 melanoma patients and 521 unmatched hospital controls in New York State, indicated there were excesses of CMM for both males and females with blue eyes and fair complexions who had blonde or red hair in childhood. When hair, skin, and eye color were analyzed together, the odds of melanoma increased as the "lightness in tone" increased. Red hair showed significantly elevated odds ratios for males (OR=2.45, $p \leq 0.05$), and both red and blonde hair showed positive associations with CMM in females (OR=3.99, $p \leq 0.10$, and 2.14, $p \leq 0.01$, respectively). Eye color showed similar results; males with blue eyes and females with blue or blue-green/gray eyes all showed significantly elevated odds ratios relative to persons with brown eyes.

Freckling

Of the epidemiologic studies of melanoma reviewed, only four investigated freckling as a risk factor and all found a positive association of CMM incidence with freckling. Although these studies defined this risk factor somewhat differently, their results were consistent regardless of how freckling was ascertained.

Using data on 78 cases and 131 unmatched, non-skin cancer controls, Klepp and Magnus (1979) found significant odds ratios for persons who responded positively to the question: "Do you have freckles, or do you freckle easily?" The risks were particularly high in those aged 20-49 years (RR=3.94 for males and 4.88 for females). In the 50-years-and-older group, only females maintained an elevated risk (RR=2.06).

In a study of CMM in white Australian women (287 cases and 574 age-matched controls), Beral et al. (1983) found a crude odds ratio of 1.9 for those who reported that they usually freckled after a 30-minute exposure to midday summer sun, relative to those who sometimes or never freckled. After adjustment for hair and skin color, however, the odds ratio associated with freckling was of borderline significance (OR=1.4, 95% C.I. 1.00-1.95).

Elwood et al. (1984b) identified freckles as an important host factor in the development of malignant melanoma, based on analysis of data on 595 age-, sex-, and residence-matched case-control pairs. The risk associated with heavy freckling in childhood and adolescence (RR=2.6) remained significant (RR=2.1, $p \leq 0.001$) even after adjustment for other pigmentation factors such as hair, skin and eye color, sun reaction, and ethnic origin.

Holman and Armstrong (1984b) questioned study subjects (511 age-, sex-, and residence-matched case-control pairs) regarding their reactions to chronic sun exposure and found a significantly elevated risk for those who only freckled or never tanned relative to those who tanned deeply (OR=3.53, 95% C.I. 1.82-6.84). After controlling for other pigmentary characteristics (acute reaction to sun, hair, skin and eye color), the risk associated with inability to tan remained significant (OR=2.44, 95% C.I. 1.19-5.02).

Reaction to Sun Exposure

Nine of the studies reviewed assessed reaction to sun exposure. Most studies reported positive associations; however, one (MacKie and Aitchison 1982) reported no significant elevation in risk for melanoma in the sun-sensitive groups, and another (Gellin et al. 1969) reported no association of CMM and sun-sensitivity in males.

In MacKie and Aitchison's study, the skin-types included four categories ranging from "always burns, never tans" (Type I) to "always tans, never burns" (Type IV). No significant differences between CMM patients and controls were found, either as a group or separately by sex. However, this study had a small sample size (113 cases and 113 controls) and was conducted within a relatively homogeneous population (Western Scotland) where 75 percent of the cases and 70 percent of the controls were skin types I or II. These facts should be considered in the interpretation of MacKie and Aitchison's results; the lack of a significant finding does not preclude a potential relationship between severe reaction to sun exposure and CMM.

In a U.S. study of 79 CMM cases and 1,037 unmatched controls, Gellin et al. (1969) found a significant difference only for females. Fifty-six percent of the cases and 38 percent of controls said they sunburned easily; conversely, 9 percent of cases and 25 percent of controls said they tanned easily. Gellin et al. (1969) reported a higher proportion of male controls (33 percent) than male cases (21 percent) who said they sunburn easily and a lower proportion of controls who tan easily (25 percent vs. 41 percent). No explanation was provided for this result based on the analysis of data on 34 male cases and 405 male controls with non-tumor skin conditions, although the result may be due to control selection of only patients with other (non-tumor) skin conditions if those conditions were related to the factors under study, such as reaction to sun exposure and skin type.

In a hospital-based, individually matched case-control study in Sydney, Australia, Lancaster and Nelson (1957) found that 62 percent of 173 melanoma patients reported that they burn easily with sun exposure, as compared with 54 percent of the non-melanoma skin cancer controls and only 36 percent of the other cancer controls.

Responses to the question, "How much sun do you tolerate?" in a Norwegian case-control study of CMM (78 cases and 131 unmatched controls) showed elevated risks for those who answered "very little" or "not very much" versus those who replied "quite a lot" or "very much" in three of the four age-sex groups (Klepp and Magnus 1979). Relative risks for cases were 6.08 for males

20-49 years, 2.42 for females 20-49 years, and 2.00 for females 50 years and over. Only males 50 and over did not have an increased risk associated with low sun tolerance.

Beral et al. (1983) found a slightly elevated but significant relative risk for cases (RR=1.4) who reported "blistering or peeling" after a 30-minute exposure to midday summer sun with no tan versus those reporting milder reactions. After adjustment for skin and hair color, however, the relative risk for this factor was not significant (RR=1.1).

Results from Lew et al. (1983), based on data from 111 melanoma cases and 107 unmatched controls, should be interpreted with caution due to the potential biases from their method of control selection described earlier; their findings, however, are in agreement with results from several other studies--the risk of melanoma was significantly increased among those who had difficulty tanning as an adolescent relative to those who did not. Elwood et al.'s study in Canada (1984) also showed a significant risk (RR=2.3) for those who sunburned and rarely tanned. The risk remained significantly elevated even after adjustment for other significant pigmentation characteristics such as skin and hair color, freckling, and ethnicity (RR=1.7, $p \leq 0.01$).

Holman and Armstrong (1984b) separated burning and tanning into acute (blister) and chronic (freckle, no tan) reactions to sunlight and found these two sun-sensitive reactions to be the most significant of the pigmentary risk factors for melanoma in their Australian case-control study (511 matched pairs), even after adjustment for hair, skin, and eye color. Burning and tanning were also analyzed separately by Graham et al. (1985), who showed a twofold significant odds for those who burned or freckled versus those who did not (OR=1.97 for males, 2.02 for females), and a twofold risk (OR=1.95) for females who answered "no" to tanning versus those who responded affirmatively (for males, the increased risk of 1.65 was not statistically significant).

Hereditary Differences

Ethnic background within the Caucasian population has a major role in skin pigmentation and, as such, has been analyzed to identify the presence of a relationship with melanoma incidence. Some early studies analyzed ethnicity using descriptive techniques on incidence data, finding lower rates of CMM for ethnic groups having darker skin tones than other Caucasian ethnic groups, e.g., Spanish or Portuguese.

IARC (1976) published melanoma incidence rates from five continents. These include data on populations from New Mexico (1969-1972) and El Paso, Texas (1968-1971), separated into Spanish-origin whites and other whites. The following age-standardized (1950 world population) CMM incidence rates were considerably higher for non-Spanish whites than for Spanish whites in each area:

		Age-Standardized Incidence/100,000	
		Male	Female
New Mexico:	Spanish	0.8	0.9
	Other white	4.8	5.3
El Paso, Texas:	Spanish	0.0	1.0
	Other white	3.8	4.8

MacDonald (1976) found similar results when she analyzed 23 years of melanoma incidence data from six major regions in Texas (56 counties). Of the 2,328 cases of melanoma, 91 percent occurred among non-Spanish whites, and only 8 percent among whites with Spanish surnames.

In Hawaii, a state with very high CMM incidence in whites, Hinds and Kolonel (1983) attempted to examine differences in melanoma between the non-Portuguese white and Portuguese white sectors of the population using 1960-1980 data from the Hawaii Tumor Registry. An estimated 10 percent of Hawaiian whites were of Portuguese ancestry, but no exact population figures were available. Analysis of proportional cancer incidence during the study period showed that melanoma accounted for only 0.5 percent of all cancer cases in Portuguese men and 0.2 percent in Portuguese women. In contrast, CMM accounted for 4.7 percent of cancer cases in non-Portuguese white men and 3.1 percent in non-Portuguese white women.

In a hospital interview study of total skin cancers in Sydney, Australia, Lane-Brown et al. (1971) used surnames and interview questions to identify ethnic background (Irish as well as Scottish and Welsh Celtic names). The study compared proportions of persons half or more Celtic (Irish, Scottish, and Welsh) between different hospital populations. The melanoma and other skin cancer groups each showed a higher proportion of persons with Celtic heritage than those groups without skin cancer. A random sample of 2,607 names drawn from the Sydney telephone directory resulted in only 26 percent Celtic names, a proportion similar to that in the non-skin cancer hospital groups. In summary, this showed that Celtic heritage was associated with higher proportions of patients diagnosed with basal and squamous cell carcinomas and malignant melanomas than patients hospitalized for reasons other than skin cancer.

Three recent case-control studies (Canada, Western Australia, and New York State) found that ethnicity was a significant risk factor for CMM. In Canada, Elwood et al. (1984) showed a significantly low risk (OR=0.5) among study subjects from Eastern or Southern European background compared with those of English origin. This odds ratio remained significant ($p \leq 0.05$) even after adjustment for other risk factors such as pigmentation characteristics and freckling. Likewise, Holman and Armstrong (1984b) found that having two or more Southern European grandparents resulted in a significantly lower risk of melanoma. When the analysis was done controlling for age at arrival in Australia and for pigmentary characteristics, the strength of this protective effect was reduced to a barely significant level. Graham et al. (1985) found

a significantly increased risk only for females (OR=2.26, 95% C.I. 1.5-3.5) with an ethnic derivation from Northern European countries (Scandinavia, Poland, Germany, France, British Isles) when compared to women from other ethnic backgrounds.

FINDINGS

The findings presented below are based on the review of epidemiologic studies in this chapter:

10.1 Epidemiologic studies have shown that Caucasian populations have much higher rates of CMM incidence and mortality than black populations. Based on 1983 SEER data, white:black ratios were 19:1 and 8:1 in males and females, respectively.

10.2 Differences in CMM incidence and mortality have also been observed between Caucasians and other races. For example, whites in New Zealand experience much higher incidence rates than New Zealand Maoris and Polynesians. Likewise, American Indians experience much lower rates of CMM than American whites.

10.3 Within the Caucasian race, differences in rates of CMM occur according to country of origin. CMM incidence rates for Hispanic whites in New Mexico, for example, are much lower than those for non-Hispanic whites; individuals from the Mediterranean countries in southern Europe tend to have lower rates than Caucasians from northern Europe; individuals of Celtic origin in Australia tend to have higher rates than non-Celtic individuals. Variation in the incidence of CMM within the Caucasian race is commonly thought to be a function of variation in genetically-determined pigmentary traits across ethnic groups.

10.4 Numerous epidemiologic studies have focused on identification of important pigmentary characteristics in the etiology of CMM. The following associations were identified in this chapter:

a) Skin color--fair complexions relative to dark complexions were associated with elevated risks of CMM in all studies reviewed.

b) Hair and eye color--red and blonde hair in childhood relative to dark hair were associated with increased risk of CMM in most studies. Blue eyes were an independent risk factor in only one of four well-controlled epidemiologic studies; however, this could be due to the homogeneous nature of most of the study populations.

c) Freckling--those who freckled readily were at consistently elevated CMM risk relative to other individuals.

d) Reaction to sun exposure--individuals who usually burned and were unable to tan were at significantly higher risk of CMM than those who tanned well in most studies reviewed.

10.5 Over the period 1974-1983, incidence rates remained stable in blacks while rates increased by 40.5 percent in white males and 27.9 percent in white females in the U.S.

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CHAPTER 11

CORRELATIONS WITH SOCIOECONOMIC STATUS AND OCCUPATIONAL FACTORS

INTRODUCTION

In this chapter, three potential risk factors for cutaneous malignant melanoma (CMM) are discussed. First, the epidemiologic studies which have examined trends in CMM according to socioeconomic status and general occupational classifications are reviewed. Second, studies on the occurrence of CMM among workers exposed to chemicals or radiation are described. Third, the epidemiologic data on the development of CMM among indoor workers exposed to fluorescent lighting are reviewed. Although these areas are addressed separately, they all focus on the potential links between CMM and occupation.

MELANOMA TRENDS ACCORDING TO SOCIOECONOMIC STATUS

Potential relationships between socioeconomic status and CMM incidence and mortality have been analyzed in several epidemiologic studies. Variables used to reflect socioeconomic status have included occupational groups (e.g., professional vs. laborer), types of work (e.g., indoor office vs. outdoor), and general indicators such as education and income. The results of these studies have not produced a clear understanding of the relationship of CMM to socioeconomic status. Several epidemiologic studies have indicated that CMM incidence and mortality are positively related to socioeconomic status (Holman et al. 1980; Lee and Strickland 1980; MacKie and Aitchison 1982; Cooke et al. 1984; Aquavella et al. 1983; Teppo et al. 1980). While some studies have shown that outdoor workers do not have an elevated risk of melanoma compared to office workers (Lee and Strickland 1980; Cooke et al. 1984), other studies have indicated that outdoor workers have slightly elevated CMM risks for normally uncovered parts of the body such as the face and neck (Beral and Robinson 1981; Vagero et al. 1986). Professional and administrative type office workers, but not other indoor workers, have been shown to be at elevated CMM risk compared to outdoor workers (Lee and Strickland 1980; Holman et al. 1980) and to have an elevated risk of CMM on normally covered parts of the body (Beral and Robinson 1981; Vagero et al. 1986).

One epidemiologic study which specifically examined trends in melanoma by socioeconomic status was conducted by Lee and Strickland (1980). Data on CMM incidence by occupation were obtained for 1968 to 1970 from the Supplement on Cancer to the Registrar General's Statistical Review of England and Wales. Mortality data for England and Wales were obtained from the Occupational Mortality Decennial Supplements for the periods 1949-1953, 1959-1963, and 1970-1972. Standardized mortality ratios (SMRs) were based on census population statistics corresponding to 1951, 1961, and 1971. Because there were no population data for the British cancer registration data, the incidence data were analyzed by proportional ratios which compared the

proportion of incident melanomas to all cancers for each occupational group. The authors noted that the ratios were susceptible to distortion by large risk differences between occupational groups (e.g., lung cancer), but stressed that they may be useful in conjunction with other information. Social class categories consisted of I (professional), II (intermediate), III (skilled workers including manual, IIIM, and non-manual, IIIN), IV (semi-skilled), and V (unskilled).

Lee and Strickland (1980) observed a general trend of increasing SMRs for CMM with increasing social class for males from 1949 to 1972 (Table 11-1). A comparison of SMRs according to finer occupational groupings (as outlined in Table 11-2) showed that outdoor workers (e.g., farmers and construction workers) did not have higher SMRs than indoor workers such as warehousemen, shopkeepers, or engineers, and had lower SMRs than professional, technical, administrative, and managerial workers. A similar comparison using the CMM incidence data also indicated higher standardized proportional registration ratios among professional and administrative workers than among construction workers, engineers, and warehousemen. Lee and Strickland (1980) concluded that their results suggested a relationship between CMM incidence and some feature of life associated with education or economic status. Lee (1982) also noted that these results showed the lack of a marked effect of outdoor occupation on CMM mortality.

A study conducted by Holman et al. (1980) also identified differences in melanoma incidence rates according to social class and occupation. Holman et al. (1980) analyzed melanoma incidence data for 1975 and 1976 obtained from hospital and pathology records in Western Australia. Information on the 120 pre-invasive melanoma (PIM) and 422 invasive malignant melanoma (IMM) cases included occupation and location of usual residence. Social classes were assigned from 1 to 4 based on socioeconomic data for each residential area. As shown in Table 11-3, for IMM cases, the highest incidence rates among males and females occurred in social class 1. Among females, the incidence rates declined with lower social class; the relationship was more complex among males. For PIM, a pattern was not evident. Controlling for country of birth and proximity to sea did not alter the apparent relationship between social class and IMM incidence. Table 11-4 indicates that the highest incidence rates occurred among professional, clerical, sales, administrative, and managerial workers, whereas the lowest rates occurred among laborers, tradesmen, farmers, and fishermen. Holman et al. (1980) observed that although these results were consistent with an association between melanoma incidence and social class, they were not what would have been expected if total exposure to the sun were a predominant causal variable. They hypothesized that the results could be explained if intermittent (e.g., recreational) sun exposure were more likely to induce malignant melanoma than continuous exposure. In addition, differences in host factors and ethnic background by social class could also partially explain these observations.

MacKie and Aitchison (1982) conducted a case-control study on 113 CMM patients presenting with primary CMM in West Scotland from 1978 to 1980 and 113 age- and sex-matched controls. Matched case-control comparisons were analyzed using conditional multiple logistic regression. Information on each

TABLE 11-1

STANDARDIZED MORTALITY RATIOS (AND NUMBERS OF DEATHS) FOR MALIGNANT MELANOMA BY SOCIAL CLASS. REGISTRAR GENERAL'S OCCUPATIONAL MORTALITY REPORTS 1949-72

Socioeconomic Class	Male	Female
V Unskilled	90 (121)	88 (99)
IV Partly skilled	85 (217)	82 (198)
IIIM Skilled manual	92 (485)	103 (524)
IIIN Skilled non-manual	123 (192)	116 (177)
II Intermediate	120 (290)	118 (293)
I Professional	143 (80)	140 (76)

Source: Lee and Strickland (1980).

TABLE 11-2

STANDARDIZED MORTALITY RATIOS (AND NUMBER OF DEATHS) FOR MALIGNANT MELANOMA, 1959-1963 AND 1970-1972, ENGLAND AND WALES, BY SELECTED OCCUPATIONAL ORDERS

Occupation Order a/	1959-1963	1970-1972
Farmers, foresters, fishermen	90 (26)	103 (20)
Construction workers	95 (19)	67 (12)
Engineering trades	87 (68)	87 (64)
Warehousemen, storekeepers, packers	85 (17)	120 (21)
Clerical workers	122 (49)	112 (38)
Sales workers	123 (58)	127 (49)
Administrators and managers	115 (30)	121 (39)
Professional and technical	117 (49)	142 (72)

a/ Selected occupation order for England and Wales.

Source: Lee and Strickland (1980).

TABLE 11-3

AGE-STANDARDIZED INCIDENCE RATES OF PRE-INVASIVE AND INVASIVE MELANOMA IN THE PERTH STATISTICAL DIVISION, DISTRIBUTED BY SOCIAL CLASS

Social Class	Males		Females	
	Number	Incidence a/	Number	Incidence
Pre-Invasive Melanoma				
1	12	5.7	22	9.2
2	8	4.5	16	9.1
3	8	4.8	8	4.6
4	12	9.3	8	5.8
Invasive Malignant Melanoma				
1	63	29.5	58	24.5
2	32	18.8	34	19.5
3	42	23.7	34	17.8
4	26	19.9	24	17.0

a/ Rates per 100,000 per year standardized to the age distribution of the total population in Western Australia in 1976.

Source: Holman et al. (1980).

TABLE 11-4

AGE-STANDARDIZED INCIDENCE RATES OF INVASIVE MELANOMA IN MEN AGED 15 TO 64 YEARS IN THE WORK-FORCE DISTRIBUTED BY OCCUPATION

Occupation	Number a/	Incidence b/
Professional workers	26	39.0
Clerical and sales workers	31	37.3
Administrators and managers	26	35.8
Sport and recreation workers	11	32.1
Transport and communication workers	12	21.9
Labourers and tradesmen	40	18.8
Farmers and fisherman	16	18.5

a/ Excludes three men aged 15-64 years whose occupation could not be ascertained.

b/ Rates per 100,000 per year standardized to the age distribution of all men aged 15 to 64 in Western Australia in 1976.

Source: Holman et al. (1980).

case included positive history of recreational or occupational sun exposure (classified as 16 or more hours outdoors per week), social class (V, unskilled, to I, professional), and history of severe sunburn. When the data were analyzed for males and females combined, melanoma patients were of higher social class and had lower recreational sun exposures than controls ($p<0.05$). Among males only, socioeconomic status and history of severe sunburn were significantly higher for cases compared to controls ($p<0.05$). Occupational exposure was significantly less in males cases than controls ($p<0.05$). Among females, the only significant difference was the higher incidence of severe sunburn among the CMM patient group. MacKie and Aitchison (1982) concluded that melanoma appeared to be more common among higher socioeconomic classes and for male professional or administrative workers. The authors questioned the accuracy of the socioeconomic status data on females since these were classified as those of their husband. They also claimed that their results confirmed the hypothesis that isolated episodes of intense burning sun exposure may be an important factor in melanoma.

In a more recent study, Cooke et al. (1984) examined CMM incidence and mortality data for 1972-1976 and 1973-1976, respectively, for New Zealand non-Maori males aged 25-64. The 501 incident cases and 142 melanoma mortality cases were classified according to occupation and then reclassified by socioeconomic status (based on income and education) and average outdoor occupational exposure (10 or more, 2-10, or 2 or less hours outdoors per week). Standardized incidence and mortality ratios were calculated for four 10-year age groups by indirect standardization based on 1971 and 1976 census data. When analyzed by major occupational group (Table 11-5), the observed number of incident melanoma cases significantly exceeded the expected number ($p<0.001$) for professional/technical and administrative/managerial workers. The observed number of incident melanoma cases was significantly lower than expected ($p<0.001$) for production, transportation, and labor occupational categories. Smaller differences were noted when similar comparisons were made for the mortality data.

Table 11-6 displays the Cooke et al. (1984) age-standardized incidence data reclassified according to anatomical site, socioeconomic status, and outdoor vs. indoor exposure. Trends in the data according to socioeconomic status were apparent for melanomas of each site (e.g., the head and neck, trunk, and upper and lower limbs) among indoor workers. Among outdoor workers, socioeconomic trends were observed only for melanomas of the trunk. This analysis was, however, limited by the small number of registrations in some groups and the fact that 37 of 501 incident cases did not have site information (these cases were spread across all age groups). The authors concluded that the elevated melanoma incidence rates among professional, technical, administrative, and managerial workers appeared to be due to differences in socioeconomic status. They observed that there was no evidence of differences in risk between indoor and outdoor workers of similar socioeconomic classes. Similar results were observed for the mortality data when analyzed according to age, socioeconomic status, and outdoor exposure.

TABLE 11-5

INCIDENT MELANOMA CASES AND MELANOMA DEATHS IN MAJOR GROUPS OF OCCUPATIONS, NON-MAORI MEN AGED 25-64 YEARS, NEW ZEALAND (1972-1976 INCIDENCE, 1973-1976 MORTALITY)

Major Occupational Group	Number of Registrations			Number of Deaths		
	Observed	Expected	O/E[a]	Observed	Expected	O/E[a]
Professional, technical	103	61	1.7 [b]	20	17	1.2
Administrative, managerial	47	29	1.6 [c]	13	9	1.5
Clerical	53	47	1.1	14	14	1.0
Sales	51	55	0.9	19	15	1.2
Service	24	27	0.9	6	8	0.8
Agricultural	64	68	0.9	18	19	0.9
Production, transport, and laboring	159	214	0.7 [b]	52	60	0.9
All specified occupations	501	501	1.0	142	142	1.0

[a] Observed/Expected.

[b] Significantly different from 1.0 ($p<0.001$; two-tailed tests).

[c] Significantly different from 1.0 ($p<0.01$).

Source: Cooke et al. (1984).

TABLE 11-6

MELANOMA INCIDENCE RATES ACCORDING TO SITE, SOCIOECONOMIC STATUS, AND OUTDOOR EXPOSURE: MEN AGED 25-64 YEARS, NEW ZEALAND (1972-1976 INCIDENCE DATA)

Site	Exposure Group	Number of Registrations	Age-Standardized Incidence Rate (per 100,000 persons)				
			Socioeconomic Status				Adjusted for Socioeconomic Status
			1,2	3	4	5,6	
Head, neck	Indoor	43	3.8	2.2	2.3	1.7	2.5
	Outdoor	22	-a	2.2	3.3	2.0	2.6
Trunk	Indoor	123	11	7.7	4.1	5.7	7.0
	Outdoor	48	-	7.3	4.8	3.9	6.2
Upper limbs	Indoor	42	4.9	2.7	1.3	-	2.2
	Outdoor	27	-	3.3	5.4	-	3.7
Lower limbs	Indoor	68	6.4	6.2	2.6	2.1	4.0
	Outdoor	37	-	6.8	4.4	5.1	4.5

a Fewer than five registrations.

Source: Cooke et al. (1984).

Cooke et al. (1984) concluded that their results did not support the hypothesis that recreational sunbathing of inadequately tanned skin is important in the etiology of melanoma. The similarity between outdoor and indoor workers implied that solar exposure was unlikely to have been important. The authors noted, however, that different patterns of recreational sun exposure (e.g., sunny winter holidays or use of sun lotions) may have sufficiently varied within social classes to have overcome the tendency of greater exposure of outdoor workers.

Several case-control studies have also examined trends in melanoma with respect to outdoor occupational exposure patterns. A Norwegian case-control study by Klepp and Magnus (1979) found outdoor work (3-4 hours per day in fresh air at work) to be more prevalent among their 35 male melanoma patients (40 percent) than among their 92 other non-skin cancer, male, non-matched controls from the same hospital (32 percent), but this difference was not statistically significant. Results from another case-control study, conducted by MacKie and Aitchison (1982) in West Scotland, are the reverse of the findings by Klepp and Magnus in Norway (1979). MacKie and Aitchison (1982) showed significantly lower levels of occupational sun exposure ($p<0.05$) among 52 male melanoma patients compared with 52 age-matched male controls. Twenty-three percent of the male cases had positive occupational exposure (16 or more hours outdoors each week) as compared with 48 percent of the controls.

In a much larger case-control study conducted in Western Canada (595 age-, sex-, and residence-matched pairs), Elwood et al. (1985) assessed sun exposure using a lifetime occupational history with information on each job, industry, and usual numbers of outdoor hours per week on the job during the summer and winter seasons. Results of a multiple logistic regression analysis showed a significantly increased relative risk of 1.6 for those with "mild" occupational sun exposure during summer (approximately 1-8 hours/week) compared to those with no occupational sun exposure. After adjustment for host factors (hair color, skin color, history of freckles) and ethnic origin, the relative risk increased slightly to 1.8 (95% C.I. 1.2-2.5) at the same mild exposure level. No increased risk was seen, however, at higher occupational sun exposure levels (8-16 hours/week, 16-32 hours/week, or 32+ hours/week).

The effect of clothing habits during outdoor work on the risk of melanoma was examined by Holman et al. (1986) in a case-control study of CMM cases in Western Australia (507 age-, sex-, and residence-matched pairs). This is one of the few studies which investigated histogenic types of CMM and sunlight exposure patterns. For all melanomas combined and all histogenic types except SSM, the risks were higher if the primary melanoma site was sometimes exposed rather than usually exposed or usually covered while working outdoors. SSM, in contrast, showed a significant increasing linear trend ($p=0.008$) for site exposure as follows: OR=1.0 for "usually covered," OR=2.16 (95% C.I. 1.14-4.10) for "sometimes exposed," and OR=2.43 (95% C.I. 1.18-4.97) for "usually exposed." This result, which contradicts the hypothesis that intermittent exposure is important in the development of SSM, was not specifically discussed by the authors.

In a cohort study using college health records from 50,000 male alumni of Harvard University and the University of Pennsylvania to identify predictive risk factors for fatal skin, blood, and lymphatic cancers, Paffenbarger et al. (1978) found an increased relative risk of melanoma (RR=3.9, p=0.01) for outdoor work prior to college. This was based on 45 deaths from malignant melanoma during the 35-year observation period (1.71 million person-years of observation) compared with 180 surviving controls (4 controls per case were chosen from classmates born in the same year and known to survive the decedent). There was no information on outdoor work after university admittance, but previous outdoor work was the only significant risk factor identified for melanoma in this study.

A study of CMM incidence data for England and Wales by Beral and Robinson (1981) revealed site-specific trends according to occupation. They examined melanoma and basal and squamous cell cancer incidence data from 1970 to 1975 for England and Wales obtained from the Office of Population Censuses and Surveys. Information for each case included occupation and, for each melanoma case, anatomical location. The anatomical location data were grouped into either exposed (head, face, and neck) or unexposed site categories. Occupational groups were classified as indoor office workers, other indoor workers, or outdoor workers. Age-specific standardized cancer registration ratios were calculated by indirect standardization and based on 1971 census data.

Table 11-7 shows the age-standardized registration ratios for melanomas of exposed and unexposed sites, and other skin cancers, by place of work for males aged 15-64 years. These results indicate that outdoor work was associated with a 10 percent excess of basal and squamous cell carcinomas, a 9 percent nonsignificant excess of melanomas of the head, face and neck, and a 22 percent deficit of melanomas of unexposed sites. In contrast, office work was associated with a 31 percent excess of melanomas of unexposed sites. These differences persisted when the data were analyzed for social class III (skilled workers) only, as shown in Table 11-8. There was, however, one main difference--office work was also significantly associated with an excess of squamous cell and basal cell carcinomas ($p<0.05$).

Beral and Robinson (1981) concluded that the similarity of melanomas of "exposed" sites and squamous and basal cell carcinomas by occupational group suggested that prolonged sun exposure may be important in the etiology of melanomas of regularly exposed parts of the body. Furthermore, the low incidence of melanomas of unexposed sites in outdoor workers indicated that occupational exposure was not associated with increased melanoma incidence on normally covered parts of the body. The authors noted that the reasons for differences between office workers and other indoor workers (who had lower melanoma and other skin cancer incidence rates) were not clear. They observed, however, that whatever the cause (e.g., a greater tendency to expose normally covered parts of the body to sunlight), it was unlikely that prolonged sun exposure was an important etiological factor in office workers.

A recent study by Vagero et al. (1986) confirms some of the findings of Beral and Robinson (1981). Vagero et al. (1986) examined incidence data on

TABLE 11-7

STANDARDIZED REGISTRATION RATIOS FOR MALIGNANT MELANOMA OF EXPOSED AND UNEXPOSED SITES AND OTHER SKIN CANCERS, BY PLACE OF WORK, MALES AGED 15-64, ENGLAND AND WALES, 1970-1975

	Outdoor Work	Office Work	Other Indoor Work	All Occupations
Squamous and basal cell carcinoma	110a (1,194)	97 (1,221)	92a (813)	100 (3,228)
Melanoma of face, head, and neck	109 (94)	102 (104)	87 (66)	100 (264)
Melanoma of other sites	78a (285)	131a (573)	85a (281)	100 (1,139)

a Differs significantly from 100 ($p<0.05$).

Source: Beral and Robinson (1981).

TABLE 11-8

STANDARDIZED REGISTRATION RATIOS (AND NUMBER OF CASES) FOR MALIGNANT MELANOMA OF HEAD, FACE, AND NECK AND OTHER SITES AND OTHER SKIN CANCERS BY PLACE OF WORK, MEN AGED 15-64 YEARS, ENGLAND AND WALES, 1970-1975, SOCIAL CLASS III ONLY

	Outdoor Work	Office Work	Other Indoor Work	All Occupations
Squamous cell and basal cell carcinoma	112a (487)	111a (391)	85a (568)	100 (1,446)
Melanoma of head, face and neck	105 (38)	106 (31)	81 (47)	100 (116)
Melanoma of other sites	71a (111)	143a (178)	75a (189)	100 (478)

a Differs significantly from 100 ($p<0.05$).

Source: Beral and Robinson (1981).

4,706 CMM cases and 4,244 basal and squamous cell carcinoma cases for 1961 to 1979 from the Swedish Cancer Environment Registry. The data were classified by occupation (office, other indoor, and outdoor workers), and anatomical location for CMM cases (covered and uncovered parts of the body). Standardized Morbidity Ratios (SMBRs) were calculated based on 1960 population census data and adjusted for age, sex, residence, and social class.

A comparison of the calculated SMBRs for males and females combined is shown in Table 11-9. The results were consistent with a slightly higher risk of melanoma of the face and neck for outdoor workers. For office workers, however, the observed number of melanomas was lower than expected for normally uncovered parts of the body and higher than expected for normally covered parts. Vagero et al. (1986) concluded that the elevated risk of melanoma of covered parts of the body among office workers was not entirely due to differences in social class. They estimated that indoor office workers, as compared to other indoor workers, may have a 10 percent greater CMM incidence after taking into account differences in age, residence, and social class distribution. The authors hypothesized that the observed differences in CMM incidence did not merely reflect risk differences between social classes such as those assumed to be caused by different patterns of sun exposure. Such differences would not explain the contrasts between office and other indoor workers within the same social class which have been observed in this and other studies (Lee and Strickland 1980; Beral and Robinson 1981). However, the authors could not rule out the possibility that within each social class, patterns of sunlight exposure and sunburn experience were different among office, other indoor, and outdoor workers.

MELANOMA IN WORKERS EXPOSED TO CHEMICALS OR RADIATION

There have been a number of studies in which an increased incidence of cutaneous melanoma has been reported in cohorts occupationally exposed to chemicals and/or radiation. Rushton and Alderson (1981) evaluated mortality records for workers in eight oil refineries in Britain. To be included in the study, workers had to have worked for at least 1 year between January 1, 1950 and December 31, 1975. The study population consisted of 34,701 white males, with 575,982 person-years of observation and a mean follow up of 16.6 years. Comparison populations were males in England and Wales for the English and Welsh refineries, and in Scotland for the Scottish refineries. Data were analyzed across all refineries or by individual refineries but there was very little ancillary information on the differences between refineries with regard to location, size of work force, type of product produced, or length of service.

Two refineries showed a significant excess of observed melanoma deaths vs. expected deaths: $p=0.0037$ for refinery B and $p=0.0003$ for refinery H. At refinery B, four out of five individuals who died from melanoma were "operators," whereas at refinery H, the six deaths included an operator, two boilermakers, a pipefitter, a laborer, and a clerk. There was no definition of the exposure pattern normally encountered by these various positions, nor was it possible to determine what either refinery produced, and thus to what these individuals may have been exposed.

TABLE 11-9

MORBIDITY RATIOS STANDARDIZED FOR AGE, GENDER, COUNTY OF RESIDENCE, AND SOCIAL CLASS, SWEDISH CANCER CASES, 1961-1979

Type of Work	Gender	Number of Cases		Standardized Morbidity Ratio	95% Confidence Limits
		Observed	Expected		
Malignant Melanoma of Uncovered Parts					
Office	m+f	142	156.0	91	77-107
Indoor, non-office	m+f	352	347.5	101	91-112
Outdoor	m+f	186	170.0	109	94-126
Malignant Melanoma of Covered Parts					
Office	m+f	1,062	980.3	108	102-115
Indoor, non-office	m+f	1,821	1,816.2	100	96-105
Outdoor	m+f	620	690.3	90	83-97
Squamous and Basal Cell Cancers					
Office	m+f	890	867.5	103	96-110
Indoor, non-office	m+f	1,875	1,970.2	95	91-100
Outdoor	m+f	1,479	1,394.1	106	101-112

Source: Vagero et al. (1986).

Hoar and Pell (1981), in a retrospective cohort study of chemists working for E.I. DuPont Company, evaluated records from 3,713 white males and 75 white females who were employed in 1959 as chemists as well as 19,262 white males and 673 white females who were "non-chemists." The authors indicated that the job title "chemist" at DuPont was difficult to define, that most chemists were exposed to a number of chemicals that changed in quantity and quality, and that different chemists rarely had the same exposures. Thus it was not possible to even estimate the kinds of chemicals to which "chemists" were exposed. The title "non-chemist" was applied only to people who had never been chemists. In addition, their exposures were also not stated. Death certificates were obtained on 105 (93 percent) of the male and 6 (100 percent) of the female deceased chemists, and on 1,863 (92 percent) of the male and 15 (79 percent) of the female deceased non-chemists.

When compared to the non-chemist cohort, melanoma incidence in the male chemists was not significantly different. However, when compared to the Third National Cancer Survey, the incidence of melanoma among male chemists was more than expected (O/E=8/3.3; standardized incidence ratio of 239, 95% C.I.=111-454). A subsequent comparison of the non-chemist cohort to the Third National Cancer Survey revealed that this group too showed a higher than expected incidence (O/E=38/17.1; standardized incidence ratio of 223, C.I. not provided).

In discussing the above finding, the authors indicated that a similar observation was made for all DuPont employees in the period 1956-1974 and that one possible explanation may have been occupational exposure to chemicals suspected of being skin carcinogens. Another possible explanation suggested by the authors was exposure to solar radiation. The majority of DuPont plants are located in the Southeastern United States, where solar exposure is greatest. Sixty-five percent of the DuPont salaried employees resided in the 15 southern states which account for 37 percent of U.S. melanoma mortality.

Holmbert et al. (1983) studied a cohort of 13,114 persons who had worked at two plants in the Swedish rubber industry for at least 12 months between January 1, 1951, and December 31, 1975. Workers were placed into one of three exposure categories. Category 1, work in the weighing and mixing department, consisted of 739 individuals. Category 2, other production work (e.g., calendaring, vulcanization, pressing, tire building, inspection, service work, floor cleaning, storage work), consisted of 9,883 individuals. Category 3, white collar work (office personnel, department heads), consisted of 2,492 individuals. An increased occurrence of malignant melanomas was found in Category 2, resulting in a risk ratio for this group of 2.50.

There is one brief report in the literature linking exposure to a specific class of chemicals with an increased incidence of melanoma. NIOSH (1976) and Bahn et al. (1976) reported increased mortality from melanoma in a cohort of workers exposed to Aroclor 1254 (Monsanto's tradename for PCBs) during a 9-year period in the late 1950's at a petrochemical plant in the northeast United States. The study evaluated information from two small cohorts: one of 51 workers at a research and development facility exposed from 1949 to 1957, and one of 41 workers in a refinery exposed from 1953 to 1958. Two melanomas occurred in the first cohort (vs. 0.04 expected, $p<0.001$). In the second

cohort of 51 workers, excess melanomas were observed; however, no detailed information was provided on exposure or method of analysis. There was no attempt to quantify or even describe exposures in this workplace and it is possible that these workers were exposed to chemicals other than PCBs.

In the period of 1972 to 1977, 19 cases of melanoma were reported among approximately 5,100 employees of the Lawrence Livermore National Laboratory (LLNL) (Austin et al. 1981). This was approximately three times the rate expected in a comparable age/race/sex-adjusted geographical segment of the population from the San Francisco Bay area. To investigate this finding, each case was matched with four controls drawn from the laboratory population and analyzed to examine the relationship of risk to occupational variables such as length of employment, cumulative radiation exposure, and job classification ("scientist" vs. "non-scientist"). Cases and controls were matched on the basis of 5-year age group, race, sex, and census tract. No relationship was evident between melanoma and any of these parameters; however, "chemists" had a relative risk of 6.97 ($p=0.011$).

In an attempt to control for socioeconomic differences between the study group and reference groups, cases and controls were matched by census tract of residence in the incidence analysis. It was not possible to evaluate the efficacy of this technique, but since the difference in melanoma incidence between the highest and lowest quartiles of SES for all census tracts in the San Francisco SMSA was only twofold, it seems unlikely that SES differences accounted for the finding at LLNL. Beyond the conclusion that this was a real increase in the incidence of melanoma that could not be accounted for by other factors such as socioeconomic status, the authors were unable to identify a work-related factor (other than job title) which showed an association with melanoma incidence in this population.

As a result of the LLNL report, Acquavella et al. (1983) conducted a case-control study of melanoma at the Los Alamos National Laboratory (LANL). Twenty cases were identified and, for each case, four controls were selected and matched on the basis of sex, ethnicity, date of birth, and date of first employment. Controls were selected from employees hired immediately before and after each case. Most controls were selected from a pool of 100 employees but occasionally this was expanded to as large as 500 in order to obtain adequate matches. The data obtained for cases and controls included a number of occupational variables such as length of employment, cumulative external radiation exposure 2 years prior to case's occurrence of melanoma, job title, and educational status. The authors concluded that there was no indication of an association between melanoma occurrence and any particular form of radiation. With regard to educational attainment, however, individuals with a college or graduate level degree had elevated risks of developing melanoma. College graduates had a standardized rate ratio (SRR) of 2.11 and those with a graduate degree had an SRR of 3.17.

MELANOMA AND EXPOSURE TO FLUORESCENT LIGHTING

Several studies have examined the potential link between exposure to fluorescent lighting and CMM. Interest in this area developed in response to

information indicating apparent differences in melanoma incidence between outdoor workers and indoor office workers who are regularly exposed to fluorescent light. Emissions from fluorescent lights often extend into the UV range, although the emitted wavelength distribution varies with the type of lamp, glass envelope, and other covers.

Beral et al. (1982) analyzed data on 274 female cases of CMM 18-54 years of age and 549 age- and residence-matched female controls from a study originally designed to investigate the association between melanoma and oral contraceptive use in New South Wales, Australia. They found exposure to fluorescent light at work to be associated with a 2.1 relative risk of melanoma (95% C.I. 1.32-3.32) as compared to no exposure at work. This risk increased with increasing duration of exposure ($p<0.001$ for trend) and was higher for women who had worked mainly in offices (RR=2.6) than for those who had worked mainly indoors but not in offices (RR=1.8). The increase in risk associated with fluorescent light exposure at work was further examined to determine whether other factors might be indirectly affecting the risk. Neither long-term nor intense short-term recreational exposure to sunlight showed a consistent relationship to increased melanoma risk, nor did stratification by the following factors diminish the overall association: amount of time spent outdoors, main outdoor activity and amount of clothing worn in childhood and at ages 20 and 30, sunburn history on various parts of the body, place of birth, hair color, skin color, use of oral contraceptives, and frequency of naevi on the body. Some of these factors, however, seemed to modify the risk of melanoma associated with exposure to fluorescent light slightly, e.g., the relative risks tended to be lower for women who had been most heavily sun-exposed, as estimated by amount of time spent outdoors in childhood and main outdoor activity at age 20 and higher for women who reported having more than an average number of naevi. In contrast with these results, there was no increase in melanoma risk for fluorescent lights in the home (RR=0.9, 95% C.I. 0.6-1.6) even when analysis was restricted to women who had never been exposed to fluorescent lights at work and who had never worked outdoors.

A small series of 27 male melanoma cases 18-56 years of age and 35 male controls of similar ages was available from the same melanoma clinic (Beral et al. 1982) and showed a similar significant increase in melanoma risk with exposure to fluorescent light among those who always worked indoors. The relative risk of CMM for males with 10 or more years of fluorescent light exposure (RR=4.4, 95% C.I. 1.1-17.5) was higher than the relative risks for women with more than 10 years of exposure, although confidence limits overlapped (10-19 years, RR=2.5, 95% C.I. 1.5-4.2; 20 or more years, RR=2.6, 95% C.I. 1.2-5.9). The males also showed slightly higher melanoma risk for ever having worked outdoors compared to those who had always worked indoors (RR=2.2, 95% C.I. 0.6-8.0). Although results are based on small numbers of male CMM cases and controls, the findings are in agreement with those from the larger study of females.

Dubin et al. (1986) also examined the association of CMM to fluorescent light exposure in an interview study of 1,103 CMM cases and 585 controls randomly chosen among new patients, ages 20 and older, at the New York

University Skin and Cancer Unit general skin clinic. A preliminary analysis of a subset of these data (Pasternack et al. 1983) yielded a significant positive association between CMM and fluorescent light exposure. A reliability study was later conducted to confirm the interview assessment of fluorescent light exposure by means of a mailed questionnaire. The reliability study data did not support the interview data that formed the basis of their preliminary report (Pasternack et al. 1983) of a positive association of CMM to fluorescent light exposure. Dubin et al. (1986) believe that interview bias may have affected the fluorescent light data, leading to overestimates of exposure only among cases but not controls. For this reason, no conclusions regarding the association of CMM to fluorescent light exposure can be drawn from this study.

Elwood et al. (1986) conducted a matched case-control study of 83 CMM patients and 83 age-, sex-, and residence-matched controls which evaluated exposure to both diffused and undiffused fluorescent lighting. No significant trends in relative risk were associated with level of exposure to fluorescent lighting through occupational or home exposure. The relative risk for individuals in the highest total occupational fluorescent light exposure category (50,000+ hours) compared to those with no occupational exposure was 1.4 (95% C.I.=0.4-5.1). Corresponding relative risks for those exposed to the highest categories of diffused (25,001-50,000 hours) and undiffused (50,000+) flourescent lighting were 1.5 (95% C.I.=0.5-4.4 and 4.0 (95% C.I.=0.8-19.2), respectively. Associations of CMM with fluorescent lighting based on a subsequent postal questionnaire were weaker than those based on the personal interviews cited above. This also occurred in the study of Dubin et al. (1986), and may involve either recall bias in personal interviews or the fact that mailed questionnaires are less reliable than personal interviews (Elwood et al. 1986).

Rigel et al. (1983) found no increased risk of melanoma associated with fluorescent-light exposure in a preliminary analysis of 114 melanoma patients and 228 matched (5-year age groups) controls from the New York University Medical Center. There was no significant difference in the proportion of indoor office workers between the cases (57 percent) and the controls (60 percent), nor was there a difference in average daily exposure to fluorescent lights (4.9 hours for cases and 5.4 hours for controls). For indoor office work, the average daily amount of fluorescent light exposure was 5.93 hours for cases vs. 5.99 hours for controls. The authors found increased risks for several risk factors, e.g., recreation activities (RR=2.4, p=0.01 for outdoor vs. indoor) and sun exposure 2 hours/day (11-20 years ago RR=2.5, p=0.0005 and 6-10 years ago RR=1.6, p=0.05). They postulate that the increased melanoma risk for indoor workers may be explained by their recreational habits and not by fluorescent-light exposure.

FINDINGS

A number of findings are noteworthy regarding patterns of CMM with respect to socioeconomic status and other occupational factors:

11.1 CMM incidence and mortality show a positive association with increasing socioeconomic status. Furthermore, total CMM incidence has been observed to be higher among "professional" and "administrative" indoor office workers, but not other indoor workers, compared to outdoor workers. Evidence indicating that outdoor workers do not have an elevated risk of melanoma compared to office workers may be confounded by differences in socioeconomic status, host factors, ethnic background, melanoma site, and histologic type.

11.2 For usually uncovered parts of the body (e.g., the face), the incidence and risk of CMM is higher among outdoor workers than among indoor office workers. For usually covered parts of the body, the incidence of CMM among indoor office workers is higher than for outdoor workers.

11.3 The incidence and risk of CMM among indoor office workers is higher for sites that are usually covered (e.g., the trunk) than for sites that are usually exposed (e.g., the face). Among outdoor workers, CMM risks are higher for usually exposed sites than for usually covered sites.

11.4 A number of studies investigating the melanoma risk of workers in refineries, or chemical or pharmaceutical plants, have failed to find a significant association between melanoma and potential exposure to chemicals, although in at least one study an increased risk of melanoma was found for male DuPont workers (both chemists and non-chemists) when compared to males from the Third National Cancer Survey. In one study from Lawrence Livermore National Laboratories, an increased risk of melanoma was observed in individuals with the title "chemist"; however, no other work-related factor demonstrated an association.

11.5 It has been suggested that the risk of developing CMM may be elevated among individuals exposed to fluorescent lighting at work. However, several studies have failed to find a significant and consistent association between CMM and exposure to fluorescent lighting at work. In addition, although two of these studies initially found an association based on personal interview data, an attempt by one study to validate its findings using a self-administered postal survey was not successful.

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CHAPTER 12

OTHER FACTORS

STEROID HORMONES AND MALIGNANT MELANOMA

Evidence for a relationship between the biological behavior of melanoma and steroid hormone action has been observed in several areas of research. These observations include differing survival prognoses favoring females over males, the rarity of the tumor in prepubescent children, the improved survival for postmenopausal and multiparous women, and the increased melanoma incidence among 30- to 50-year-old women. Effects of pregnancy and exogenous hormones on growth and development of melanomas have also been shown. Estrogen receptors have also been observed in human melanomas (McCarty et al. 1980).

Effects of Endogenous Hormones

Several studies indicate that sex hormones may influence melanocyte activity and the natural history of malignant melanoma. Based on the observed rapid increase in mole counts in both sexes during puberty, MacKie et al. (1985) suggested the presence of a hormonal influence on the pigment-producing activity of nevi. The authors suggested that this could result from either a new appearance and proliferation of pigment-producing nevi or the activation of the melanin-producing enzyme pathway of pre-existing, inactive, non-pigment-producing nevi.

Hodgins (1983) noted that the pigmentation changes of genital and areolar skin at puberty and in pregnancy suggest that gonadal hormones influence at least some populations of melanocytes. Greene et al. (1985) stated that they counsel high-risk family members (those with dysplastic nevi) to pay particular attention to nevi during periods of hormonal flux (i.e., puberty and pregnancy).

Several epidemiologic studies have indicated that the observed sex differences in melanoma incidence and mortality could be related to hormonal differences. Hodgins (1983) concluded, however, that there is no clear evidence linking these differences to levels of steroid hormones. For example, the prognosis for men with malignant melanoma is worse than for women. Hodgins cited Shaw et al. (1978), who concluded that better survival resulted at least in part from the earlier stage at presentation and prognostically more favorable sites among women. However, when male patients were matched to female patients by age, and size and thickness of lesion, the female survival advantage among premenopausal stage I patients compared to matched male patients persisted. The survival advantage was much less for postmenopausal women compared to matched male patients. The results, Hodgins noted, supported the concept of a barrier to tumor metastasis in premenopausal women.

The observation of higher melanoma incidence and mortality rates among reproductive and menopausal-aged women than among men of the same age in the

British Isles led Lee and Storer (1980) to suggest that a hormone-dependent variant of melanoma may account for the difference. The authors conducted a descriptive comparison of WHO mortality data from eight European countries and Office of Population Censuses and Surveys incidence data from England and Wales. Age-specific female-to-male mortality ratios indicated higher female mortality rates relative to male rates in the British Isles from 1955 to 1974, whereas the reverse was observed for Australia, North America (the U.S. and Canada), Japan, and Scandinavia (Denmark, Norway, Sweden, and Finland). Lee and Storer (1980) did not offer an explanation for the higher British Isles mortality ratios. They noted, however, that a similar pattern of age-specific sex ratios (i.e., risks for females compared with males peaked in the latter half of reproductive life, and decreased or leveled off in middle age) was observed in these different populations.

Excess female mortality and incidence rates relative to those in males in the British Isles was greatest from ages 30-44. The elevated sex ratio from ages 30-49 did not change from 1950 to 1974. Lee and Storer (1980) suggested that the low rates for malignant melanoma in the British Isles, compared to those for Australia and New Zealand, permitted the observation of a hormone-dependent variant of melanoma in the British Isles.

Lee and Storer (1982) analyzed age-specific changes in the sex ratio of malignant melanoma for several countries of Europe, North America, Australia, and Japan using WHO mortality data. The female/male mortality ratio was less than 1.0 for all countries examined, in contrast to the female excess in the British Isles (Lee and Storer 1980). In each of these populations, however, female/male sex ratios peaked during the reproductive years and declined in middle age. The authors tested whether an interaction of sex and age on CMM mortality rates could have been produced by birth cohort effects and sex differences in incidence and mortality. An examination of the data by 5-year birth cohort intervals indicated a persistent increased female risk in the reproductive years. Using a mathematical model to separate age and cohort effects, Lee and Storer observed that interaction terms for age and sex and year of birth and sex were both significant. They concluded that the specific variation in female-to-male ratios may reflect the same biologic progress that underlies changes in melanoma survival in relationship to childbearing (e.g., decreased survival among pregnant women).

Holman et al. (1984) conducted a case-control study on 276 female melanoma patients identified in the West Australia Lions Melanoma Research Project from 1980 to 1981. Two hundred and seventy-six age- and electoral-subdivision-matched controls were selected from the Australian Commonwealth Electoral Roll, and a few from public school student rolls. The authors observed no consistent evidence of a relationship of incidence rates of different histogenic types with age at menarche, duration of menstrual life, or number of pregnancies of over 20 weeks' duration.

Effects of Pregnancy

In a brief communication in Lancet, an anonymous writer (Anon 1971) stated that while the relationship of pregnancy and melanoma used to be a matter of

debate, pregnant women run the same risk of developing melanoma as non-pregnant women, and tumor behavior is similar in the two groups. Scattered evidence has indicated, however, that pregnancy can activate metastatic disease in a previously treated melanoma, or increase its growth rate (Lee and Storer 1982; McCarty et al. 1980).

In a study by Foucar et al. (1985), 86 pregnant white patients visiting the obstetrics clinic of the University of Iowa Hospitals and Clinics between June and August 1982 permitted the removal of 128 nevi for study. Fifty-one non-pregnant female controls and 50 male controls were obtained from the Department of Pathology files of the University of Iowa Dermatology Clinic. Controls were excluded if they were not between the ages of 16-39. In addition, controls with evidence of atypical nevi were not included. Case and control nevi were compared using a graduated scoring system for atypia ranging from 1 to 16. The 128 nevi from pregnant patients did not include any lesions with sufficient atypia to suggest malignancy. The histopathologic features among cases' nevi were identical to those seen in the male controls' nevi. However, based on small but noticeable differences among histopathologic "activation" measures between cases' nevi and nevi from female controls, Foucar et al. (1985) suggested that mild changes in some nevocellular nevi may occur during pregnancy. The authors noted, however, that a potential bias in selecting controls may have resulted from elimination of controls with clinical features potentially associated with histopathologic atypia.

Most epidemiologic investigations on pregnancy and melanoma have focused on differences in survival of melanoma patients by pregnancy status at or near the time of diagnosis. In an analysis of survival data for female melanoma patients of childbearing age, White et al. (1961) observed that pregnancy did not have an adverse effect on survival even after stratifying by age and stage of disease. The study population consisted of 18 women seen at Stanford Hospital and 53 women from the California Tumor Registry aged 15 to 39 years at CMM diagnosis. The patients were divided into a pregnant group (N=30) (those pregnant within 1 year before and 5 years after diagnosis), a non-pregnant group (N=31), and a pregnancy-undetermined group (N=10). Five-year survival rates were examined for the three groups and indicated a higher survival rate for pregnant (73 percent) than non-pregnant patients (55 percent), although the difference was not significant due to the small sample size. To test the robustness of the observed differences between the pregnant and non-pregnant groups, a range of extreme assumptions concerning the makeup of the pregnancy-undetermined group was applied. The results indicated that within the limits of the data, 5-year survival rates among pregnant women were similar to, or greater than, rates among non-pregnant women. Within three age groups (under 20, 20-29, 30-39), survival rates were still equal to or more favorable than rates for non-pregnant women. When analyzed by stage of disease, White et al. (1961) observed that among those with localized disease (25 cases pregnant, 21 non-pregnant), 5-year survival rates were slightly higher among pregnant patients (88 percent) than non-pregnant patients (81 percent). It should be emphasized that the number of women in this study was small and may not have been adequate for the detection of differences by pregnancy status. The authors concluded that, based on their data, pregnancy did not appear to have a deleterious effect on survival.

Shiu et al. (1976) found lower 5-year survival rates in pregnant women who had experienced activation of a lesion during a previous pregnancy, based on a survival analysis of 251 female cases ages 15-45 who received treatment at the Memorial Sloan-Kettering Cancer Center from 1950 to 1969. Cases were selected if accurate recorded data on pregnancy at the time of admission were available. The authors observed no significant difference in 5-year survival rates for Stage I patients (N=165) between nulliparous, parous non-pregnant, and pregnant women. Among 86 Stage II patients, however, significantly lower survival rates ($p \leq 0.05$) were observed for pregnant patients (29 percent) and parous patients who had lesion activation in a previous pregnancy (22 percent) as compared with nulliparous patients (55 percent) and other parous patients (51 percent) combined. Age differences did not account for the differences in 5-year survival rates. Shiu et al. (1976) concluded that the differences in survival rates and frequency of symptoms in Stage II patients (e.g., bleeding, ulceration, and elevation of lesion) "strongly suggest an adverse influence of pregnancy on women with stage II melanoma."

Hodgins (1983) has noted, however, that suggestions of adverse effects of pregnancy upon malignant melanoma have not been supported by more recent epidemiologic studies. Elwood and Coldman (1978) observed that 5-year survival rates did not differ among 254 ever-pregnant and 51 never-pregnant melanoma patients. The study population was comprised of 305 consecutive melanoma patients seen in Vancouver and diagnosed between 1960 and 1976. The authors noted that their results differed from those of Hersey et al. (1977) who studied 443 consecutive female patients seen in Sydney from 1961 to 1971. Substantially better survival rates for ever-pregnant women were reported; the largest difference in survival was for women over 50 with survival rates of 73 percent (ever-pregnant) and 53 percent (never-pregnant). After restricting their series to cutaneous lesions (89 percent of the total) and adjusting for stage at diagnosis, Elwood and Coldman (1978) still did not observe any association between survival and pregnancy history. Elwood and Coldman concluded that the inconsistency between their results and those of Hersey et al. argued against the hypothesis of improved survival among ever-pregnant melanoma patients.

Houghton et al. (1981) compared 3- and 5-year survival rates among female melanoma patients aged 15 to 40 years of age using data obtained from the Connecticut Tumor Registry from 1950-1954, 1960-1964, and 1970-1974. The study included 12 patients diagnosed during pregnancy (cases) and 175 patients not pregnant at the time of diagnosis. Each case was matched with two non-pregnant patients according to age, anatomic site, and stage of disease at diagnosis. No differences in survival between the two case groups were noted. The 3-year survival rate was 65 percent among pregnant patients versus 67 percent among matched non-pregnant patients; the 5-year survival rate was 55 percent among pregnant versus 58 percent among matched non-pregnant cases. The expected number of pregnant women among the 187 patients reviewed, estimated from Connecticut livebirth rates, was 13.3, compared to the observed 12 pregnancies, suggesting that melanoma incidence did not substantially increase during pregnancy. Houghton et al. (1981) noted that survival rates were significantly lower among pregnant cases when age, anatomic site of primary lesion, and stage at diagnosis were not considered.

Effects of Exogenous Hormones

Several studies have examined the possible relationship between oral contraceptive (OC) and other hormone use and melanoma. Beral et al. (1984) concluded, based on available epidemiologic evidence, that "while oral contraceptives and other exogenous sex hormones are clearly not major determinants of melanoma, the accumulating evidence suggests that they may increase the risk of disease."

Jelinek (1970) observed that pigmentary changes (melasma) caused by oral contraceptives suggest that estrogen or progesterone could control skin melanin. According to Jelinek, estrogens stimulate melanocytes and progesterone causes the pigmentation to spread, indicating that the total amount of both hormones could increase melasma incidence. Jelinek (1970) stated, however, that the putative relationship between malignant melanoma and OC use could be adequately explained by chance. MacKie et al. (1985) observed that neither pregnancy nor OC use stimulate development of new moles, although some pre-existing moles have been found to temporarily darken during pregnancy. Hodgins (1983) noted that in spite of the observed pigmentary changes associated with OC use (attributable mainly to estrogens), there is little evidence to suggest any link between CMM and the contraceptive pill.

Lederman et al. (1985), in a prospective study of 289 Caucasian female Stage I melanoma patients, conducted a multivariate analysis to examine the effects of prior estrogen and progesterone use on tumor characteristics and survival. The cases were consecutively evaluated and prospectively entered into a natural history study at the Massachusetts General Hospital and New York University. Hormone users presented with thinner tumors than nonusers; 76 percent of OC users and 64 percent of menopausal estrogen (MPE) users had primary tumors less than 1.69 mm, as compared with 58 percent of nonusers. Users of OCs in the year prior to CMM diagnosis had significantly thinner tumors than nonusers ($p \leq 0.01$) in the year before diagnosis. Univariate analysis showed that exogenous hormone use was not associated with increased risk of death from CMM. Life table analysis revealed slightly greater 5- and 9-year survival rates in hormone users. Nine-year survival rates were 90 percent for OC users, 87 percent for MPE users, and 81 percent for non-users. The finding of thinner tumors in hormone users may have explained their apparently more favorable survival. The fact that estrogen users had thinner tumors may have been due to a direct effect of estrogens, the tendency of hormone users to seek medical attention sooner than non-users, or that hormone users tend to be under closer medical surveillance than non-users.

Lee and Storer (1982) noted that in the British Isles population, the elevated female-to-male melanoma incidence ratio did not change over successive 5-year periods during a 25-year span from 1951 to 1975. These data suggested that the large-scale introduction of OCs did not produce the elevated ratio.

Using the same methodological approach as Lee and Storer (1982), Stevens et al. (1980) examined incidence data from Connecticut (1935-1974), Denmark (1943-1972), and Finland (1953-1974), and mortality data from the United

States (1951-1975), Canada (1951-1975), and England and Wales (1951-1975). The authors observed that there was no perturbation in female melanoma incidence rates relative to male incidence rates at or after the introduction of oral contraceptives. On the basis of these descriptive data, Stevens et al. (1980) argued that there is no association between OC use and malignant melanoma since, if there were an association, male incidence and mortality rates would not be a constant multiple of female rates over an extended period of study.

Beral et al. (1984) conducted a case-control analysis of the effect of OC and hormone use, and pregnancy history on risk of melanoma. The cases consisted of 287 white women aged 15-84 years who were seen at the Sydney Hospital. General population controls were matched by age and area of residence to cases diagnosed between 1974 and 1978 ("old" cases). Controls selected from hospital inpatients were matched to "new" cases (those interviewed between 1978 and 1980) by age only. Case-control comparisons indicated that women with melanoma were more likely to have taken oral contraceptives for long periods of time. A consistently increased risk of melanoma was only observed in those who had begun OC use at least 10 years before diagnosis and whose use continued for 5 or more years relative to non-users (relative risk [RR]=1.5; 95% CI 1.03-2.14). This elevated risk persisted after controlling for reported hair and skin color, frequency of moles on body, place of birth, and measures of sunlight and fluorescent light exposure. Socioeconomic status, which has been associated with CMM (see Chapter 11), was not controlled for in this study. If there were an association between socioeconomic status and OC use, the failure to control for socioeconomic status may confound the observed results. Beral et al. (1984) also observed that cases were more likely than controls (but not significantly) to have used hormones to regulate periods (RR=1.9), to have received hormonal replacement therapy (RR=1.4), and to have been given hormone injections to suppress lactation (RR=1.4).

Based on conclusions from several studies, Beral et al. (1984) stated that while most studies reported weak or no associations of CMM to ever-use of OCs, the five studies examining data on prolonged OC use found increased risks (not always statistically significant) associated with long-term pill use. As shown in Table 12-1, relative risk estimates for long duration of OC use are in the range of 1.4 to 4.4. These relative risks are of the same order of magnitude as those for recognized pigmentary risk factors such as red or blonde hair and fair skin. It should be kept in mind, however, that some of these results may be confounded by socioeconomic status.

Endocrine Therapy

In breast cancer, the presence of specific estrogen receptors in a tumor has provided an indication of responsiveness to endocrine therapy. Several studies have searched for hormone receptors in malignant melanomas in the hope of identifying patients who might respond to hormone treatment. Studies have shown that steroid receptors are a necessary, if not sufficient, requirement for steroid-hormone responsiveness in target tissues (Fisher et al. 1976).

Occurrence of Hormone Receptors. Based on a review of 14 published studies, Hodgins (1983) concluded that melanomas generally contain low

TABLE 12-1

SUMMARY OF FINDINGS FROM DIFFERENT STUDIES ON MELANOMA AND ORAL CONTRACEPTIVE USE

	Relative Risk	
	Ever-Use of Oral Contraceptives Versus Never-Use	Long-Term Use of Oral Contraceptives Versus Shorter-Term Use or Never-Use a/
Case Control Studies		
Beral et al. (1977)	1.9	No data
Adam et al. (1981-a)	1.1	1.6
Adam et al. (1981-b)	1.34	1.4
Bain et al. (1982)	0.93	3.0 b/
Holly et al. (1983)	1.15	4.4 b/
Beral et al. (1984)	1.0	1.5 b/
Cohort Studies		
Beral et al. (1977)	1.4	1.7
Adam et al. (1981)	0.3	No data
Kay (1981)	1.5	No data
Ramcharan et al. (1981)	3.5 b/	No data

a/ Definitions for long-term use were as follows:

Beral et al. (1977): total duration of use of 4+ years.

Adam et al. (1981): total duration of use of 5+ years;
a = data from postal survey;
b = data from GP records.

Bain et al. (1982): total duration of use of 2+ years beginning 10+ years before diagnosis.

Holly et al. (1983): total duration of use of 5+ years beginning 12+ years before diagnosis (superficial spreading melanoma only).

Beral et al. (1984): total duration of use of 5+ years, beginning 10+ years before diagnosis.

b/ Differs significantly from 1.0 ($p \leq 0.05$).

Source: Beral et al. (1984).

estrogen receptor concentrations, below those considered significant for predicting hormone responsiveness for breast cancer. Ellis et al. (1985) noted, however, that several studies describing hormonal receptors in human malignant melanoma have found that 0-78 percent of melanomas have detectable levels of estrogen receptors, and from 0-100 percent of melanomas have detectable levels of progesterone receptors.

McCarty et al. (1980) examined tumors from 20 patients aged 23 to 80 years hospitalized at the Duke Comprehensive Cancer Center. No restriction was made concerning age, sex, race, or menstrual status of the patients included in the study. Seven of the 20 tumors showed high affinity estrogen binding of more than 3 fmol/mg cytosol tissue protein by dextran-coated charcoal analysis (DCCA). No relationship was observed between estrogen binding and age, sex, menstrual status, or parity. No evidence of high affinity progesterone binding was observed in any of the 20 tumors. The authors cautioned, however, that their results also supported the hypothesis that the enzyme tyrosinase may mimic estrogen receptor binding. The possibility that steroids may interact with nonreceptor proteins such as tyrosinase gives less credence to the specificity of estrogen binding to receptors in melanoma skin tumors.

Rumke et al. (1980) conducted hormone-receptor assays on 21 metastatic tumors from 17 male patients, and 22 metastic tumors from 17 female melanoma patients. Estrogen and androgen receptors were detected in 7 out of 31 cutaneous metastases. No relationship was observed between estrogen receptor and sex, age, androgen receptor, or prognosis. The study showed that estrogen and androgen receptors can be present in some melanoma metastases but at levels generally too low to be considered of relevance to endocrine treatment.

Creagan et al. (1980) assayed 38 tumor specimens from 34 melanoma patients for cytoplasmic estrogen receptors (ER) by the dextran-coated charcoal method. Only 4 of the 34 patients (12 percent) had detectable ERs, leading the authors to conclude that the chemical usefulness of the ER assay in melanoma is probably limited.

Fisher et al. (1976) analyzed biopsies from 35 malignant melanoma patients and found 16 (46 percent) with cytoplasmic receptors for estrogen. Equal percentages were observed for males and females. Using the Scatchard technique, the authors observed a straight line plot suggesting that estradiol was binding to a single class of high affinity, limited capacity receptor sites.

Ellis et al. (1985) investigated a related topic: whether hormone-receptor binding in melanocytic lesions could be indicative of a potential for malignancy. Estrogen and progesterone binding was examined in 22 melanocytic lesions from 14 patients with the dysplastic nevus syndrome and in 21 patients with acquired intradermal nevi using a fluorescent hormone binding technique. Large amounts of both estrogen and progesterone binding were seen in nevi from patients with dysplastic nevus syndrome, while most of the acquired intradermal control nevi were negative for binding. The authors concluded that positive estrogen and progesterone binding in melanocytes from patients with dysplastic nevi may correlate with clinical lesion changes during times of normal hormonal change (e.g., puberty, pregnancy, and OC use). The authors noted that the

predictive value of estrogen and progesterone receptors in melanocytic lesions for malignancy remains unproven.

Effects of Endocrine Treatment. In a 1983 review article, Hodgins (1983) concluded that estrogens and anti-estrogens appeared to be useful in treatment of some melanomas, but more work was needed to identify patients likely to respond. There was little evidence concerning the effects of castration, androgen, or antiandrogens in the treatment of melanoma. Hodgins cautioned that glucocorticoids and retinoids, while able to inhibit the growth of melanoma cells, have widespread negative health effects. Finally, Hodgins stated that assays of steroid sex hormone receptors in melanomas appeared to offer little help in selecting patients for endocrine treatment. While premalignant melanocytic lesions and early-stage tumors might be estrogen-dependent, Hodgins suggested that as tumors spread, hormone-resistant variants become established. Tumors could then contain a mixed population of hormone-responsive (staining) and hormone-insensitive (nonstaining) cells.

Most hormonal treatments for CMM involve administration of the anti-estrogen tamoxifen (Hodgins 1983). Hodgins noted that in 10 reported trials on 154 patients with advanced disease, partial or complete remissions lasting from 3 weeks to over 1 year were observed in 9.7 percent of patients. Hodgkins (1983) assessed the relationship of estrogen receptor content of melanoma and response to tamoxifen in 58 of the 154 patients; 31 percent (N=18) contained receptors. The response rate among the 58 patients was 10.3 percent, similar to the overall rate of remission (9.7 percent). The majority of the 18 receptor-containing tumors were not responsive to tamoxifen. Hodgins concluded that although 10 percent of melanoma patients responded to anti-estrogen treatment, response was not predicted by presence of estrogen receptors.

Hodgins also reported that Fisher et al. (1976) observed partial responses to diethylstilbestrol in 2 of 18 patients. Hodgins noted the paradox of a response to anti-estrogen treatment when prognosis appeared better for women than men. Since diethylstilbestrol was effective in treating some patients, Hodgins questioned whether tamoxifen was acting primarily as an anti-estrogen or as a weak estrogen.

Rumke et al. (1980) commented that Fisher et al. (1978) similarly showed that the presence of estrogen receptors did not correlate with a response to diethylstilbestrol treatment. In the Fisher et al. (1978) study, two responsive patients did not indicate estrogen-binding activity, while 4 of the 18 patients with estrogen-receptor in cells from metastases did not respond. Rumke et al. (1980) noted that although hormonal dependence of melanoma growth rate has been shown, it occurs in so few patients with advanced disease that endocrine therapy for CMM is not a customary practice, as it is for mammary carcinoma. After observing measurable androgen binding activity in 11 of 43 melanoma metastases, two young male patients were given an anti-testosterone treatment and one of these also received ethinyloestradiol in high doses. These treatments had no effect on disease progression. Rumke et al. (1980) tentatively concluded that receptor determinations were not useful in the management of patients with advanced disease.

Adler and Gaeta (1979) caution against use of stribestrol, estrogen, or estrogen-progesterone combinations by females with a diagnosis or past history of melanoma since, in some instances, reactivation of tumor growth has been observed after hormonal treatments.

OCCURRENCE OF MELANOMA IN IMMUNOSUPPRESSED PATIENTS

Immunosuppression can occur through a variety of mechanisms. Some patients are born with diseases that have immunosuppressive components. By far the most common type of immunosuppression, however, is iatrogenic; drugs given to transplant recipients and patients with autoimmune diseases suppress the immune response in an effort to promote graft survival or decrease the autoimmune disease process. Cytotoxic anti-cancer drugs frequently have an immunosuppressive side effect, and cancers themselves have been shown to exert a suppressive effect on the immune system, especially malignancies of the reticulo-endothelial system.

Patients who are immunosuppressed, for whatever reason, have an increased susceptibility to certain malignancies. For transplant patients, there is an increased risk of skin cancers in particular (Penn 1980; Maize 1977; Sloan et al. 1977; Hardie et al. 1980; Penn 1978). Because malignant melanomas carry antigens on their surface and because the cellular inflammatory infiltrate is said to correlate with prognosis (Balch et al. 1978), the question has been raised whether the incidence of malignant melanoma is increased in immunosuppressed patients.

Numerous case studies which report CMM in immunosuppressed patients have been published. Comparisons with expected numbers of CMM based on incidence rates or control groups were not conducted. Bencini et al. (1983) reported two melanomas in a group of 105 renal transplant patients. In another report (Penn 1980), 906 organ transplant recipients developed 399 skin cancers, 14 of which were CMM. Hardie et al. (1980) reported two melanomas in a group of 301 organ recipients, with fatal results. Among 50 patients on immunosuppressive therapy for glomerulonephritis or collagen diseases, one patient developed melanoma (Walker et al. 1976). In the same report, none of the 135 kidney allograft recipients developed melanoma. In a series of 1,884 renal allograft recipients, 3 developed melanoma (Sheil 1977). Brody et al. (1977) reported 21 second malignancies among 1,028 patients originally treated for Hodgkin's disease; one of the 21 cancers was diagnosed as CMM (Brody et al. 1977). In another case report, one patient developed a melanoma in a preexisting mole 5 years after renal transplantation (Younis et al. 1980). Chaudhuri et al. (1980) reported six cases of melanoma in patients who received immunosuppressive therapy; Hill (1976) reported on five patients who developed skin malignancies after immunosuppressive drug therapy for lymphoma, one of which was CMM.

Greene et al. (1981) reported clinical and histological data on 13 patients who developed 14 cutaneous malignant melanomas after renal transplantation. The primary CMMs were histologically reviewed for 13 of the 14 tumors. Ten of the melanomas arose from a precursor nevus. There was also an abnormal host response to the tumor in 10 of the 13 patients, indicated by

the absence of the normal lymphocyte/macrophage infiltrate. Greene et al. (1978), in their earlier study of 4,869 patients with chronic lymphocytic leukemia, observed that CMM developed in 9 patients, compared to the 1.34 expected (based on incidence rates for the general population from the Connecticut Tumor Registry), for an increased relative ratio (RR) of 6.7 ($p \leq 0.05$). When treatment modalities were compared, there was no significant increase in risk of CMM for untreated patients (RR=3.2, 95% C.I.=0.4-12.0). However, patients treated with chemotherapy (RR=12.0, 95% C.I.=3.0-43.8) or radiation (RR=16.8, 95% C.I.=5.4-51.2), were at significantly elevated risk of CMM relative to expected numbers of cases based on age, sex, and time-specific incidence rates from the NCI End Results Program. Thus, increased risk of CMM was associated with immunosuppressive treatment regimes, although it should be noted that these risk estimates were based upon very small numbers of observed cases of CMM as second primary tumors.

Hoover (1977) reported on a series of 16,290 renal transplant recipients, six of whom developed CMM. The relative risk based on a comparison with expected CMM rates for the Connecticut Cancer Registry (1966 and 1971) was calculated as 3.9 (95% C.I. = 1.4-8.5). The degree of immunosuppression of these patients was not addressed. Birkeland et al. (1975) reported a significant ($p \leq 0.001$) increase in CMM only in female patients among 418 renal transplant recipients. However, the percentage of females in the recipient group was not given. Kinlen et al. (1979) evaluated tumor incidence in both immunosuppressed non-transplant and immunosuppressed renal transplant patients. The expected numbers of CMM cases were derived from population incidence rates in an area whose incidence of melanoma was thought to be similar to that of the study population. Kinlen et al. (1979) found an observed/expected ratio of 5.0 for renal transplant recipients and 9.0 for non-transplant immunosuppressed patients. Spector and Filipovich (1980) studied cancers arising in patients with naturally occurring immunodeficiency diseases. Two melanomas occurred in a registry of 298 patients for a relative risk of 2.9; however, the 95% C.I. = 0.8-9.0. These data are from Greene et al. (1981), who discussed this study and received additional data from the authors so that the observed/expected ratio could be calculated based on age- and sex-specific rates for melanomas in the U.S.

More recently, a report appeared which specifically examined the incidence of CMM in patients who had been treated for Hodgkin's disease (Tucker et al. 1985). Eight cutaneous malignant melanomas were diagnosed in 6 of 1,405 patients with Hodgkin's disease. The relative risk was 8.0 (95% C.I.=3-17). Of the six melanomas histologically reviewed, all had a sparse inflammatory cell infiltrate, as did those from renal transplant patients (Greene et al. 1981). Precursor nevi were identified in five of the six CMM tumors, a finding also in agreement with Greene et al. (1981).

FINDINGS

Two different topics potentially related to melanoma have been discussed in this chapter: steroid hormones and CMM, and melanoma among immunosuppressed patients. A few general findings can be drawn from the epidemiologic data for these areas:

12.1 With the possible exception of long-term oral contraceptive (OC) use, hormonal status does not appear to affect the risk of CMM. The potential effects of short-term OC use are not known. Epidemiologic results relating OC use to melanoma may, however, be confounded by several factors, such as socioeconomic status.

12.2 Available epidemiologic evidence indicates that pregnant females have similar risks of developing CMM as non-pregnant females. In addition, survival rates have not been observed to significantly differ between pregnant females with melanoma and non-pregnant females with melanoma after controlling for age, anatomic site, and stage at diagnosis. Limited evidence has indicated that pregnancy may, however, activate metastatic disease in a person with a previously treated melanoma, or increase the growth rate of a previously untreated primary CMM.

12.3 CMMs have been reported to occur at an increased rate in immunosuppressed patients. The tumors which appear in immunosuppressed patients may have a worse prognosis (Greene et al. 1981; Tucker et al. 1985); they may lack the normal macrophage/lymphocyte inflammatory infiltrate (Balch et al. 1978) associated with a good prognosis.

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CHAPTER 13

PREDISPOSING CONDITIONS/LESIONS FOR MELANOMA

There are certain genetic conditions which are known to be associated with an increased incidence of melanoma. This chapter reviews information about two such conditions, dysplastic nevus syndrome and xeroderma pigmentosum (XP). It examines how knowledge gained from investigation of the dysplastic nevus syndrome may explain the development of melanoma in the normal population and also reviews information on both congenital and acquired nevi as risk factors in the development of malignant melanoma. The chapter also summarizes what is known about the role of solar radiation in the development of normal acquired nevi as well as in the progression of dysplastic nevi to cutaneous malignant melanoma (CMM). Information about XP is reviewed in order to gain insight into the factors that contribute to a vastly increased rate of melanoma in patients with this disorder. In addition, information about the action spectrum of the molecular defect in XP is reviewed in order to evaluate the role of UVB in the cutaneous cancers which these patients develop. Finally, a third syndrome, albinism, is evaluated in order to understand what the reported normal incidence of melanoma in albinos means in light of the apparently protective role of melanin in the development of CMM.

DYSPLASTIC NEVUS SYNDROME

According to Greene (1984), "dysplastic nevus syndrome" (DNS) was first identified in 1976. It was originally characterized as familial melanoma associated with a distinctive cutaneous pattern of unusual (dysplastic) nevi (Elder et al. 1981). Subsequent investigations have identified these dysplastic nevi in familial and nonfamilial settings and in individuals with or without melanoma, leading to the classification of DNS kindred into four types (A through D) with the risk of melanoma increasing from one type to the next, as indicated in Figure 13-1 (Kraemer and Greene 1985; Greene et al. 1985b). Type A kindred comprise nonfamilial (sporadic) and type B familial dysplastic nevus syndrome. Type C kindred are comprised of a single individual with dysplastic nevi and melanoma but no family history of either (this is one form of so-called "sporadic" melanoma). The last group, type D, are kindred with either one (type D1) or at least two (type D2) family members with both melanoma and dysplastic nevi. As a familial condition, DNS is apparently inherited in an autosomal dominant fashion with a highly penetrant gene possibly linked to the Rh locus (Greene et al. 1983; Bale et al. 1986).

The frequency of familial DNS is not known; however, as of 1985, 150 melanoma-prone families had been identified by the National Cancer Institute (NCI) and it has been estimated that there may be as many as 32,000 people with familial DNS in the U.S. These individuals could account for as much as 5.5 percent of all cases of CMM in the U.S. Furthermore, dysplastic nevi (DN) have been described in between 25 to 35 percent of patients with melanoma and in as much as 5 percent of the general population, potentially making DN very important as precursor and marker lesions for this disease. It should be noted however, that as many as 4.6 million people living in the U.S. are

DYSPLASTIC NEVUS SYNDROME TYPE	DESCRIPTION	MELANOMA IN KINDRED?	DYSPLASTIC NEVI IN TWO OR MORE BLOOD RELATIVES?	MELANOMA RISK	NUMBER OF PEOPLE AFFECTED
A	Sporadic Dysplastic Nevi	–	–	LOW	MANY
B	Familial Dysplastic Nevi	–	+		
C	Sporadic Dysplastic Nevi with Melanoma	+	–		
D-1	Familial Dysplastic Nevi with Melanoma	+	+		
D-2		+ +*	+	HIGH	FEW

*AT LEAST TWO BLOOD RELATIVES WITH CUTANEOUS MELANOMA

FIGURE 13-1

CLASSIFICATION OF KINDREDS WITH DYSPLASTIC NEVUS SYNDROME

Source: Kraemer and Greene (1985); Greene et al. (1985b).

estimated to have at least one dysplastic nevus. The risk of individuals in this population is under investigation; it is clearly substantially less than that of individuals with the familial disease (Kraemer and Greene 1985; Greene et al. 1985a).

The worldwide distribution of DNS is also not known, but families have also been identified in Germany, France, Great Britain, the Netherlands, Japan, Australia, and New Zealand (Kraemer and Greene 1985; Elder 1986).

Relationship to Common Acquired Nevi

The characteristics of dysplastic nevus syndrome are best considered in comparison with ordinary acquired nevi (moles). Typically, acquired nevi are absent at birth, first appear in early childhood, increase in number through middle adult life, and decrease in number thereafter. The average white middle-aged adult may have 10 to 40 moles, usually on sun-exposed areas of the body and especially above the waist (Kraemer and Greene 1985; Greene et al. 1985a). As a general rule, common acquired nevi are smooth round or oval, pigmented lesions which are sharply demarcated from the surrounding skin (Greene et al. 1985a; Kraemer and Greene 1985). Their pigment is most often a uniform brown or tan, however, some nevi show mottled or stippled variations in these colors.

The characteristic cell type of the common acquired mole is the nevus cell. Nevus cells, although basically a subset of melanocytes, differ from melanocytes by generally being somewhat larger and by lacking dendritic processes (Elder et al. 1981; Lever and Schaumburg-Lever 1979). Another distinguishing characteristic is the aggregation of nevus cells into nests or clusters. This is not an obligate characteristic, however, because many nevi show unusual concentrations of melanocytes located basally without the nested organization (Elder et al. 1981).

Nevus cells in the epidermis and dermis show considerable variation in their appearance. In the lower epidermis and upper dermis, nevus cells are usually cuboidal or oval in shape, possess a well demarcated homogeneous cytoplasm, a large round or oval nucleus, and frequently contain melanin (Lever and Schaumburg-Lever 1979). Such cells are sometimes referred to as "epithelioid" or "type A" cells (Elder et al. 1981, Lever and Schaumburg-Lever 1979). Nevus cells in the mid dermis (type B cells) are smaller than type A cells; they rarely contain melanin and thus may resemble lymphocytes, which has led them also to be characterized as small or "lymphocytoid" (Elder et al. 1981). Nevus cells in the lower dermis (type C) resemble fibroblasts or Schwann cells, since they are usually elongated and possess a spindle-shaped nucleus (Lever and Schaumburg-Lever 1979). Sometimes also referred to as "neuroid" cells, these nevus cells do not contain melanosomes and are tyrosinase negative. Type B cells may have both cholinesterase and the enzymes of melanogenesis and are considered to be transitional between type A and type C cells, according to Elder et al. (1981), leading to the suggestion by these authors that "the neurotized cells of dermal nevi arise from the epidermal nevus cells by the process of 'abtropfung' and of subsequent maturation..." This concept of nevus cell maturation views the acquired nevus

as "...an evolving lesion in which melanocytes ('nevus cells') proliferate in the epidermis, drop into the dermis and undergo maturation there" (Elder et al. 1981).

Nevi in which the nevus cells lie primarily on the dermal-epidermal junction are termed "junctional" nevi. This is the initial state of most nevi, which are generally first observed as tiny (1 to 2 mm) pigmented "dots" on the surface of the skin (Clark et al. 1984). These small lesions gradually enlarge to a maximal diameter of 4 to 7 mm (Elder et al. 1985; Kraemer and Greene 1985). After this initial lateral development, most nevi develop further along one of two paths. One group becomes arrested and remains a stable population of uniformly brown flat lesions. In the second population, while lateral growth ceases, vertical growth begins, with cells also descending into the dermis (Clark et al. 1984). The resulting elevated pigmented papule is commonly known as a compound nevus. In the next stage in nevus development, nevus cells continue their descent into the dermis and disappear from the dermo-epidermal junction; the resulting lesion is a non-pigmented (pink or flesh-colored) papule (dermal nevus). The natural history of the common acquired nevus ends with the return to normal of the skin, either through the sloughing off of a pedunculated papular remnant or by differentiation of nevus tissue along neural (Schwannian) lines (Elder et al. 1981). This process of evolution occurs over many decades and may stop at any point along the way, thus giving rise to the continuum of nevi seen on a given individual.

Characteristics of Dysplastic Nevi

In dysplastic nevus syndrome, affected individuals tend to have larger and more numerous nevi. Such individuals may have between 25 to 75 abnormal nevi, although even 100 would not be unusual and a nevi counts of 200 or more has been observed (Elder et al. 1981). Typically, dysplastic nevi range in size between 6 and 15 mm in diameter; however, this cannot be taken as pathognomonic, as some common acquired nevi may be as large, and patients with DNS may have both dysplastic as well as normal nevi.

Dysplastic nevi follow the same initial time course as ordinary acquired nevi--absent at birth, then appearing in the first years of life. The first indication that a patient may have DNS is an abnormally large number (20 to 40) of small, uniform, deeply pigmented nevi generally noticed between the ages of five and eight. With the onset of puberty, some of the nevi may take on an aberrant morphology, such that by the late teens or early twenties the syndrome is fully manifested. Another characteristic of DNS is that nevus development does not cease with middle age, as is seen with normal acquired nevi, but rather continues, though at a slower pace, throughout life (Greene et al. 1985a; Kraemer and Greene 1985).

Dysplastic nevi have a characteristic color and morphology that distinguishes them from ordinary acquired nevi. DN are generally variegated in color, showing random mixtures of tan, brown, dark brown, and pink. Their margins are diffuse, often fading into the adjacent skin. DN are predominantly flat (i.e., macular), colored lesions, but may have a complex topology ranging from a "pebbled" appearance to that of a central elevated

papule surrounded by a colored area which is not elevated (Kraemer and Greene 1985; Greene et al. 1985a).

Histologically, there are two characteristics that must be present in order to make the diagnosis of dysplastic nevus: a few or many (but almost always less than 50 percent) of the component melanocytes display nuclear pleomorphism and hyperchromatism, and there is a dermal lymphocytic and fibroblastic host response. In addition, there are associated patterns of nevus cell arrangement, including variations in the size and shape of the nests, bridging of the nests between the rete ridges and, in the dermis, a tendency of the nevus cells to be of the small type without neurotization (Elder et al. 1981; Elder 1986).

Relationship of DNS to Melanoma

Progression of dysplastic nevi into frank superficial spreading melanoma has been documented in familial DNS and, even in patients with the sporadic form of melanoma, dysplastic nevi have been demonstrated contiguous to melanoma in 36 percent of 300 superficial spreading melanoma (Elder et al. 1981). In a prospective study of 14 families with familial melanoma (2 family members with melanoma), of 51 evaluable patients with melanoma, nevi played a role in melanoma development in all; in 49 of the 51, the nevi were dysplastic (Greene et al. 1985b)

Almost 90 percent of the melanomas observed in patients with DNS are SSM, and the bulk of the remainder (8 percent) are nodular. HMFM (lentigo maligna), which comprises about 16 percent of melanomas in the normal population, only accounts for 1 percent of melanomas in DNS patients. The trunk is the predominant location and the median age is 32--considerably younger than the 51 years observed for the general population (Kraemer and Greene 1985).

Kraemer et al. (1983), in attempting to quantify the risk of melanoma in DNS patients as compared to the general public, estimated that the type D2 individual had a melanoma risk 395 times that of the general population, and a lifetime melanoma risk of 100 percent. Other DNS patients are estimated to have a relative risk 26 times greater than the general population, and a lifetime melanoma risk of 20 percent. If these estimates are recalculated using current estimates of DNS prevalence (5 percent), the estimated risk falls to about 10 times greater than the normal population, which is consistent with unpublished observations from the Pigmented Lesions Group at the University of Pennsylvania, where patients with dysplastic nevi are followed (Elder 1986).

Abnormal Sensitivity to UV in DNS

The finding in xeroderma pigmentosum (XP) patients that their sensitivity to sunlight was associated with a decreased ability to repair UV-induced DNA damage (discussed in detail later in this chapter) led to similiar investigations in patients with DNS. The first report of such an investigation was that of Smith et al. (1982), in which fibroblast strains from five FM/DNS

families were examined for their survival, and DNA synthesis and repair characteristics after irradiation with either 254 nm UV or gamma radiation. Fibroblasts from FM/DNS patients showed an enhanced UV sensitivity ranging in severity from low normal to a twofold increase comparable to that seen in the form of XP termed XP variant. A similiar sensitivity to gamma radiation was not demonstrable, nor was it possible to demonstrate a defect in DNA repair synthesis. The efficiency of pyrimidine dimer repair in FM/DNS strains was normal, and the recovery of DNA repair after irradiation was also essentially normal.

In additional studies of the same fibroblast strains, this group (Smith et al. 1983) investigated the response of these cell lines to the carcinogen, 4-nitroquinoline 1-oxide (4NQO). This compound induces a type of DNA damage which is not repaired by XP cells; as a consequence it has been termed "UV-like" (Cleaver 1983). Smith et al. (1983) found that three of the six FM/DNS showed increased cell killing as compared to normal controls when exposed to 4NQO. Investigations of the inhibition and recovery of DNA synthesis in the affected cell lines indicated that this was not the mechanism of their increased sensitivity to 4NQO nor was DNA repair synthesis deficient. As an alternative hypothesis, these authors suggest that some class of DNA damage other than pyrimidine dimers may constitute the potentially lethal lesions induced by 4NQO in the sensitive FM/DNS cell-lines. This hypothesis was supported by their preliminary observation that one of the FM/DNS cell lines showed increased cell killing compared to normal cells following exposure to long wavelength (365 nm) UV, whose main cytotoxic effects are not related to pyrimidine dimer formation.

Although the UV- and carcinogen-induced repair synthesis experiments indicate that excision repair of pyrimidine dimers is not compromised in DNS patients, the fidelity of the repair process was not addressed by these experiments. More recent work has investigated this question by examining mutagenesis at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus in lymphoblastoid cells from FM/DNS patients as compared to those from normal or XP individuals (Perera et al. 1986). Four parameters were examined in these studies: survival following 254 nm irradiation, frequency of mutants per clonable cell following increasing doses of UV, recovery of DNA synthesis following irradiation, and strand breakage and repair as measured by alkaline elution. The only abnormality demonstrable in DNS cells was a dose-related increase in HGPRT mutants with increasing doses of 254 nm radiation. Survival, recovery of DNA synthesis, and DNA strand breakage and repair were all normal following irradiation.

One possible interpretation of the finding that DNS is associated with hypermutability but normal excision repair is that this syndome is associated with an error-prone DNA repair process. As indicated by Perera et al. (1986), this hypothesis (that genetic instability may contribute to the development of melanoma in susceptible kindreds) derives additional support from the finding that karyotypic analysis of DNS individuals with or without melanoma shows excessive numbers of apparently random chromosomal changes in number and structure (Caporaso et al. 1986).

Work by Richmond et al. (1986) suggests that the random chromosomal changes may be related to the acquisition by nevus cells of the ability to produce endogenous mitogenic growth factors. This ability in turn may be due to mutation in a regulatory gene controlling production of such factors.

The finding by Perera et al. (1986) of apparently normal survival in lymphoblastoid lines from DNS patients conflicts with the observations of Smith et al. (1982) that fibroblasts from DNS patients showed abnormal survival characteristics. The two groups used cell lines derived from the same individuals, yet came to very different conclusions about the survival characteristics of these cells. This may be due to great differences in approaches; however, it surely warrants further investigation.

Other information which may be important to the analysis of the role of UVR in melanoma development comes from work by Smith and Paterson (1981) in which they compared the responses to 254 or 313 nm of cells from patients with disorders featuring either sensitivity to sunlight or sensitivity to ionizing radiation. The first group of patients contained one patient with photosensitive myositis (PM) and basal cell carcinoma (BCC), two XP patients, and one patient with Bloom's syndrome (BS). The second group of patients contained four with ataxia telangietasia (AT), one AT heterozygote, five with Franconi's anemia (FA), two with Rothmund Thomson Syndrome (RTS), and one with hereditary retinoblastoma.

A very interesting pattern of responses to these two wavelengths was found. Cells from the patient with PM and BCC were sensitive (i.e., showed a reduced colony forming ability) to 313 nm alone, whereas the XP and BS patients were sensitive to both UV wavelengths. In the second group of patients, two of four AT strains showed hypersensitivity to 313 nm only, one FA strain was sensitive to both 254 nm and 313 nm, and normal sensitivity to both wavelengths was shown by the remaining four FA and two AT strains, as well as the RTS, AT heterozygote, and hereditary retinoblastoma strains.

Biochemical studies of the strains sensitive to 313 nm UV radiation suggested that this sensitivity was not due to pyrimidine dimers. In investigating the yield of pyrimidine dimers induced at the two wavelengths, it was discovered that the cell line which was sensitive to 313 nm on the basis of colony forming ability showed no more pyrimidine dimers than cells without such sensitivity. Furthermore, the repair of pyrimidine dimers in the 313 nm-sensitive strain was equal to that in a normal strain.

Smith and Paterson (1981) also draw attention to the fact that the three strains with preferential sensitivity to 313 nm are also cosensitive to ionizing radiation (in particular γ-rays). There is genetic heterogeneity in the response of AT strains with respect to their responses to DNA damaging agents, however, and this may explain the heterogenicity of AT cell-responsiveness observed here. One possible explanation for the observed differences in cosensitivity to ionizing radiation and mid-UV observed in these studies is that γ irradiation induces a spectrum of lesions, one of which is identical to that induced by 313 nm. Thus the cosensitivity seen in the PM/BCC patient is due to an identical defect in the same repair pathway.

The difference in the different AT strains could then be explained on the basis that those that are not sensitive to irradiation at 313 nm develop other lesions after γ irradiation that they are not able to repair because of a defect in a repair pathway separate from the one responsible for the sensitivity to 313 nm.

These authors conclude their report by suggesting that "(a) mid UV appears to be a more appropriate probe than far UV for cellular sensitivity to sunlight; (b) non-dimer coproducts may have biologically important consequences if their repair is singularly inefficient and (c) mid UV has a partially radiomimetic biologically damaging action on human cells..." (Smith and Paterson 1981).

Other observations which appear to support the conclusions of Smith and Paterson are those by Tyrell (1984) and Colella et al. (1986) with regard to mid-UV induction of mutation to ouabain resistance. In contrast to mutation to 6 thioguanine resistance, which can be induced by many different DNA damaging events, mutation to resistance to ouabain seems to involve base-pair substitution events only (Colella et al. 1986). Tyrell found that irradiation of human lymphoblasts with 313 nm light induced 10 times more ouabain-resistant mutants than irradiation with either 302 or 254 nm UV. Colella et al. (1986) extend the Tyrell (1984) observation to 308 nm. Taken together, these findings suggest that certain UVB wavelengths, particularly those bordering UVA, may induce a different kind of lesion from UVC.

Relationship of Congenital and Acquired Melanocytic Nevi to Melanoma

In addition to the association of dysplastic nevi with melanoma described above, there is also evidence that both congenital and acquired melanocytic nevi may be associated with an increased risk of melanoma. Congenital melanocytic nevi differ from the acquired melanocytic nevi in that they appear as pigmented lesions at birth, are generally relatively large, are composed of nevus cells that penetrate into the lower two-thirds or deeper of the reticular dermis, and often involve dermal appendages and neurovascular structures (Mark et al. 1973; Rhodes et al. 1985). The majority of congenital nevi (>90 percent) fall in the "small" category by virtue of being less than 4 mm in size. The designation "large" is generally applied to lesions which cannot be excised easily, with "giant" being a subset of "large" and "gigantic" or "garment" being applied to nevi which cover a major anatomic area (Rhodes 1983). Congenital nevi 10 cm or larger occur at a frequency of less than 1 in 20,000 newborns (Mark et al. 1973), yet it is this class of congenital nevi for which the best documentation of an increased risk of melanoma exists; it is estimated that such nevi are associated with at least a 6.3 percent increase in lifetime risk (Rhodes 1983). The so-called "small" lesions were once estimated to be associated with an increased risk to age 60 of as high as 4.9 percent (Rhodes and Melski 1982); however, a recent re-evaluation of the diagnostic criteria by which to identify small congenital nevi has led this group to urge "...caution when interpreting the histologic association ¢they! reported previously for small congenital nevi and cutaneous melanoma" (Rhodes et al. 1985).

It has also been noted that, on the basis of clinical history, primary melanoma has been associated with a pre-existing nevus in from 18 to 85 percent of such tumors, whereas on the basis of histopathology, nevi have been identified contiguous to melanoma with a frequency between 18 and 72 percent (Elder et al. 1981). Very few of the studies summarized above indicated the type of nevus reported.

Clark et al. (1984) believe that, the common acquired melanocytic nevus is a precursor lesion to melanoma. These authors have concluded that there are six lesional steps in tumor progression, the first one being a common acquired melanocytic nevus. If the nevus does not follow a normal differentiation pathway but acquires the characteristic of lentiginous hyperplasia, then it has started down the pathway to melanoma. Subsequent steps include the acquisition of melanocytic nuclear atypia (i.e., melanocytic dysplasia) followed by progression to the radial, then the vertical growth phases of primary melanoma, and finally metastatic melanoma. In this scheme the dysplastic nevus is the second step down an aberrant pathway of differentiation.

What leads to this aberrant differentiation process is not clear. Conceivably, one possible stimulus is a promotional effect of sunlight. Holman et al. (1983) found that there was a seasonal variation in the functional component of pigmented nevi that corresponded with heavy exposure to sun. The junctional component observed by Holman et al. (1983) may well equate to the lentiginous melanocytic hyperplasia described by Clark et al. (1984). Such a promotional effect may allow the nevus cell to express the endogenous mitogenic factor described by Richmond et al. (1986) so that cell division once promoted by sunlight now becomes permanently "turned on" by an endogenous mitogen. This in turn would lead to the cytogenetic abnormalities observed in tissue specimens of nevi and melanomas (Caporaso et al. 1986) and in cultured cells from nevi and melanomas (Richmond et al. 1986). It would be interesting to know if other cells, e.g., fibroblasts and lymphocytes from dysplastic nevus syndrome patients, acquire the ability to produce endogenous mitogens following UV irradiation. If such were the case, this might explain the hypermutability (Perera et al. 1986) and other abnormal responses (Smith et al. 1982; Smith et al. 1983) observed in these cells following UV radiation.

Frequency and Distribution of Nevi in Normal Populations

The frequency of nevi in the normal population has been the subject of several studies (Pack et al. 1952; Nicholls 1973; Cooke et al. 1985; Mackie et al. 1985). The study by Pack et al. (1952) looked at all moles and determined an average value of 14.6 moles per white adult. Nicholls (1973) evaluated only moles 2 mm in diameter or larger and did a complete age, sex, and site distribution evaluation for 15 age categories and 10 sites per sex. The population evaluated was from Sydney, Australia. No details were given on how his population was selected but more than 85 percent of the study population were under 20 years of age. His data indicate that, in this population, males have their peak number of moles by age 15 while the peak age for females is 20-29. Furthermore, the peak number in males was higher than that in females, and the distribution was different; males had more moles on their trunk and

females showed the highest concentration on their legs. Nicholls (1973) concluded that sunlight is important to the development of pigmented moles because the number of moles reaches the peak frequency on the more sun-exposed areas sooner than on the less sun-exposed areas.

A study by Mackie et al. (1985) used a population selected from healthy non-hospitalized volunteers with no family history of melanoma and (in the case of the older age groups which were drawn from long-stay geriatric patients) without a history of drug therapy that might have affected the melanocyte system. Total body mole counts were performed on 432 individuals (204 males and 228 females) whose ages ranged from 4 days to 96 years. Information was gathered on each subject's phenotype with regard to skin type, hair and eye color, and tendency to freckle. A mole was defined as any brown pigmented lesion >3 mm in diameter which was present throughout the year even without solar stimulation. The study subjects were presumably drawn from the population of Glasgow although this was never stated and the population was identified only as "Scottish" and "a Caucasian population in a temperate climate."

Mean and median mole counts were calculated for males and females by decade intervals with the last interval being "80+." Table 13-1 presents the data from this analysis organized by sex and decade. In the first decade (0-9 years), the respective mean mole counts for males and females were three and two and the median counts were two and zero. Counts begin to rise sharply in the second decade, and peaked in the third decade, with the respective peak means for males and females being 22 and 33 (respective medians: 24 and 16). After the third decade, counts slowly decline. The rapid rise was associated with puberty in both sexes, leading the authors to suggest that hormonal activity may either stimulate the pigment production of existing but non-pigment-producing nevus cells, or may lead to the expansion of the pigment-producing nevus cell system.

Although this study indicated that total body maps were made of mole location, the analysis by site was limited to moles on palms, soles, upper arm (shoulder to arm), trunk, and lower leg (knee to ankle). Moles on soles and palms were found in 6 men and 10 women (3.9 percent of the population); 75 percent of these lesions occurred on palms. In evaluating the site distribution in the group of 226 subjects aged 20-59, the 122 women had a mean total body mole count of 26 with a distribution of upper arm: 30 percent; trunk: 20.5 percent; and lower leg: 17.5 percent. For the 104 males, the mean total body mole count was 16 and the distribution was upper arm: 20 percent; trunk: 36 percent; and lower leg: 17.5 percent. Male and female values were significantly different for total counts and for arm and leg but not for trunk. The highest number of moles per surface area of skin was found on the female upper arm.

Individuals in this study were asked to identify any moles which had been present on their skin since the age of five or earlier. Fifty-two reponded positively but more than half of the lesions identified had characteristics of acquired nevi. Nevertheless, individuals who identified moles as having been present from birth were in the upper 10 percent of their age group for total

TABLE 13-1

TOTAL BODY MOLE COUNTS IN 432 HEALTHY CAUCASIAN VOLUNTEERS

Age (Years)	Mean Number of Moles			Median Number of Moles		
	Female	Male	Male:Female Ratio	Female	Male	Male:Female Ratio
0-9	3	2	1:5	0	2	
10-19	23	18	1:3	16	10	1:6
20-29	33	22	1:5	24	16	1:5
30-39	25	11	2:3	19	10	1:9
40-49	22	20	1:1	11.5	15	0:8
50-59	16	7	2:3	12	4	3:0
60-68	10	6	1:7	3.5	4	0:8
70-78	6	6	1:0	3.5	2	1:8
80+	6	4	1:5	3	2	1:5

Source: Mackie et al. (1985).

mole counts, possibly indicating a "group of individuals who have an active melanocyte system and who may be at greater risk of developing malignant melanoma at any body site in later life." An evaluation was also made of the association of mole counts with pigmentary factors such as skin type, hair and eye color, and tendency to freckle. No positive associations were found.

Mackie et al. (1985) also compared the site distribution information to a parallel case-control study of melanoma patients in the same geographic region in which they observed a significant association of increased mole counts with melanoma risk (Swerdlow et al. 1984) as compared to age- and sex-matched controls. These authors conclude that the prevalence by site observed for nevi is not the same as that seen for CMM, and thus reject the hypothesis that melanoma occurs on the sites with the greatest numbers of benign nevocytic nevi.

At about the same time as the study reported above, Cooke et al. (1985) reported on a community-based evaluation of the distribution of moles in adults in New Zealand. The survey was performed in the winter of 1981 and included 78 percent of the adult population of the town of Milton, Otago, New Zealand. Nevi were counted on all parts of the body except the abdomen and buttocks for all subjects and the anterior chest for women. In order to allow comparison between sexes, counts for the anterior chest for men were excluded from the reported values. Counts were made under two sets of criteria. Both excluded freckles, lentigines, and "any arrays of similarly and uniformly pigmented macules"; one count (hereafter termed type I) included only those nevi >2 mm for which there was no degree of diagnostic uncertainty, whereas the second count (type II) included all moles regardless of size and even with a small degree of uncertainty. These two different types of counts were performed in order to allow comparison with the counts performed by Nicholls (1973) and Pack et al. (1952).

A type I count was performed of 872 people, 436 men and 436 women. Type II counts were performed on 105 men and 73 women. Table 13-2 presents the summary data from this study. Since the study was of adults only, the first age group evaluated is equivalent to that of the third decade in the Mackie et al. (1985) study. As a consequence, the large increase in nevi number with the onset of puberty observed by Mackie and her co-workers is not shown by these data. For the type I count, there is a decrease in the number of nevi with increasing age; however, the decrease is not as sharp as that seen in the Mackie et al. study. In addition the data from Cooke et al. (1985) show no significant difference between the sexes.

Table 13-3 shows a comparison of summary information from all four of these studies. On the basis of a comparison of their findings to those of Nicholls (1973) and Pack et al. (1952), Cooke et al. (1985) suggest that the prevalence of moles has increased as malignant melanoma has become more common. However, as these authors point out, this conclusion is based on observations from three groups whose study populations are separated by time and space. When the comparison is made between two studies done at approximately the same time but on different continents, the conclusion is no longer clear-cut, for the mean number of moles is very similar, and yet the

TABLE 13-2

MEAN NUMBER OF MOLES IN NEW ZEALAND ADULTS a/

Age (Years)	I Mean Number of Moles, >2 mm b/		II Mean Number of Moles of All Sizes b/	
	Males	Females	Males	Females
20-29	17 (115)	16 (108)	47 (29)	53 (22)
30-39	17 (113)	16 (107)	43 (26)	52 (16)
40-49	13 (83)	16 (74)	28 (24)	24 (15)
50-59	14 (75)	13 (85)	27 (18)	26 (15)
60-69	14 (50)	9 (62)	48 (8)	21 (5)
20-69	15 (436)	14 (436)	38 (105)	39 (73)

a/ Moles on the anterior chest, abdomen, and buttocks are not included.

b/ Numbers of subjects shown in parentheses.

Source: Cooke et al. (1985).

TABLE 13-3

COMPARISON WITH PREVIOUS SURVEYS

Place and Time of Survey	Incidence of Malignant Melanoma per 100,000 [a]	Mean Number of Moles in Comparable Body Areas: Diameter >2 mm, Males	Mean Number of Moles in Comparable Body Areas: Diameter >2 mm, Females	Mean Number of Moles in Comparable Body Areas: All Sizes (both sexes)
New York c. 1950	2	--	--	12 [b]
Sydney c. 1970	11	9	12	--
New Zealand 1981	15	15 [c]	14 [c]	39
Glasgow 1982	5	16 [d]	26 [d]	--

[a] The sources of these estimates, which are standardized for age using a world standard population, are given in the discussion.

[b] Adjusted for omission of certain body areas, using data on site distribution from the paper by Pack et al. (1952).

[c] Directly standardized to the age distribution in the Sydney survey.

[d] Diameter >3 mm.

Source: Mackie et al. (1985).

melanoma incidence rate is 3 times higher in New Zealand than in Scotland. Indeed, if Mackie et al. (1985) had counted nevi >2 mm instead of >3 mm, it is very likely that their counts would have been much greater than those observed by Cooke et al. (1985). This comparison too may have its flaws, however, because the population studied by Mackie et al. would probably have been very uniform in its Celtic ethnicity whereas the New Zealand population is likely to have been much more heterogeneous in its genetic makeup. It is conceivable that one characteristic of the population studied by Mackie et al. was a greater tendency to produce nevi.

Relationship of Nevi to Sunlight

In a study designed to investigate whether the distribution and prevalence of nevi was associated with exposure to sun, Kopf et al. (1978) evaluated the distribution of nevocytic nevi on the lateral and medial aspects of arms in 1,000 individuals. Only those nevi that were "smooth-surfaced, pigmented (tan-brown-black)..., 2 mm or more in diameter, either visibly or palpably raised..." were counted. Macular lesions were excluded to avoid the problem of having to differentiate between lentigines, ephelides, and junctional nevi. The population was drawn principally from patients of the Skin and Cancer Unit who were being treated for "...various unrelated dermatological problems," and some were friends or relatives of these patients. There were 607 women and 393 men; 93 percent of the population was white, 5.5 percent was Black, and 1.5 percent was Oriental. Information on the age, sex, race, amount of sun exposure, and tanning ability of each individual was determined via a history and physical examination.

In the population of 1,000 individuals, there were 349 elevated nevi on the lateral aspects of the arms and 116 on the medial aspects. Of the 1,000 subjects, 234 had one or more nevi on the lateral aspect of their arms while only 101 had nevi on the medial aspect. Figure 13-2 shows the age distribution of subjects with nevi on the lateral and/or medial aspect of the arms. In all decades of life, there was a greater percentage of individuals with nevi on the lateral aspects of their arms than on the medial aspects. In most instances, these differences were statistically significant. This observation only held true for whites; the percentage of blacks with nevi on the lateral aspect was equal to the percentage of those with nevi on the medial aspect.

When these data were analyzed with respect to sun exposure, individuals were divided among four categories: practically none, little, moderate, and much. In all groups, the number of subjects with nevi on the lateral aspects significantly exceeded the number with nevi on the medial aspects. There also appeared to be an inverse relationship between the amount of exposure to the sun and the prevalence of nevi on the lateral aspects of the arm. The authors suggest that one possible interpretation of these findings is "that exposure to sun not only elicits nevocytic nevi, but that excessive or cumulative exposure leads to their disappearance." The authors also evaluated whether the ability to tan was related to the number of nevi on the lateral or medial aspects of the arms, but no association was found.

LATERAL VS MEDIAL NEVI

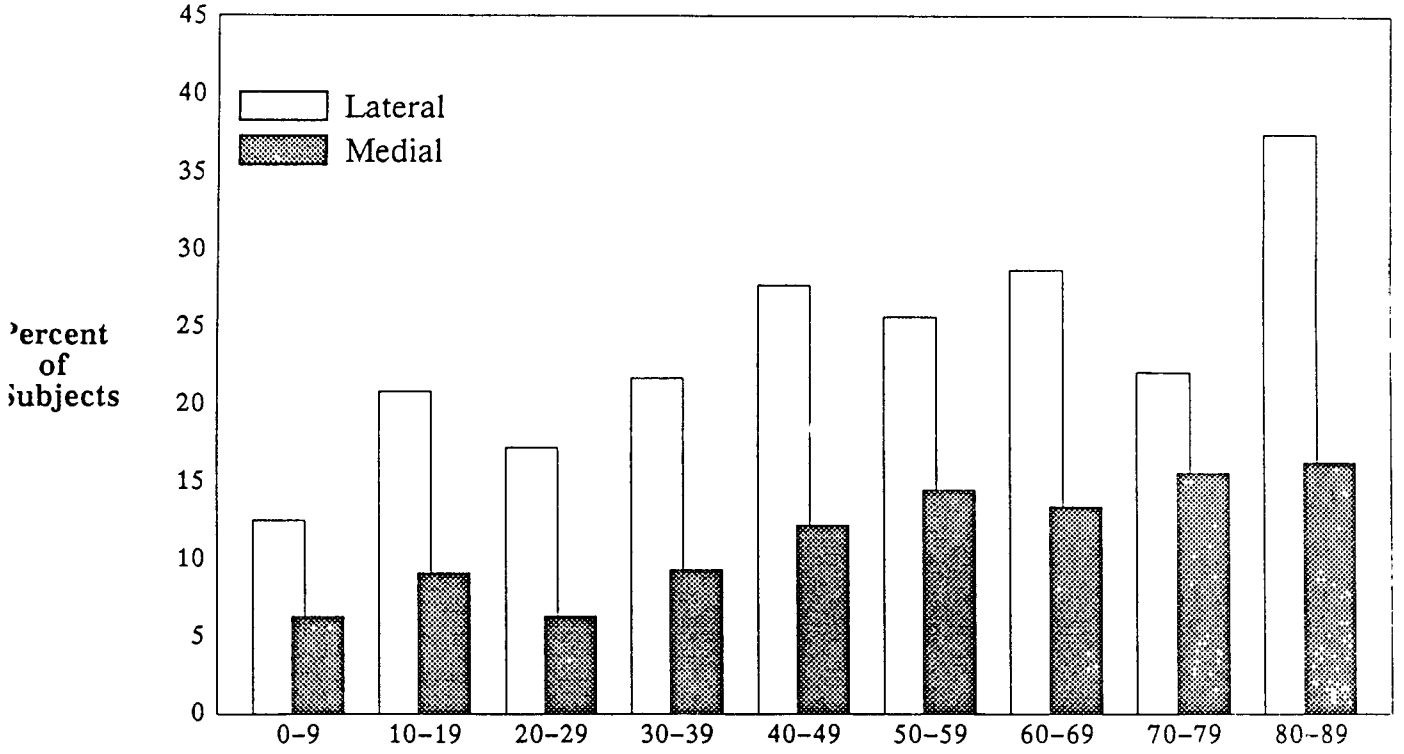

FIGURE 13-2

AGE DISTRIBUTION OF SUBJECTS WITH NEVI ON THE LATERAL AND/OR MEDIAL ASPECTS OF THE ARMS

In this histogram the portion of the bars below the horizontal lines represents the percent of subjects who have nevi on both lateral and medial aspects of the arms.

Source: Kopf et al. (1978).

A subsequent paper by this same group (Kopf et al. 1985) investigated the relationship of nevi to sun exposure in individuals with dysplastic nevus syndrome. The population examined was a group of 80 patients, all of whom had had one or more nevi histologically confirmed as dysplastic. Thirty-one percent of the patients had prior or concurrent CMM at the time of examination and 23 percent had family histories of CMM in at least one first-degree relative. Thirty-two of the patients were men and 48 were women.

Nevi on various aspects of the thorax (lateral, anterior, or posterior) were counted if they were 4 mm or larger and were black, tan, dark or light brown, or dark tan. Nevi were not characterized histologically; thus they were referred to as nevocellular nevi even through some or many of them may have been dysplastic nevi. Table 13-4 shows the frequency distribution by sex of nevi across the three locations, as well as the cumulative total. The data in the table clearly indicate that in DNS patients there are relatively fewer nevi on sun-protected sites compared to sun-exposed sites, suggesting that sunlight may play a role in the induction of nevocellular nevi in patients with DNS (Kopf et al. 1985).

Holman and Armstrong (1984b), in one of a series of reports on a case-control study which examined the relationship of melanoma to a number of risk factors, present data addressing the relationship of nevi to sun exposure. Table 13-5 shows the percent distribution of number of palpable nevi on the arms as a function of the age at arrival in Australia. There was a significant trend ($p=0.009$) toward a greater proportion of migrants having increasing numbers of nevi if they arrived in Australia before 10 years of age. These authors use these data in support of their suggestion that exposure to sunlight in childhood may be a factor in the production of benign nevi. They also found that the prevalence of nevi was directly related to the frequency of painful sunburn (Holman 1983). In a subsequent report (Armstrong et al. 1986) in which the response of controls was specifically examined, a number of interesting associations were observed. Among pigmentary characteristics the best association was with skin color of the upper arm, and the highest prevalence of nevi was in those of intermediate darkness. Among sun exposure variables the highest prevalence of odds ratio (POR=2.18) was observed for three to six painful sunburns as a child; however, the confidence interval included one, and seven or more sunburns gave a POR of 0.97. After adjusting for the effects of other sun-exposure variables, the POR of nevi increased approximately linearly with increasing numbers of painful sunburns up until the age of 10. The only factor which gave a statistically significant POR was usual summer suntan over arms (POR=2.13, C.I.: 1.20-6.38).

Epidemiologic Evidence Relating Nevi to Melanoma

A number of case-control studies have specifically examined the relationship of nevi to melanoma incidence (Holman and Armstrong 1984a, b; Swerdlow et al. 1984; Green et al. 1985; Elwood et al. 1986). The study by Holman and Armstrong (1984a) reported on a comparison of 511 cases diagnosed with melanoma in Western Australia in 1980 and 1981 with 511 population-based controls who were chosen to match the cases by sex, 5-year birth interval, and residence in electoral subdivision. A number of constitutional risk factors

TABLE 13-4

FREQUENCY DISTRIBUTION OF NEVOCYTIC NEVI IN THREE THORACIC LOCATIONS IN PATIENTS WITH THE DYSPLASTIC NEVUS SYNDROME (both sexes combined)

Thoracic Area	Number of Patients	Number of Nevi	Average Number of Nevi
Lateral	80	177	2.2a
Anterior	80	361	4.5b
Posterior	80	506	6.3c
Total	80	1,044	13.0

p values: a vs. b, $p<0.001$; b vs. c, $p=0.04$; a vs. c, $p<0.001$.

Source: Kopf et al. (1985).

TABLE 13-5

PERCENTAGE DISTRIBUTION OF NUMBER OF PALPABLE NEVI ON THE ARMS ACCORDING TO AGE AT ARRIVAL IN AUSTRALIA IN CONTROLS OF CELTIC, ENGLISH, OR AUSTRALIAN ETHNICITY

Age at Arrival in Australia[a]	Distribution, Percent According to Number of Palpable Nevi		
	None	1-4	5
Birth or before 10 years (334)	54.7	36.2	9.0[b]
At or after 10 years (94)	68.1	28.7	3.2

[a] Numbers in parentheses are number of control subjects.

[b] p=0.009 for the trend to increasing proportions of those born in or arrived in Australia before 10 years of age in each nevus count category.

Source: Holman and Armstrong (1984b).

were assessed by interview, e.g., ability to tan, and other parameters were objectively measured e.g., counts of palpable nevi, measurement of actinic skin damage, and skin color. Nevi were counted only on the arms and only below the axillae. In order to be sure not to count freckles, only nevi that were palpably raised above the surrounding skin were counted. (Such a procedure would skew the count in favor of compound and intradermal nevi and against junctional nevi.) Two parameters related to nevi were examined in this study and analyzed with respect to their relationship with the various histogenetic types of melanoma: number of raised nevi on the arm and number of excised benign nevi. Table 13-6 shows the result of that analysis: Both a history of excised moles and increasing number of raised nevi on the arms are strong risk factors for melanoma. In a stepwise analysis of the roles of nevi, pigmentary characteristics, and family history, all were important factors which apparently acted independently of one another. For example, number of nevi >10 had an original odds ratio (OR) of 11.31; after controlling for pigmentary characteristics and family history, the OR for this parameter was 10.35.

Swerdlow et al. (1984) compared 131 melanoma cases with 108 controls, assessing the association of melanoma with benign nevi as ascertained by dermatological examination. The cases came from patients presenting in Glasgow and Edinburgh between 1977 and 1984 and ranging in age between 15-84 years. Analysis was by stratum-matched logistic regression with stratum-matching for age, sex, and city of treatment. These authors evaluated a number of nevi-related factors for their association with melanoma risk: presence of color variation or an irregular edge in nevi, number of all nevi, and number of large nevi >7 mm. Relative risks were calculated without and with an adjustment that controlled for hair and eye color, skin type, and amount of sun exposure, and excluded individuals with dysplastic nevi. (Dysplastic nevi were found in 21 cases but no controls.) The highest unadjusted relative risks (RR) were observed for color variation (RR=36.41, 95% C.I. = 4.67-256.34, $p<0.01$) and irregular edge (RR=43.49, 95% C.I. = 5.85-323.11, $p<0.01$); however, these were no longer significant once adjusted for pigmentary and exposure factors and the dysplastic nevus trait. The presence of large numbers of nevi remained a significant risk factor even after adjustment. With 10-24 nevi, the unadjusted RR was 6.61 (95% C.I. = 2.61-16.78, $p<0.01$) and the adjusted RR was 6.39 (95% C.I. = 2.31-17.68, $p<0.01$). With 25 or more nevi, the unadjusted RR was 24.83 (95% C.I. = 8.42-73.20, $p<0.01$) and the adjusted RR was 19.63 (95% C.I. = 4.75-81.18, $p<0.01$). The presence of large nevi was also a significant risk factor; for 1-4 such nevi the adjusted RR was 5.41 (95% C.I. = 1.84-15.90, $p<0.01$). Although the authors do not explicitly state this, the range for the risk ratio for dysplastic nevi in this study (21 cases but no controls were affected) includes infinity. Furthermore, many of the features evaluated, including large size, greater numbers, variegation, and irregular borders, are features of dysplastic nevi.

Green et al. (1985) performed an analysis in which the nevi-related characteristic of concern was the presence of pigmented nevi on the left arm below the tip of the shoulder. Lesions were counted as nevi if they were dark brown, either macular or raised, and at least 2 mm in diameter. Cases were

TABLE 13-6

RELATIONSHIPS OF MALIGNANT MELANOMA TO HISTORY OF EXCISION OF BENIGN MOLES AND NUMBER OF RAISED NEVI ON THE ARMS

Factor	Number of Case-Control Pairs	OR	95% CI
Number of excised benign moles	507		
None		1.00	
1		1.38	0.86-2.21
>2		5.09a	0.26-11.46
>1 excised benign moles With histogenetic type:			
HMF	86	1.50	0.57-4.01
SSM	267	2.35b	1.29-4.32
UCM	89	1.83	0.63-5.55
NM	51	2.00	0.63-6.70
Number of raised nevi on the arms	507		
None		1.00	
1-4		1.96	1.44-2.65
5-9		4.03	2.37-6.85
>10		11.3c	4.92-25.98
>Raised nevi on the arms with histogenetic type:			
HMF	86	1.54	0.73-3.27
SSM	267	3.00d	1.98-4.57
UCM	89	1.60	0.81-3.20
NM	51	3.00c	1.13-8.43

a
$p<0.0001$ for linear trends in OR.

b
$p<0.01$ for difference of OR from 1.0.

c
$p<0.05$ for difference of OR from 1.0.

d
$p<0.0001$ for difference of OR from 1.0.

Source: Holman and Armstrong (1984a).

residents of Queensland, Australia, who presented with primary CMM between 1 July 1979 and 30 June 1980. The analysis was performed on 183 cases and 183 controls matched to the cases by age (within 5 years), sex, and district of residence in Queensland. Table 13-7 shows the unmatched relative melanoma risks associated with the presence of nevi on the arm. Interestingly, these researchers do not see a strong trend in risk with increasing numbers of nevi; the major risk factor appears to be the presence of any lesion. These investigators also examined the relative risk associated with a wide variety of pigmentary characteristics (e.g., propensity to sunburn or freckle, hair, skin or eye color, and depth of tan), and then adjusted for the presence of nevi by stratified analysis. With the exception of all factors except eye color, this adjustment reduced the relative risks associated with the pigmentary traits examined. When all phenotypic characteristics were analyzed using matched pairs and in a stepwise fashion, the major risk factors were the presence of nevi (RR=30.1, 95% C.I. = 10.3-87.5), red (RR=5.9, 95% C.I. = 1.5-23.1) or blonde (RR=3.5, 95% C.I. = 1.3-9.5) hair, and propensity to sunburn (RR=3.5, 95% C.I. = 0.9-13.2).

Green et al. (1985) suggest that the "mole-proneness" described in their studies is the most important risk factor for melanoma and that the trait represents a tendency of melanocytes to proliferate. They do not feel that the evidence is strong enough to conclude that nevi are necessary precursors to melanoma, however. One alternate interpretation that these authors offer for their finding that there is not an increased risk with increasing numbers of nevi, is that normal nevi could be phenotypic markers that indicate a genetic predisposition to melanocyte proliferation.

The most recent study that directly examined the relationship of nevi to melanoma was a case-control study of 83 patients from urban and suburban Nottingham (U.K.) who first presented with CMM between 1 July 1981 and 31 March 1984 (Elwood et al. 1986). Controls were selected at random from all eligible comparison individuals who had been inpatients or outpatients at a Nottingham hospital in the same time period. Selection of controls was made via a computerized system which identified individuals independently of the number of visits. Data were gathered by home interviews using a structured questionnaire. Because this study was also used to assess the potential role of exposure to fluorescent lighting, a complete occupational history was included in the questionnaire, as well as information on pigmentary characteristics and normal reaction to sun. Skin and hair color were assessed using comparison charts developed for the Western Canada study (Elwood et al. 1984). Only raised nevi were counted and the count was limited to lesions on the upper arm to the shoulder.

The pigmentary characteristics evaluated in this study included numbers of nevi on the upper arm, estimated number of moles (by subject), freckles as a child and as an adult, hair color as a child and as an adult, eye color, reaction to sun, and history of sunburn. The greatest risk factor was 3 or more moles on the upper arm (RR=17.0, 95% C.I. = 6.6-43.8, $p<0.001$); an estimate by the patient of 15 or more moles on the body was associated with a relative risk of 6.7 (95% C.I. = 2.7-17.0, $p<0.001$). Freckles as an adult were associated with an RR of 7.0 (95% C.I. = 3.3-14.5, $p<0.001$) whereas

TABLE 13-7

DISTRIBUTION OF 183 CASES OF MELANOMA AND 183 CONTROLS IN RELATION TO NUMBER OF NEVI ON THE ARMS, AND ASSOCIATED CRUDE RISK OF MELANOMA

	Number of Nevi on Arms				
	None	2-4	5-10	>10	Any
Cases	29	93	44	17	154
Controls	137	28	14	4	46
Relative risk[a]	1.0	15.7	14.9	20.1	15.8

[a] Unmatched relative risk. There were too few discordant pairs in which the control had nevi to do the matched analyses of separate categories of number of nevi.

Source: Green et al. (1985).

remembered freckles in childhood showed a lesser RR of 4.3 (95% C.I. = 1.7-11.1, p=0.002) for those individuals with many obvious freckles. Red or blond hair as an adult was a slightly stronger risk factor than the same hair color as a child; the relative risks were 2.5 and 2.2, respectively, (p=0.02 and 0.03, respectively). Skin reaction to sunlight was divided into four responses: tan, no burn; tan, no burn if protected; burn and tan; burn easily, tan rarely. All but the first showed significant relative risks (RR=4.7, 3.6 and 4.6). History of a painful sunburn (pain for 2 days or more) was also associated with a significant RR of 3.2 ($p<0.001$). In order to evaluate the interrelationships of these factors, Elwood et al. (1986) performed a multivariate analysis. The analysis indicated that the major risk factors in this study were three or more nevi on the upper arm, freckles as an adult, and reaction to sunlight. Three or more nevi showed the greatest RR of 13.3 (95% C.I. = 4.0-43.9); freckles as an adult after multivariate analysis had an RR of 6.0; and the RR of the three reactions to sun ranged from 3.9 for tan, no burn if protected, to 1.8 for burn easily, rarely tan. An interesting outcome of this analysis is the independence of the two risk factors, number of moles and extent of freckling on face and arms. The authors conclude that "...these two simple measures are not merely aspects of the same host characteristic, but ¢may be! related to melanoma in different ways." This epidemeologic distinction is supported by histologic evidence as well: nevi are proliferative lesions of melanocytes whereas freckles, while characterized by hyperpigmentation, are not associated with melanocytic proliferation except in slight degree (Rhodes 1983).

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum (XP) is a hereditary disease which has been found worldwide in individuals of Caucasian, Oriental, or Negroid racial background. In North America, XP occurs at a frequency of about 1 in 250,000; in Japan and Israel the frequency is higher (1 in 40,000 and 1 in 100,000, respectively) (Kraemer and Slor 1984). XP is generally inherited in an autosomal recessive fashion, although one family with a dominant form of the disease has been described. The disease affects both males and females in approximately equal numbers (Kraemer and Slor 1984).

In homozygotes, XP is characterized by a variety of cutaneous manifestations including a high incidence of non-melanoma and melanoma skin cancer (Cleaver 1983). Data summarized in Lynch et al. (1967) indicate a melanoma incidence rate in XP patients of 3 percent (300 per 100,000). A later review of the literature found a 5 percent melanoma incidence in 830 patients worldwide. However, as high as a 50 percent CMM incidence has been observed in several small studies in Europe and the U.S. (Kraemer and Slor 1984). This contrasts with the 3 percent incidence observed in 141 patients from Japan (Takebe et al. 1985). Kraemer et al. (1984), in evaluating the increased risk of XP patients below the age of 20, found a 2,000-fold increase in melanoma and a 4,800-fold increase in basal and squamous cell carcinoma.

Studies using fibroblasts from XP patients indicate a defect in DNA repair which is accompanied by a hypersensitivity to the cell-killing and mutagenic effects of UVB. These observations have led to the suggestion that DNA repair

plays a role in protection against UV-induced neoplasia (Kraemer et al. 1983). By virtue of the increased risk of both melanoma and non-melanoma in XP patients, these findings suggest as well that failure to repair UV-induced damage to DNA is one possible route by which melanomas develop. This section explores characteristics of the disease XP, and how the disease differs among various populations, as well as what is known about the molecular mechanism of XP, and how this information relates to a role for UVB in melanoma development.

XP exists in two clinical forms. The major form principally involves the skin and eyes; the other has neurological manifestations as well. In the extreme case, XP with neurological symptoms is known as deSanctis-Cacchione syndrome. In a recent literature review of 800 patients, the frequency of patients with neurologic abnormalities was 20 percent; however, it was indicated to be higher in Japan (Kraemer and Slor 1984).

The clinical symptoms of XP generally begin very early, with many patients displaying an acute sun sensitivity in early infancy. Minimal sun exposure may result in prolonged erythema, edema, and blistering (Robbins et al. 1974). A lower than normal minimal erythema dose may be the first diagnostic indication of the disease; however, other skin changes, such as the development of freckles and the characteristic dryness and scaliness which gave the disease its name (i.e., xeroderma: "parchment skin"), are also pathognomonic (Cleaver 1983).

The two clinical forms of XP can be further divided into subgroups on the basis of complementation analysis. Complementation analysis is performed by fusing fibroblasts (to make a heterokaryon) from affected individuals and determining if the ability to repair DNA damage is restored in the heterokaryon. Restoration of repair indicates that the two cells have different but complementary defects such that each provides what the other lacks in order to repair UV damage. On the basis of complementation analysis, nine different types of XP have been characterized. Groups A, B, D, G, and H are the neurologic forms; the non-neurologic forms are groups C, E, F, and "variant" (Cleaver 1983). Patients in the various complementation groups appear with different frequency among different populations (Table 13-8), with Japan having far more group A and far fewer group C patients than observed in other nations (Takebe et al. 1985).

The DNA repair defect in groups A through H appears to be an inability to perform the initial step of pyrimidine dimer excision. As discussed in detail in Chapter 18, pyrimidine dimers are the principal photoproduct of the interaction of 254 nm UV with DNA. The repair process which handles the repair of these dimers is termed nucleotide excision repair; it involves the sequential function of a UV-endonuclease, an exonuclease, a DNA polymerase, and a ligase. The endonuclease nicks the DNA next to the dimer, the exonuclease excises the damaged region plus up to 100 adjacent nucleotides, the polymerase fills in the gap using the intact opposite strand as a template, and the strand is resealed by the ligase (Kraemer and Slor 1984). The defect in XP appears to be in the first step of this process--the endonucleolytic strand breakage. This was once thought to be due to a defect in the UV endonuclease; however, the existence of eight complementation groups suggests

TABLE 13-8

GENETIC GROUPS OF XP PATIENTS

Area	Complementation Group								Variant
	A	B	C	D	E	F	G	H	
Japan	27	0	3	3	2	4	0	0	21
USA	3	1	5	5	0	0	0	1	2
Europe	10	0	14	8	2	0	2	0	5
Egypt	7	0	12	0	0	0	0	0	5

Compiled at the 16th International Congress of Dermatology, Tokyo, May 1982, with additional cases (Modhell et al. 1983; personal communication from Y. Fujiwara).

Source: Takebe et al. (1985).

that there are at least eight different genes whose normal function is required for this process. Indeed, other information (presented in Paterson et al. 1984) suggests that there are a variety of different defects in the various XP cells. Cell extracts from groups A, C, and D excise dimers from UV-damaged "naked" DNA with normal kinetics, yet group A cell extracts are deficient in the removal of dimers from UV-damaged chromatin, possibly because they are missing some factor which allows access to the DNA in order to effect repair of thymine dimers. There are also data suggesting that some of complementation groups A-H have mutations in regulatory genes mediating multiple repair mechanisms. Thus, strains in groups A, B, C, D, G, and H have partial defects in post-replication repair, and extracts of cells from groups A, B, C, D, and E possess reduced photolygase activity which may jeopardize their ability to perform the ligation step in DNA repair.

Paterson and his colleagues (Paterson et al. 1984) were intrigued by the paradoxical observation that one group of XP cells, group D, while appearing totally unable to recognize dimer-containing sites, still performed a substantial amount of UV-induced unscheduled DNA synthesis (UDS). In investigating this discrepancy, these workers gathered data which indicated that during post-UV incubation of strains from groups A and D, the phosphodiester bond between the two dimer-forming pyrimidines can be cleaved, leaving the DNA chains held together at the dimer site by a cyclobutane bridge. In group A cells, DNA repair aborts at this stage; however, in group D cells, there is an apparent abortive attempt to insert a normal DNA patch. These processes are compared in Figure 13-3.

As indicated in the figure caption, the proposed mechanism requires the hypothesis that the first step in mammalian excision repair is the action of a dimer phosphodiesterase rather than either the dimer glycosylase or the exonuclease complex seen in bacterial systems. Confirmation that this process also occurs in normal excision repair and is not just a characteristic of XP cells was gained in subsequent studies (Gentner et al. 1984) and supports the observation by LaBelle and Linn (1982) that the putative UV endonucleolytic activity of humans proceeds first by hydrolysis of the intradimer phosphodiester bond.

The variant form of XP has a different defect--cells from these individuals lack a gene product necessary for accurate post-replication repair (Cleaver 1983). This is reflected in an increased sensitivity of XP variant cells to caffeine inhibition of DNA synthesis after UV treatment (Kraemer and Slor 1984).

ALBINISM

Albinism is the designation given to a variety of genetic disorders which have in common a hypomelanosis derived from metabolic defects in the melanocyte systems of the eye and skin. There are many different forms of albinism; however, in all but one (the BADS syndrome), melanocytes are normal but fail to synthesize adequate amounts of melanin (Witkop et al. 1983).

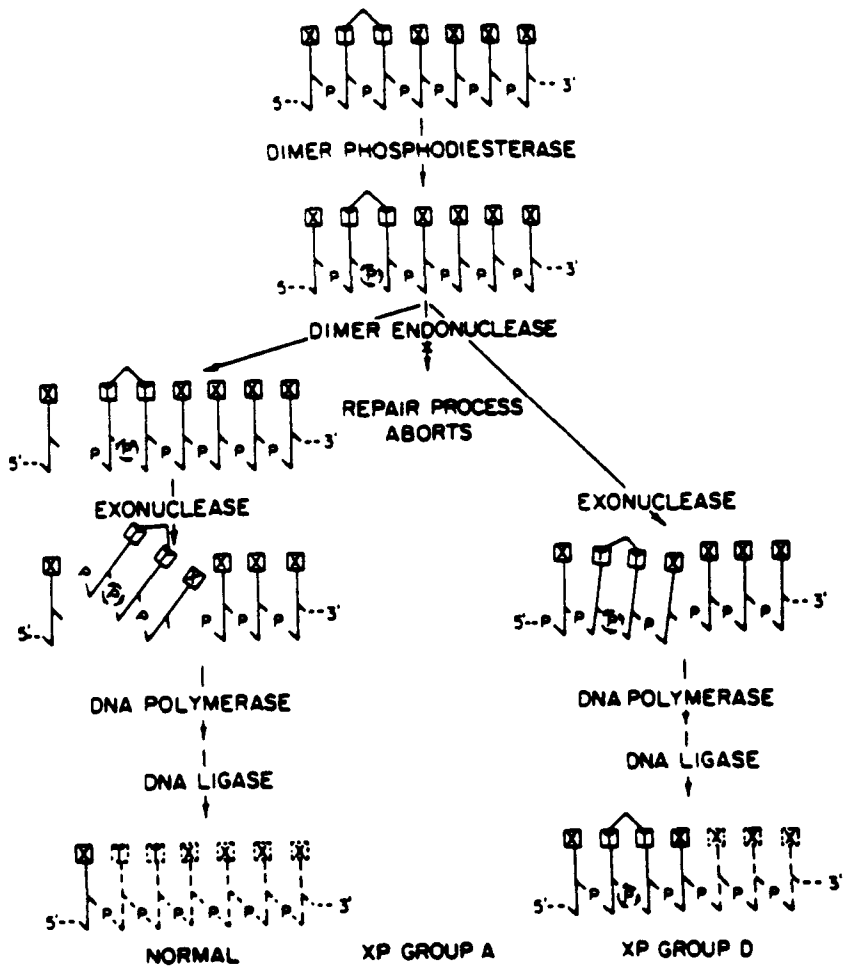

FIGURE 13-3

MODEL OF THE NUCLEOTIDE MODE OF EXCISION REPAIR IN NORMAL HUMAN CELLS (LEFT), XP GROUP A CELLS (MIDDLE), AND XP GROUP D CELLS (RIGHT)

Source: Paterson et al. (1984).

There are three broad classes of albinism: oculocutaneous albinism (OCA), which involves decreased pigmentation in hair, skin, and eyes; ocular albinism (OA); and oculocutaneous albinoidism. OCA exists in ten distinct forms, OA in two forms, and oculocutaneous albinoidism in one. Table 13-9 gives a comparison of the distinguishing pigmentary characteristics of the 10 forms of OCA.

As indicated in Table 13-10, the most common form of OCA in the U.S. is the ty-pos type. Caucasians in the U.S. have an incidence of 1:37,000, and Blacks an incidence of 1:15,000 (Witcop et al. 1983). Other populations show much higher incidences of ty-pos albinism: 1:85-1:240 among South Western Amorindian populations; 1:5,000 in Nigerians in Laos; and 1:1,100 among Ibos (Witcop 1981). It has been estimated that the incidence of all types of albinism in the world population is slightly less than that seen in the U.S. (1:20,000), while the Irish have been estimated to have a slightly greater prevalence of all types (1:10,000) (Witcop et al. 1983).

Given the reduced or absent ability to form melanin in albinism it would be expected that individuals with albinism would be particularly susceptible to solar-induced neoplasia. This is indeed the case for non-melanoma skin cancer. It is paradoxical that there is a paucity of sun-induced melonoma in albinos.

FINDINGS

The information presented above reviews the relationship of dysplastic nevus syndrome to CMM, evidence relating ordinary acquired and congenital melanocytic nevi to melanoma, and the role of sunlight to the induction of nevi. The following findings can be drawn from this information:

13.1 Dysplastic nevi are a risk factor for melanoma independent of freckling and pigment.

13.2 The possession of melanocytic nevi (congenital or acquired) also may be a risk factor.

13.3 Exposure to sunlight appears to encourage the appearance and perhaps the disappearance of nevi and dysplastic nevi from the skin.

13.7 Information from XP patients indicates that individuals who have an inability to repair solar radiation-induced DNA damage also have a high incidence of melanoma relative to the normal population.

13.8 The best characterized defect in XP patients is an inability to excise pyrimidine dimers, suggesting that the repair of such lesions can be important to the prevention of melanomas.

13.9 Albinos are highly susceptible to the development of non-melanoma skin cancer (especially squamous cell carcinoma) but obviously do not have an increased incidence of malignant melanomas.

TABLE 13-9

COMPARISON OF THE PIGMENTARY CHARACTERISTICS OF HYPOMELANOTIC DISEASES WITH FEATURES OF *OCULOCUTANEOUS* ALBINISM

Characteristic	Ty-Neg	Ty-Pos	Ym	HPS	CHS
Hair color	White throughout life	White, yellow-tan; darkens with age	White at birth; yellow-red by 6 months	White, red, brown	Blonde to dark brown; steel gray tint
Skin color	Pink to red	Pink-white to cream	White at birth; cream, slight tan on exposed skin	Cream-gray to light normal	Pink to pink-white
Pigmented nevi and freckles	Absent	May be present and numerous	Present	Present	Present
Susceptibility to skin neoplasia	++++	+++	Unknown	+++	++
Eye color	Gray to blue	Blue, yellow-brown; age- and race-dependent	Blue in infancy; darkens with age	Blue-gray to brown; age- and race-dependent	Blue to dark brown
Serum tyrosine levels	Normal	Low normal to normal	Normal	Normal	Normal
Melanocyte-simulating hormone levels	Normal	Normal	Unknown	Unknown	Unknown
Melanosome in hair bulbs	Stages I and II only	To early stage III, polyphagosomes	To stage III polyphagosomes	To stage III, polyphagosomes, pheomelanosomes	Giant to normal stage IV
Incubation of hair bulbs in tyrosine	No pigmentation	Pigmentation	None to questionable increase	Pigmentation	Pigmentation
Other	Heterozygotes have less than half normal tyrosinase activity	^{3}HOH test suggests heterogeneity in ty-pos albinos	Hair bulb test shows increased red or yellow with tyrosine-cysteine incubation	Platelet defect; ceroid storage; cytoplasmic bodies in monocytes	Susceptibility to infection; giant lysosomal-like granules; lymphoreticular-like malignancy

Source: Adapted from Witkop et al. (1983).

TABLE 13-9 (Continued)

COMPARISON OF THE PIGMENTARY CHARACTERISTICS OF HYPOMELANOTIC DISEASES WITH FEATURES OF OCULOCUTANEOUS ALBINISM

Cross Syndrome	Brown OCA	Rufous OCA	Autosomal Dominant OCA	Black-Locks-Albinism-Deafness Syndrome
White to light blonde	Beige to light brown in Africans	Mahogany red to deep red	White to cream with reddish tint	Snow white with pigmented locks
Pink to pink-white	Cream to light tan on exposed skin	Reddish brown	White to cream	White with melanized macules
Present	May be present	May be present	May be present	May be present in macular areas
Unknown ++++	Similar to Caucasians in Africa +	Low	Unknown	Unobserved, but probably
Gray-blue	Hazel to light brown	Reddish brown to brown	Gray to blue	Gray-blue
Normal	Unknown	Unknown	Unknown	Unknown
Unknown	Unknown	Unknown	Unknown	Unknown
Scanty; stage III; some stage IV	Stage I to stage III, some lightly pigmented stage IV, polyphagosomes	Unknown	Stage I to early stage III; no structural abnormality	No melanocytes in white hair and skin; normal melanocytes and melanosomes in pigmented hair and skin
Pigmentation	Pigmentation	Pigmentation	Pigmentation. Increased tyrosine activity in Golgi	White hair--0; pigmented hair--pigment increases
Oligophrenia; microphthalmia; gingival fibromatosis; athetosis	This defect recognized to date only in Africans and New Guineans	Seen in New Guineans and Africans	Melanocytes present in normal numbers	Profound sensorineural deafness; probably due to failure of embryonic neural elements to migrate from crest to ear

Source: Adapted from Witkop et al. (1983).

TABLE 13-10

ESTIMATES OF PREVALENCE OF TY-POS AND TY-NEG ALBINOS IN THE GENERAL POPULATION OF THE UNITED STATES BY RACE a/

Population	Albinism Prevalence		
	Ty-Neg	Ty-Pos	Combined
White	1:39,000	1:37,000	1:19,000
Black	1:28,000	1:15,000	1:10,000
Total United States	1:37,000	1:31,000	1:16,800

a/ Corrected for 88 percent white and 12 percent black, disregarding other racial components.

Source: Revised from Witkop (1983).

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CHAPTER 14

A COMPARISON OF MELANOMA AND NON-MELANOMA SKIN TUMORS

A comparison of information on cutaneous malignant melanoma (CMM) and non-melanoma skin tumors may provide insight into the role of solar radiation and other etiological risk factors in the development of different types of skin cancer. Prolonged sun exposure is considered to be the dominant risk factor for non-melanoma skin tumors. Through an examination of the similarities and dissimilarities between CMM and non-melanoma skin tumors, the potential role of solar radiation in the development of CMM can be evaluated.

The study of non-melanoma skin tumors (i.e., basal and squamous cell carcinomas) is difficult because most patients are seen and treated in offices and are rarely hospitalized. In addition, the study of these tumors is made more difficult by the perception that they are relatively trivial problems since most are successfully treated (e.g., by surgical excision). Several population-based non-melanoma skin tumor data bases have been developed, though they have generally required special surveys for data collection. This chapter will briefly review the studies that have specifically addressed the differences and similarities between CMM and non-melanoma skin tumors and other relevant epidemiologic information.

NON-MELANOMA SKIN TUMORS

There are two major forms of non-melanoma skin tumors: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Although most skin cancer statistics combine the two cell types, the limited data available from the U.S. and several other countries indicate differences between these tumors with respect to a number of characteristics.

Basal cell carcinomas are neoplasms of the germinal layers of the epidermis and the appendages which differentiate toward glandular structures (Scotto and Fraumeni 1982). As a rule these tumors are slow growing and follow a relatively benign course, although on rare occasions they may result in extreme morbidity, mutilation, or, if they metastasize, death (Pollack et al. 1982).

Basal cell carcinomas are believed to arise from a pluripotent epithelial cell present in the epidermis. It has been hypothesized that an abnormal interaction between these pluripotent stem cells and the surrounding connective tissue induces the cells to differentiate neoplastically (Pollack et al. 1982; Kent 1976). These tumors appear to be very stromal-dependent, however, and it has been suggested that they will rarely metastasize to a foreign tissue bed unless they take along a portion of their stroma (Pinkus 1953). This hypothesis has been confirmed in part by studies which have shown that basal cell tumor cells cultured in vitro in the absence of accompanying connective tissue convert to a keratinizing epithelium (Flaxman 1972; Kubilus et al. 1980). It has also been shown that autotransplants fail if the cells are transferred without stroma (Epstein et al. 1984).

Squamous cell carcinomas are neoplasms of the epidermis that differentiate toward keratin formation (Scotto and Fraumeni 1982). SCCs are far less fastidious in their growth requirements in vitro and will grow under a variety of conditions. They are generally more aggressive than BCCs and account for about three-fourths to four-fifths of the deaths attributable to non-melanoma skin cancer (Dunn et al. 1965).

As described in detail in Chapter 2, melanomas are neoplasms of pigment-forming cells that are derived from the embryonic neural crest. Although melanomas are far less common than BCCs or SCCs, they are generally more lethal. As a result, the raw mortality figures for non-melanoma are similar to those for CMM (Scotto and Fraumeni 1982).

INCIDENCE AND AGE

Non-melanoma skin tumors are among the most common malignant neoplasms occurring in white populations. Based on a 1-year survey (1977-1978) conducted by the National Cancer Institute (NCI), it was determined that non-melanoma skin cancers developed in approximately 400,000 white Americans each year (Scotto and Fraumeni 1982). The annual age-adjusted incidence rate for this survey period was estimated to be $232.6/10^5$ among whites. For comparison, the estimated incidence rate for all other cancers among whites in the United States based on 1973-1976 data from the Surveillance, Epidemiology and End Results (SEER) Program was $318.9/10^5$. Among blacks, the annual age-adjusted incidence rates for non-melanoma skin tumors and all other cancers were $3.4/10^5$ and $347.3/10^5$, respectively.

The incidence of BCC is generally several times greater than the incidence of SCC. Similarly, the incidence of SCC exceeds that of CMM (Lee 1982; Epstein et al. 1984; Eastcott 1963). For example, based on data collected for 62 skin cancer cases registered from 1956 to 1960 in three public hospitals in New Zealand, Eastcott (1963) observed that 73 percent of the cases had BCC, 15 percent had SCC, and 7 percent had CMM. Lee (1982) presented data on 2,019 skin cancer cases in Switzerland for 1974 to 1978 and showed that approximately 69 percent of the cases had BCC, 20 percent had SCC, and 11 percent had CMM.

These relative differences in BCC, SCC, and CMM persist when males and females are examined separately. Based on a comparison of BCC and SCC incidence data from Scotto and Fraumeni (1982) and CMM incidence data from NCI (1985) for white American males and females, the incidence of BCC was approximately four to six times greater than the incidence of SCC, which in turn was approximately three to seven times greater than the incidence of CMM (see Table 3-1).

As has been described in earlier chapters, the incidence of CMM has been increasing over the past several decades. Lee (1982) has estimated that the incidence of BCC as well as SCC is increasing as fast as or faster than the incidence of CMM. Epstein et al. (1984) have pointed out that the rate of increase in SCC is greater than that in BCC. Scotto and Fraumeni (1982),

however, noted when comparing the NCI 1971-1972 and 1977-1978 survey data that the observed incidence increases applied mainly to BCC. The authors noted that the incidence of BCC among United States whites increased by approximately 15 to 20 percent over the 6-year period between surveys.

In general, older individuals (i.e., over 60 years of age) are at higher risk of developing non-melanoma skin tumors than younger individuals. Vitaliano and Urbach (1980) observed that only 3 percent of a total 424 BCC and SCC cases from the Tumor Clinic of the Skin and Cancer Hospital in Philadelphia were under 40 years of age. However, Emmett (1982) and Harris (1982) have observed that SCC and BCC are no longer only diseases of old age since an increasing number of younger people have been presenting with non-melanoma skin tumors. Harris (1982) suggested that the occurrence of non-melanoma skin tumors among younger individuals was consistent with increased sunlight exposure among these age groups.

The age-specific incidence patterns for SCC and BCC are not completely identical, suggesting that different etiological mechanisms may exist. Although incidence rates for SCC and BCC have been reported to rise with age and level off at the oldest age groups (Scotto and Fraumeni 1982), the increase with age was sharper for SCC than BCC. Laerum and Iversen (1981) summarized study results indicating that among a group of BCC cases, 15 percent were less than 50 years of age and 65 percent were less than 70 years of age. Among a group of SCC cases, in contrast, Laerum and Iversen (1981) observed that 70 percent were over 70 years of age.

ANATOMICAL DISTRIBUTION

The anatomical distribution of non-melanoma skin tumors differs from that of melanomas. Non-melanoma skin tumors predominantly occur on regularly exposed sites, whereas melanomas occur on both regularly exposed and non-exposed sites, depending upon the histologic type of tumor and the sex of the individual. Scotto and Fraumeni (1982) noted that the tendency for non-melanoma skin tumors to develop in exposed areas was consistent with the belief that exposure to solar radiation is a dominant risk factor. As already described in Chapter 5, the observed anatomical distribution of melanomas has also been attributed in part to patterns of sunlight exposure.

Table 14-1 compares the distribution of CMM with the distributions of BCC and SCC by sex for tumors occurring in whites in the United States (Scotto and Fraumeni 1982). The data for SCC and BCC were collected as part of the 1977-1978 NCI survey; the CMM data were collected from 1973 to 1976 (Scotto and Nam 1980). The predominant sites for both SCC and BCC on both males and females were the face, head, and neck. These areas accounted for 60 percent or more of the total non-melanoma skin tumors. Most of the remaining BCCs occurred on the trunk, whereas most of the remaining SCCs occurred on the upper extremities. This distribution of tumors differs from that for CMM, which follows a more even distribution among sites and occurs predominantly on the trunk among males and the lower extremities among females. A comparison of 1974-1978 skin tumor data from Switzerland in Table 14-2 shows similar tumor site distributions (Lee 1982).

TABLE 14-1

PERCENTAGE OF TUMORS BY ANATOMIC SITE FOR NON-MELANOMA SKIN CANCER AND MELANOMA AMONG WHITE MALES AND FEMALES IN THE UNITED STATES

Anatomic Site	[a] BCC		[a] SCC		[b] Melanoma	
	Male	Female	Male	Female	Male	Female
Face, head, and neck	81.2	84.1	74.8	60.1	27.0	17.0
Trunk	12.0	8.9	4.5	5.3	38.0	22.0
Upper extremities	4.9	3.4	18.1	25.8	22.0	26.0
Lower extremities	1.3	2.9	1.3	5.7	13.0	35.0
Other sites	0.5	0.7	1.4	3.2	NA	NA

[a] Non-melanoma skin tumor data were for 1977-1978.

[b] Based on Scotto and Nam (1980) as cited in Scotto and Fraumeni (1982).

Source: Scotto and Fraumeni (1982).

TABLE 14-2

DISTRIBUTION BY SEX AND ANATOMIC SITE OF SKIN TUMORS: CANTON OF VAUD, SWITZERLAND, 1974-1978

Anatomic Site	BCC		SCC		Melanoma	
	Male	Female	Male	Female	Male	Female
Head and neck	540 (71.2)	505 (78.7)	202 (80.5)	103 (72.5)	27 (28.7)	22 (16.7)
Trunk	130 (17.1)	76 (11.9)	8 (3.2)	11 (7.7)	34 (36.2)	24 (18.2)
Upper limbs	14 (1.8)	17 (2.6)	26 (10.3)	19 (13.4)	14 (14.9)	27 (20.4)
Lower limbs	15 (2.1)	18 (2.8)	5 (2.0)	7 (4.9)	11 (11.7)	51 (38.6)
Other	58 (7.6)	26 (4.0)	10 (4.0)	2 (1.4)	8 (8.5)	8 (6.1)
Total	758 (100.0)	642 (100.0)	251 (100.0)	142 (100.0)	94 (100.0)	132 (100.0)

Source: Levi and Chapallaz (1981) as cited in Lee (1982).

There are some differences in the observed distributions of SCC and BCC which suggest that these non-melanoma skin tumors may respond differently to different dosages of sun exposure. The available epidemiologic data generally show that BCC is more likely to develop on regularly unexposed sites compared with SCC. Pollack et al. (1982) noted that although it is well-established that sun-exposed areas are more prone to BCC, in at least one study (Urbach et al. 1972) approximately one-third of the BCCs occurred in light-protected regions. Laerum and Iversen (1981) observed that among a group of SCC and BCC cases, 90 percent of the BCCs and approximately 50 percent of the SCCs occurred on the head and neck. They estimated that of these tumors, two-thirds of the BCCs occurred on sites of the head and neck receiving the highest UV radiation doses (e.g., the nose) whereas all the SCCs occurred at these sites. Hilstrom and Swanbeck (1970) examined only SCC cases and observed that about 80 percent of the SCCs occurred on the head. Facial SCCs occurred relatively equally between males and females, but of the SCCs on the external ear, 90 percent occurred among males and only 10 percent among females. Emmett (1982) examined only BCC cases and observed that 75.5 percent occurred on the head and neck, 16 percent on the limbs, and 8.4 percent on the trunk. Lee (1982) noted that although BCC and SCC tend to be more concentrated on exposed sites than superficial spreading melanoma (SSM) or nodular melanoma (NM), the distribution of BCC (somewhat similar to CMM) did not precisely correspond with sun-exposed areas.

RISK FACTORS

Several features common to both CMM and non-melanoma skin tumors have been identified in epidemiologic studies, including susceptibility to burn, a latitudinal gradient in incidence, and predisposing host factors such as red/blonde hair and blue/light eyes. The applicability of these risk factors, all of which are somehow related to sunlight exposure, to both non-melanoma skin tumors and CMM suggests that solar radiation is indeed involved in the development of both types of skin cancer. However, differences between CMM and non-melanoma skin tumors (for example, with respect to anatomical distribution and age-specific patterns of incidence) also suggest that a more complex set of risk factors may be involved in the development of CMM that non-melanoma skin tumors. In this section, features believed to be associated with these different skin tumors, and the hypotheses that have been forwarded to explain these findings, will be reviewed.

As already noted, prolonged sun exposure is considered to be the dominant risk factor for non-melanoma skin tumors (NRC 1982; Scotto and Fraumeni 1982; Green and O'Rourke 1985; Lee 1982; Beral and Robinson 1981). Scotto and Fraumeni (1982) and others (Scotto et al. 1981; Laerum and Iversen 1982; Emmett 1982) have cited several observations supporting this hypothesis:

- the tendency for non-melanoma skin tumors to develop in sun-exposed sites;
- the higher incidence rates among occupational groups with outdoor exposures compared to those with indoor exposures;

- the latitudinal and UV radiation gradient showing highest incidence rates in geographic areas of relatively high UV radiation exposure;

- the inverse correlation between non-melanoma skin tumor incidence and degree of skin pigmentation;

- the high risk among genetically predisposed individuals (e.g., those with xeroderma pigmentosum);

- the predisposition for non-melanoma skin tumors to develop among light-skinned individuals who are susceptible to sunburn and who have red/blonde hair, blue/light eyes, and a Celtic heritage; and

- the capacity of UV radiation to induce non-melanoma skin tumors in experimental animals.

In particular, the observed variations in non-melanoma incidence by latitude support an association with sun exposure. For example, Scotto and Fraumeni (1982) observed, based on the 1977-1978 NCI survey data, that the incidence of SCC and BCC in the United States showed a latitudinal gradient with higher rates in the south. These results are displayed in Figures 14-1 and 14-2 for white males and white females, respectively. Also shown in these figures are 1973-1976 CMM data from the SEER program. The latitudinal gradients for CMM were least pronounced. However, only a small number of data points (as shown in Figures 14-1 and 14-2) were used to examined the latitudinal gradients of CMM, BCC, and SCC.

Prolonged sun exposure may also be a risk factor for specific types of CMM. Green and O'Rourke (1985) noted that chronic sun exposure has been implicated in the causation of non-melanoma skin tumors, but that a different disease-exposure relationship may predominate for CMM, which often occurs on irregularly exposed areas. The authors hypothesized that a positive association between CMM and non-melanoma skin tumors would suggest an etiological role for cumulative sun exposure in CMM.

To test this hypothesis, Green and O'Rourke (1985) conducted a case-control study of 232 CMM patients and 232 age-, sex-, and residence-matched controls in Queensland. The case data were collected from patients presenting with a first primary cutaneous melanoma between 1 July 1979 and 30 June 1980. A random sample of cases was drawn from a population of 871 potential cases and was stratified by geographic location of residence in order to ensure proportional representation from the less densely populated interior part of the state. The controls were randomly selected from the Queensland electoral rolls. Case-control information included history of lifetime sun exposure (based on all outdoor occupations held for more than 6 months and all recreations ever pursued on a regular basis after 10 years of age), complexion, hair color, propensity to sunburn, social class, country of birth, and ethnicity. The face and left forearm were also examined for actinic tumors (i.e., solar keratosis, BCC, and SCC).

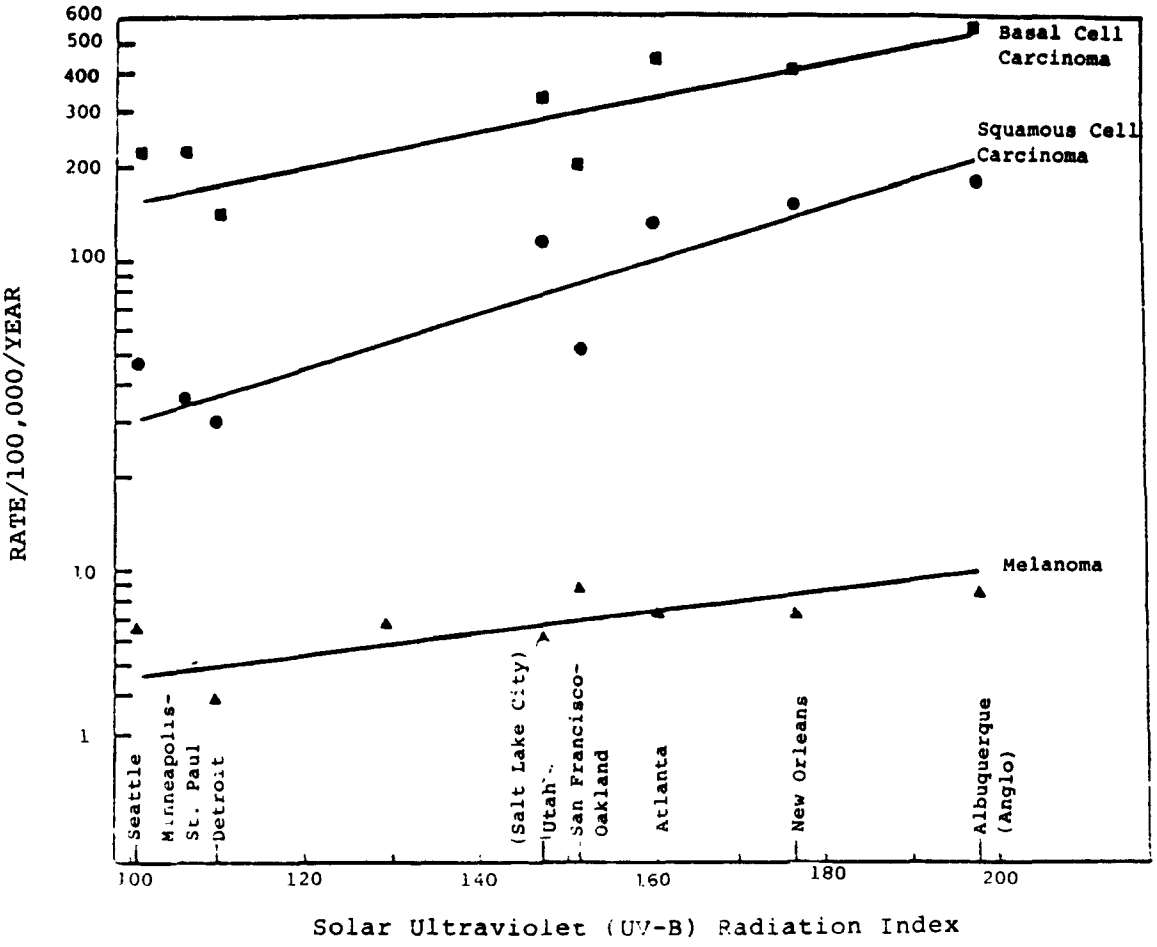

FIGURE 14-1

ANNUAL AGE-ADJUSTED INCIDENCE RATES FOR BASAL AND SQUAMOUS CELL CARCINOMAS (1977-1978) AND MELANOMA (SEER DATA, 1973-1976) AMONG WHITE MALES a/

a/ According to annual UV-B measurements at selected areas of the United States, with regression lines based on exponential model.

Source: Scotto and Fraumeni (1982).

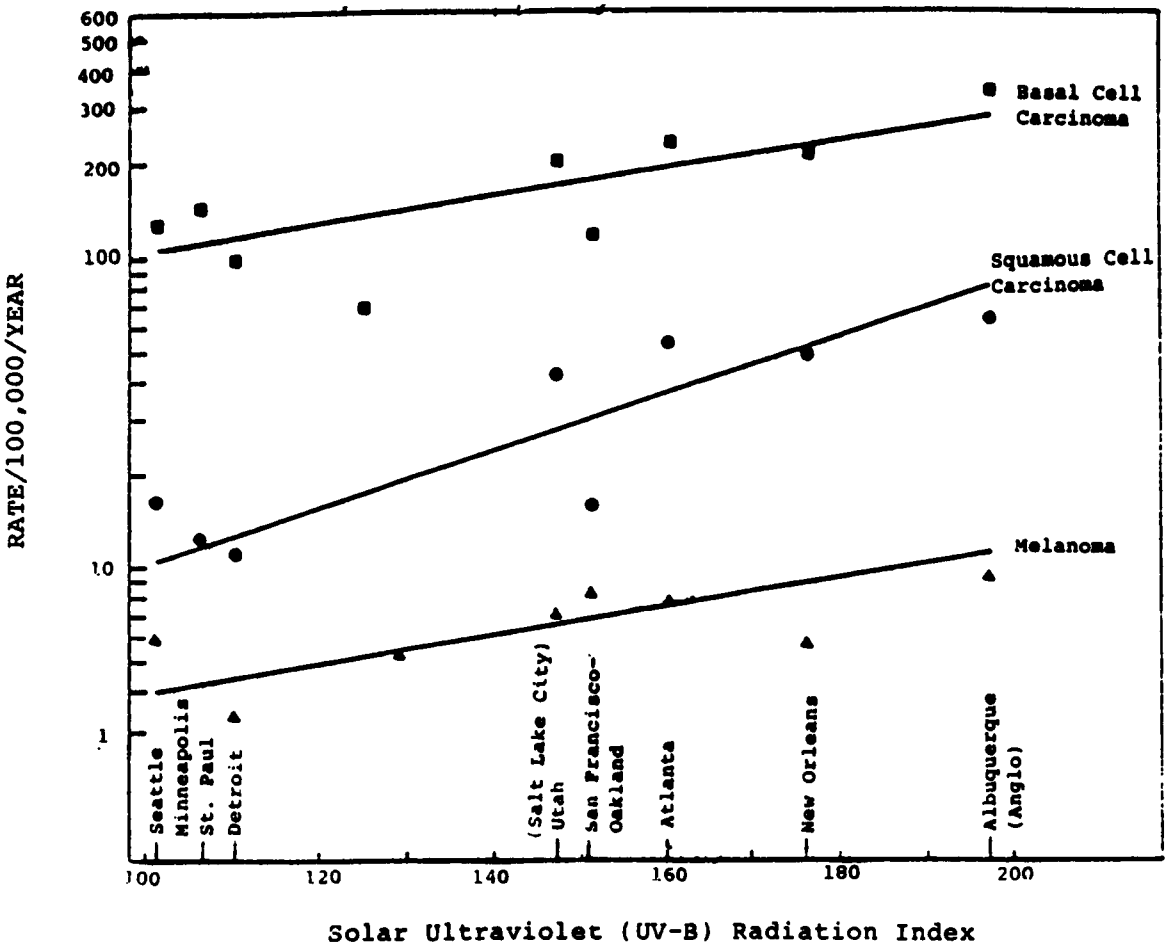

FIGURE 14-2

ANNUAL AGE-ADJUSTED INCIDENCE RATES FOR BASAL AND SQUAMOUS CELL CARCINOMAS (1977-1978) AND MELANOMA (SEER DATA, 1973-1976) AMONG WHITE FEMALES a/

a/ According to annual UV-B measurements at selected areas of the United States, with regression lines based on exponential model.

Source: Scotto and Fraumeni (1982).

As shown in Table 14-3, Green and O'Rourke (1985) observed a greater percentage of actinic tumors on the face and forearms of CMM cases than of controls after adjustment for age and the presence of nevi. The results remained basically unchanged after adjustment for social class, ethnicity, and migrant status. The major risk factor appeared to be the presence of any non-melanoma tumor since there was no trend of increasing risk with increasing number of tumors. The relative risk (RR) associated with the presence of actinic tumors was highest among CMM patients with lentiginous maligna (also known as Hutchinson's melanotic freckle) melanoma (LMM) (RR=5.2, 95% C.I. = 1.7-15.8). Lee (1982) has, in fact, suggested that the pathogenesis of LMM is closely analogous to that of the non-melanoma skin tumor SCC.

Cumulative hours of sun exposure were also higher among cases than controls. The relative risks of CMM after adjustment for age, presence of nevi, hair color, and sunburn propensity were 3.2 (95% C.I. = 0.9-12.4) for 2,000-50,000 hours of exposure and 5.3 (95% C.I. = 0.9-30.8) for 50,000 or more hours of exposure. In the control population alone, total hours of sun exposure and hair color were also associated with risk of actinic tumors.

Based on the established link between chronic sun exposure and actinic tumors, and the results showing an increased occurrence of actinic tumors among CMM patients, Green and O'Rourke (1985) concluded that large cumulative UV radiation exposures were associated with an increased risk of CMM.

Vitaliano and Urbach (1980) examined several risk factors for SCC and BCC in a case-control study. The study included 366 BCC and 58 SCC cases seen at the Tumor Clinic of the Skin and Cancer Hospital in Philadelphia (dates were not specified). A group of 294 white controls without carcinoma were selected from the skin and cancer outpatient department. Information compiled on each case and control included cumulative solar exposure based on vocational and military history, time spent sunbathing, and participation in outdoor sports (as a spectator or participant). Exposure was divided into four categories: E1=0-9,999 hours, E2=10,000-19,999 hours, E3=20,000-29,999 hours, and E4=30,000 or more hours. The host factors examined included complexion (pale or mild-dark), age (0-59 years or 60 and over), and ability to tan (tans or burn-sensitive).

Based on a logistic regression of the case-control data, Vitaliano and Urbach (1980) identified the most important risk factors for BCC and SCC as follows:

BCC: cumulative solar exposure ($p<0.001$) >> ability to tan ($p<0.001$) >> age ($p<0.005$) >> complexion ($p<0.025$)

SCC: cumulative solar exposure ($p<0.001$) >> age ($p<0.001$) >> ability to tan ($p<0.005$)

Cumulative solar exposure was the most important risk factor for both SCC and BCC. Ability to tan was also important even at low levels of exposure. Complexion was a less important risk factor for SCC than for BCC.

TABLE 14-3

DISTRIBUTION OF 232 CASES OF CUTANEOUS MALIGNANT MELANOMA AND 232 CONTROLS ACCORDING TO PRESENCE OF ACTINIC TUMORS: ESTIMATED RISK IN RELATION TO PRESENCE OF ACTINIC TUMORS ON THE FACE, AFTER ADJUSTING FOR PRESENCE OF NEVI ON THE ARMS AND FOR AGE

Class of Melanoma (No.)	Site of Actinic Tumors	No. of Cases (%)	No. of Controls (%)	RR a/ (95% Confidence Interval)
All classes (232)	Face	95 (41)	34 (15)	3.6 (1.8-7.3)
	Arm	109 (47)	52 (22)	
LMM (49) b/	Face	31 (63)	13 (27)	5.2 (1.7-15.8)
	Arm	34 (69)	19 (39)	
SSM, nodular, IND (183)	Face	63 (34)	21 (11)	2.8 (1.1-7.2)
	Arm	75 (41)	33 (18)	

a/ RR = relative risk: 1.0 is taken as a base-line category representing absence of actinic tumors on the face.

b/ LMM is the same as HMFM.

Source: Green and O'Rourke (1985).

Table 14-4 presents the estimated relative risks (RRs) of BCC and SCC for the combinations of risk factors considered in the Vitaliano and Urbach (1980) study. The authors concluded that the most important difference between SCC and BCC was their relationship with cumulative exposure. As shown in Table 14-4, a higher exposure level was required for BCC than for SCC to reach similar RRs. The authors noted that the maximum response of BCC to solar exposure occurred in exposure category E4 (30,000 or more hours), whereas for SCC it occurred in exposure category E3 (20,000-29,999 hours). They observed that the results were consistent with the belief that exposure to UV radiation has a greater effect on the development of SCC than on BCC although an association between BCC and sunlight does exist.

Variations in the incidence ratio of BCC to SCC by latitude again suggest that the two forms of non-melanoma skin tumors respond differently to solar exposure. The results of MacDonald and Bubendorf (1964, as cited in Vitaliano and Urbach 1980) showed that the BCC/SCC ratio decreased from approximately ten-to-one in northern United States cities to approximately two- or three-to-one in southern rural areas. Similarly, Scotto and Fraumeni (1982) noted that the ratio of SCC incidence to BCC incidence increased with decreasing latitude and increasing sunlight exposure (see Figures 14-1 and 14-2). Pollack et. al. (1982) commented that dosimetry studies revealed a poor correlation between BCC density in a site and UV radiation dose. They suggested that etiological factors for BCC other than UV radiation, such as the presence of areas of scarring and epidermal nevi, may exist.

Beral and Robinson (1981) examined the similarities and dissimilarities between the anatomic distributions of CMM, BCC, and SCC to determine whether different sun exposure patterns were likely to be involved in different types of skin tumors. As described in Chapter 11, Beral and Robinson (1981) observed that BCC, SCC, and melanomas of the head, face, and neck had similar distributions among outdoor workers, suggesting that prolonged exposure to sunlight was important in the etiology of melanomas of exposed parts of the body as well as BCC and SCC. The results also suggested that prolonged sun exposure was not involved in the etiology of melanomas of unexposed parts of the body (e.g., trunk and limbs) among office workers.

FINDINGS

The observed similarities between CMM and non-melanoma skin tumors strongly suggests that exposure to solar radiation, known to be the predominant risk factor for non-melanoma skin tumors, is also involved in the etiology of CMM. However, the available epidemiologic evidence indicates that these tumors may respond somewhat differently to different etiological factors. The following findings regarding the relationships of CMM and non-melanoma skin tumors to sunlight exposure and other risk factors can be drawn:

16.1 Prolonged sun exposure is considered to be the dominant risk factor for non-melanoma skin tumors. Similarities in the observed patterns of non-melanoma skin tumors and CMM suggest that prolonged sun exposure may also play a role in the development of

TABLE 14-4

ESTIMATED RELATIVE RISKS OF BASAL AND SQUAMOUS CELL CARCINOMA FOR 32 COMBINATIONS OF FACTORS

Exposure Grade (Total Exposure, hr)	Tans				Burn-Sensitive			
	0-59 yrs		60+ yrs		0-59 yrs		60+ yrs	
	Dark	Pale	Dark	Pale	Dark	Pale	Dark	Pale
Basal Cell Carcinoma								
E4 (30,000 or more)	3.19	4.94	4.99	7.76	6.10	9.43	9.57	14.80
E3 (20,000-29,999)	2.86	4.43	4.49	6.95	5.47	8.47	8.58	13.29
E2 (10,000-19,999)	1.77	2.75	2.79	4.32	3.39	5.26	5.32	8.25
E1 (0-9,999)	1.00	1.55	1.57	2.43	1.91	2.96	3.00	4.65
Squamous Cell Carcinoma								
E4	7.09	22.79	28.61	90.12	26.61	84.66	107.70	347.08
E3	7.09	22.79	28.61	90.12	26.61	84.66	107.17	347.08
E2	4.42	5.72	17.94	23.08	16.60	21.41	66.99	86.52
E1	1.92	1.00	7.76	4.03	7.19	3.74	29.19	15.06

Source: Vitaliano and Urbach (1980).

CMM particularly HMFM. These similarities include an elevated risk among light-skinned individuals who have a susceptibility to sunburn, blue/green eyes, red/blonde hair, and a Celtic heritage, and among predisposed susceptible individuals (e.g., xeroderma pigmentosum patients). A latitudinal gradient and notable incidence increases over the past several decades have also been observed for both CMM and non-melanoma skin tumors.

16.2 Differences between non-melanoma skin tumors and CMM indicate, however, that prolonged sun exposure is only one of a complex set of risk factors that may be involved in the etiology of CMM. The differences between CMM and non-melanoma skin tumors include their overall anatomical distributions by sex, the concentrations of CMM on usually unexposed sites and non-melanomas on usually exposed sites, and the potential importance of nevi in the development of CMM.

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SECTION III

REVIEW OF THE EXPERIMENTAL EVIDENCE

CHAPTER 15

ADVERSE EFFECTS OF SOLAR RADIATION: EVIDENCE FROM CELLULAR/MOLECULAR STUDIES

INTRODUCTION

Although it may be possible on the basis of epidemiologic evidence to draw conclusions as to whether sunlight is a causal agent for cutaneous malignant melanoma, the determination of whether UV-B is an active component of such a process will require a thorough understanding of the molecular and cellular effects induced by UV-B. This chapter is designed to present a review of the information relevant to assessing the role of UV-B in cellular and molecular events. The information is treated generically in separate sections detailing effects at the cellular or molecular level, followed by a section integrating observations and relating them to melanoma and melanocytes.

As indicated in Figure 3-6, the energy from solar radiation reaching the earth is principally derived from wavelengths in the visible range (400-800 nm), although significant amounts of energy in the ultraviolet (200-290 nm: UV-C; 290-320 nm: UV-B; 320-400 nm: UV-A) and infrared (800-17,000 nm) ranges are also received. The photobiology of sun-induced lesions is primarily concerned with the wavelengths that reach the earth's surface and have biologic effects. A significant amount of biological research has been done using wavelengths in the UV-C (200-290) range, however, so that the biologic effects of this band of radiation are particularly well characterized. As a consequence, wherever possible, information on UV-B, UV-A, and visible light are compared and contrasted with information on UV-C.

EFFECTS AT THE CELLULAR LEVEL

At the cellular level, solar radiation and its component ultraviolet and visible wavelengths have been observed to cause such changes in cells as the induction of cell division and/or differentiation, the loss of specialized functions, mutation, transformation, and death. Subsequent subsections will discuss these changes, and how they relate to the initiation or promotion actions of carcinogenesis and in the next section, those events occurring at the molecular level that are thought to be responsible for the changes observed at the cellular level will be reviewed. Wherever possible the material reviewed will be prioritized so as to first present information on mammalian epidermal cells, followed by information on other animal cells; in some instances, information on bacterial cells, where informative or instructive, will also be cited.

Cell Division/Differentiation

A single in vivo exposure of human skin to UV-B radiation can cause the epidermis to thicken, thereby increasing the tolerance of skin to subsequent radiation. This response is due to a sustained increase in keratinocyte mitosis and is associated with similar changes in the rates of DNA, RNA, and protein synthesis (Gange and Parrish 1983).

Most of the work elucidating this mitotic response has used single exposures of human or animal skin, although similar studies using repeated exposures have found similar responses. Following irradiation, the first change observed (1 to 6 hours after irradiation) is a reduction in macromolecular synthesis, accompanied by a considerable increase in DNA repair (which peaks immediately after irradiation and is diminished in 5 hours) (Epstein et al. 1970). This change in DNA repair is followed by an increase in macromolecular synthesis and mitosis that generally persists for several days and may last as long as a week. UV-B and UV-C are the most effective wavelengths for this response, although it has also been seen with UV-A.

The pathway by which this thickening proceeds is not known. However, concomitant with the stimulation of proliferation, UV irradiation induces a large increase in epidermal ornithine decarboxylase. The increase is first seen at 2 hours post-irradiation, reaches a first plateau at 4 hours and a more sustained plateau at 24 to 30 hours, then declines to normal after 48 to 72 hours. At peak concentration the level of ornithine decarboxylase may be 200 times greater than that seen initially. What makes this an interesting observation is that ornithine decarboxylase is the rate-limiting enzyme in the synthesis of the polyamines putresine, spermidine, and spermine, which are increased during proliferative states. Tumor promoters such as phorbol esters also induce ornithine decarboxylase, although with a somewhat more rapid time-course (O'Brien 1976)--one that is similar to that seen with multiple UV-B exposures (Lowe 1981)

UV-B radiation exposure also induces melanocyte division. In a study of the mitiotic activity of epidermal melanocytes from C57BL mice, Rosdahl and Szabo (1978) observed that a five- to sixfold increase in the epidermal melanocyte population of the ear was associated with tritiated thymidine (^{3}HTdr) labeling of 65 to 80 percent of the melanocytes. The administration of the ^{3}HTdr was timed in such a way as to ensure that the labeling was the result of DNA duplication and not repair. The authors suggest that the high percentage of labeled cells is indicative that the UV-B-induced increase in melanocyte population is primarily the result of mitosis, and that the activation of tyrosinase negative "precursor cells" or the invasion of dermal melanocytes probably contributes little to the increase in melanocyte numbers observed. Interestingly, these authors also observed that 26 to 55 percent of melanocytes in the control ear (which was shielded from irradiation) were also labeled. There was no increase in the number of melanocytes in the control ear, suggesting that the labeling was not being stimulated by a systemic effect of irradiation. This conclusion contrasts, however, with that of Scheibner et al. (1986), who evaluated the kinetics of melanocyte density in human skin before and after sunbathing. These authors felt that "sunlight appeared to stimulate melanocytes, both directly in sun-exposed skin and, indirectly, to a lesser extent, in non-sun-exposed skin, 6-8 weeks after cessation of sun-exposure."

Other investigators, studying the response of melanocytes in the mouse trunk epidermis, have concluded that the increase in the number of active melanocytes after exposure of black mice to UVR involves both proliferation and recruitment of amelanogenic melanocytes (Miyazaki et al. 1974). This work

finds support in the observation by Uesugi et al. (1979) that indeterminate cells containing 100 angstrom (intermediate) filaments are precursors of the melanotic melanocytes that appear in UVR-irradiated trunk skin. In human skin, there is a great variation in dopa reactivity among nonirradiated melanocytes, leading to the suggestion that there may be large numbers of amelanotic or weakly melanogenic melanocytes which escape detection in sheets of nonirradiated epidermis but which upon irradiation with UV develop uniformly intense dopa reactivity (Quevedo et al. 1969; Quevedo and Fleishmann 1980).

The effects of UVR described above are equivalient to those ascribed by Slaga (1983) to be the major function of skin promoters: "...epidermal hyperplasia, and an increase in polyamines, prostaglandin and dark basal keratinocytes...." Two stages of promotion are recognized in mouse models of tumor promotion. Characteristics of the first stage are 1) that only one application of a first stage promotor such as phorbol esters, HgO2, or wounding is needed; 2) the action is partially reversible, 3) an increase in dark basal keratinocytes is important and 4) the increase can be inhibited by anti-inflammatory steroids and protease inhibitors. The second stage of promotion is mutually reversible and then later becomes irreversible. Polyamines and epidermal cell proliferation are thought to belong to the second stage (Slaga 1983). On the basis of this information, sunlight would seem likely to be both a first and second stage promoter. It behaves like a first stage promoter in that high doses are known to induce "dark basal" (hyperkeratotic) keratinocytes (Gschnait and Brenner 1982; Ley and Applegate 1985); a process which in marsupials has shown to be mediated via pyrimidine dimers (Ley and Applegate 1985). This in turn suggests that it may be reversible (before cell division) via the intercession by photoreactivating enzyme or other repair processes. Sunlight behaves like a second stage promotor that it induces polyamine synthesis and epidermal cell proliferation.

Loss of Specialized Function

Exposure to UVR has been found to result in impairment of antigen presenting cell function in both the mouse and man (Greene et al. 1979). The original observation resulting in this discovery was that of Kripke (1974): that most UV-induced tumors are rejected by normal syngeneic hosts but not by UVR-treated hosts. Investigation of this phenomenon led to the discovery that UVR-treated mice were immunosuppressed due to the presence of UV-tumor-antigen specific suppressor lymphocytes (Ts) (Kripke et al. 1977; Daynes et al. 1977), and an investigation of the reasons for the generation of such suppressor cells led to the discovery of a defect in antigen presenting cell function. (A more detailed discussion of this system is presented in Chapter 18.) About the same time it was determined that the cell responsible for antigen presentation in the skin was the Langerhans cell (LC) (Stingl et al. 1978; Toews et al. 1980) and that these cells are very sensitive to ultraviolet radiation (Toews et al. 1980; Aberer et al. 1981). In the work by Toews et al. (1980), C57BL/6 mice were irradiated with 100 J/m^2 once a day for 4 days (using the output from an unfiltered FS20 sunlamp) on a shaved 2.5 cm^2 area of abdominal wall skin, and then tested in a standard immunizing

regimen for development of delayed type hypersensitivity (DHS) to dinitrofluorobenzene (DNF). The radiation regimen produced moderate thickening of the epidermis but no significant cellular infiltrate, yet normal immunization did not occur. Furthermore, there was a direct correlation between the number of ATPase-staining LCs in the skin and the ability of the skin to permit sensitization during the time period following radiation when LC were repopulating the irradiated skin. Subsequent experiments showed that the specific unresponsiveness of UV-irradiated skin was local--irradiation of abdominal wall skin did not alter the DHS response of dorsal skin.

The loss of ATPase positive cells observed by Toews et al. (1980) was first interpreted to be the result of cell death or emigration. However, subsequent work by Aberer et al. (1981) confirmed the work of Toews et al. and extended it to show that after UV radiation, LCs lose their ability to react with antibody to the Ia surface antigen. These experiments also showed that despite their loss of ATPase staining, many LCs remained in the epidermis and could be detected by electron microscopy. Furthermore, additional work by Streilein et al. (1980) showed that UVR delivered at 100 J/m^2 per day for 4 days did not affect the immunogenicity of skin grafts in donor-host pairs differing only by the I region of the major histocompatibility complex. Since Langerhans cells are the main source of I region antigens in the skin, this suggested that UVR does not destroy LC. An action spectrum for the effect of UV on LC (Noonan et al. 1984) indicates that while very low doses of 270 and 290 nm UV radiation produced significant alterations in the morphology and ATPase staining of LC, similar doses of 270 nm radiation did not. However, these authors also showed that at 320 nm, where there was no effect on the numbers or morphology of LC, there was a significant effect on DHS, thus demonstrating that UV effects on LC and UV-induced suppression of DHS could be separated through the use of different wavelengths of UV radiation (Noonan et al. 1984).

Mutation

Ultraviolet light is mutagenic for both bacteria and mammalian cells. In bacteria, UVR-treated cells, if subsequently treated with photoreactivating light, show a substantially decreased frequency of mutants per survivor, leading to the conclusion that pyrimidine dimers are responsible for much of the observed mutagenesis (Hall and Mount 1981). Peak et al. (1984) derived action spectra for DNA dimer induction, lethality, and mutagenesis in E. coli over wavelengths between 254 and 405 (Figure 15-1), and found that all three end-points decreased in efficiency in a similar fashion as the wavelengths of radiation increased. Between 300 and 320 nm, all characteristics showed differences of about 2.5 orders of magnitude. Furthermore, between about 250 and 320 nm, the values for the three end-points either coincide with or closely parallel Setlow's (1974) proposed average DNA action spectrum. In the UV-A range (above 325 nm), the spectra for the three end-points diverge sharply, with lethalities at the UV-A wavelengths approximately ten times greater relative to mutagenicity than at the shorter wavelengths.

The mechanism by which UV-induced mutations are produced in bacteria is still under investigation. There are efficient repair processes available to bacterial cells for the removal of pyrimidine dimers. Nevertheless, the close

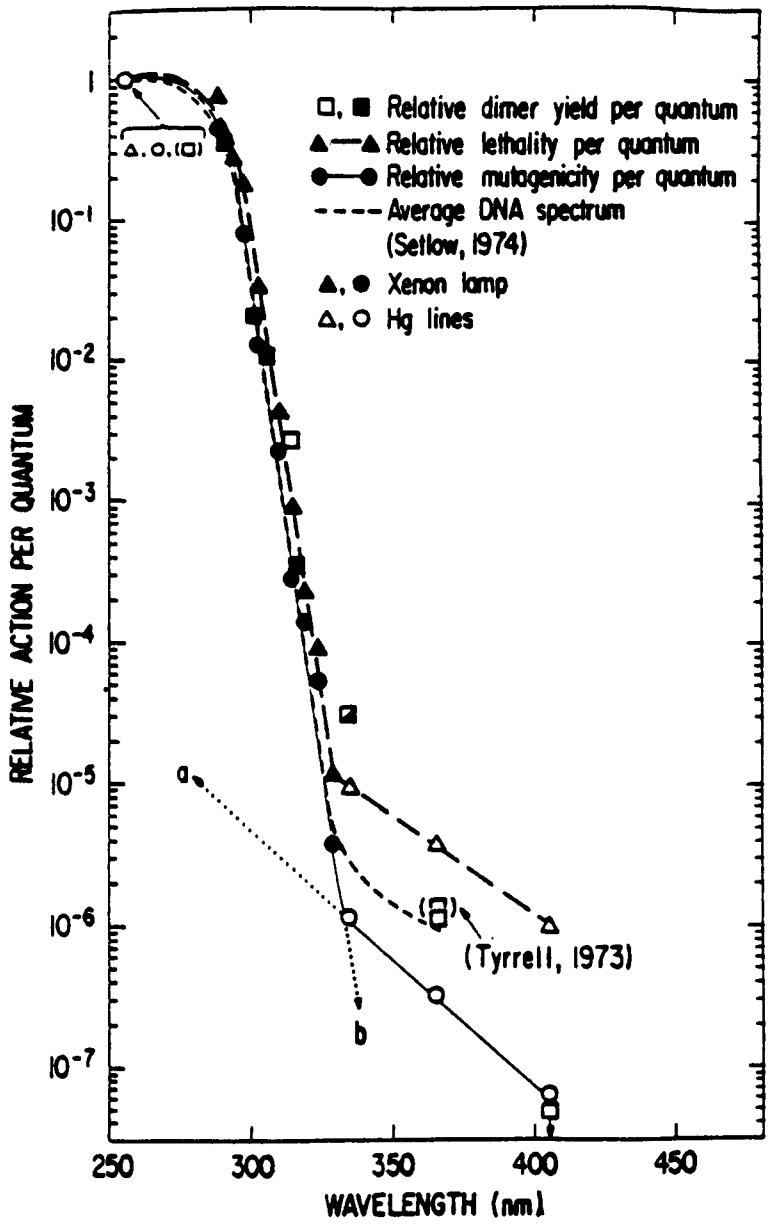


FIGURE 15-1

ACTION SPECTRA FOR DNA DIMER INDUCTION, LETHALITY, AND MUTAGENESIS

Source: Peak et al. (1984).

association between the action spectra for UV-induced mutations and pyrimidine dimers at wavelengths below 320 suggests that pyrimidine dimers are somehow involved. Two possibilities are suggested by the evidence. First, analysis of UV-induced mutations shows that many of them are produced opposite pyrimidine pairs in the DNA strand which serves as the template for replication--suggesting that the mutations may have occurred because of some type of DNA misrepair past pyrimidine dimers. Since pyrimidine dimers disrupt normal base pairing, what may have occurred is the insertion of one or two incorrect bases opposite the damaged sites (Hall and Mount 1981).

Studies of irradiated bacteriaphage lambda suggest an alternative hypothesis, for mutations in the phage DNA occur even when the host bacterial cell is irradiated and the phage added subsequently. One explanation for this observation is that host cell functions, induced by UV irradiation, may relax the fidelity of replication, thereby producing mutations during the replication of undamaged DNA (Hall and Mount 1981).

Experiments performed using fibroblasts from xeroderma pigmentosum (XP) patients and contrasting their responses to normal human fibroblasts (Mahler et al. 1979) suggest that unexcised pyrimidine dimers present in cellular DNA at the time of cell division are also responsible for the production of mutations in mammalian cells. These authors found that normal human fibroblasts which were UVR-irradiated, then stimulated to undergo cell division by immediate replating, showed much higher numbers of mutations than similarly irradiated cells which were maintained for 7 days as nondividing monolayer cultures, thus indicating that normal human cells can repair the damage (presumably by excision repair) induced by UVR. XP cells, by comparison, gave comparable number of mutants whether replated immediately or given 7 days of incubation. Since XP cells are unable to excise pyrimidine dimers, these experiments suggest that unexcised dimers present at the time of cell division may have been responsible for the production of mutations.

The early experiments in XP cells were performed principally at 254 nm. Subsequent work provides an action spectrum for lethality in XP fibroblasts which indicates that between 254 and 313 nm, pyrimidine dimers are the major lethal lesions. At UV wavelengths above 313, however, lethality is mediated by a different, unknown mechanism (Keyse et al. 1983).

The importance of mutation to an assessment of the role of UV-B in melanoma development lies in a theory of carcinogenesis which suggests that somatic mutation in mammalian cells is the first step down a pathway which includes malignant transformation and ends in neoplasia and metastasis (Trosko and Chu 1975). Peak and his colleagues (Kubitschek et al. 1986) have built upon that hypothesis to derive estimates of the increase in mutagenesis and basal and squamous cell skin cancer which might be expected from increased fluences of solar UVR resulting from ozone depletion. Their conclusions (which are based on the action spectrum for mutagenesis in E. coli; unpublished information in similar studies in mammalian cells; information on the epidermal transmission rate of the various UV wavelengths; and consideration of a biological amplification factor taken from van der Leun [1984] were that a 3 to 5 percent stratospheric ozone depletion rate would lead to an increase in

non-melanoma skin cancer rates of about 10 to 20 percent. If UV-B is mutagenic for melanocytes, then similar predictions for melanoma are reasonable.

Transformation

In vitro transformation is thought to be correlated, albeit imperfectly, to in vivo tumorigenesis (Heidelberg 1977). As such, it has been used extensively to characterize the potential carcinogenicity of a wide variety of chemicals and physical agents. Cells which have been induced in vitro to undergo loss of certain normally-seen growth controls are frequently, although not always, tumorigenic in mice. A hierarchy of transformational changes is recognized and the ability of cells to grow without attachment to a solid substrate (loss of anchorage dependence) is generally accepted as the best correlate to tumorigenicity (Freedman and Shin 1974).

While most of the in vitro experimentation with UVR has used lamps that emit most of their radiation at 254 nm, there is some information from studies using both monochromatic and polychromatic light sources, producing wavelengths between 290 and 400. Withrow et al. (1980) compared the transformation of murine BALB/c 3T3 cells with a germicidal and a GE 275 watt sunlamp and found both were capable of transforming these cells in vitro to anchorage independent growth. Although studies on the in vitro transformation of epidermal cells are rare, work by Ananthaswamy and Kripke (1981) indicates that transformation of primary cultures of BALB/c epidermal cells is possible with a UV-B-emitting FS40 sunlamp. Six of the seven resultant transformed lines produced tumors when injected into immunosuppressed mice. These tumor cell lines lacked histologic characteristics of epidermal cells but were shown by electron microscopy to possess the intermediate cell junctions that are characteristic of epidermal cells.

In the same laboratory, Fisher et al. (1984) transformed the murine fibroblast cell line 10T1/2 with a germicidal (primarily emitting 254 nm) lamp and showed that, like their in vivo transformed counterparts (Kripke 1977), the in vitro transformed cell lines grew preferentially in UV-B-irradiated mice. This was not true of cell lines transformed with the carcinogen 3-methylcholantrene or with X-irradiation, indicating that there was an antigenic similarity between cells transformed in vitro and in vivo with UVR.

It could also be shown that FS40 UV irradiation in vitro of murine fibrosarcomas which were induced in vivo with UV-B, increased their metastatic potential (Fisher and Cifone 1981). In an additional experiment, Ananthaswamy (1984a) found that fibroblasts removed from mouse skin irradiated with UVR in vivo showed transformation when they were grown in vitro. Importantly, not only do these studies demonstrate that UVR is capable of transforming cells in vitro, but they also allow the comparison of in vitro and in vivo studies and demonstrate the validity of investigating in vitro transformation in order to understand the in vivo effects of UVR.

It is possible to use inexpensive filters to remove the shorter wavelengths from polychromatic UVR sources such as the FS40 sunlamp. Such

experiments show that as one removes the shorter wavelengths, the dose of UV required to transform and mutate cells increases (calculated as per surviving cell) (Suzuki et al. 1981; Ananthaswamy 1984b).

Thus, whereas the dose of polychromatic UV-B required to give a transformation frequency of about 10^{-3} per surviving cell is 500 J/m^2 for an FS40 lamp, it is about 4000 J/m^2 for an FS40 lamp filtered by polystyrene which removed the wavelengths from 280-294 (Ananthaswamy 1984b). Filtration by Mylar, which removes wavelengths below about 315 nm, further reduces both mutation and transformation frequency (Suzuki et al. 1981). Since the FS40 lamp emits less radiation at the shorter UV-B wavelengths, the inference from these studies is that the shorter UV-B wavelengths have greater transforming effectiveness. This is actually borne out by experiments with monochromatic light. Doniger et al. (1981) developed action spectra for transformation, lethality, and thymine dimer formation using a monochromatic light source. In dose response studies comparing pyrimidine dimer formation (indicative of DNA damage; discussed in detail in later sections of this chapter) and transformation of Syrian hamster embryo cells, the slopes of the dose-response curves were not always parallel. The discordance was greatest at 290 nm. The lowest exposure required for equivalent cell transformation, lethality, and pyrimidine dimer formation was at 270 nm. Comparing results at 290 and 297 nm, the relative effectiveness was 2.3 to 8.7 for dimer formation and 7.4 to 47 for transformation. Therefore, as the wavelength decreases, the effectiveness of UVR in transforming cells increases more rapidly than one would predict on the basis that the pyrimidine dimer is the sole lesion responsible for tranformation. A similar spectrum was found for induction of anchorage-independent growth in human fibroblasts (Sutherland et al. 1981). These authors also found a maximum effectiveness at 265 nm; transformation at 290 nm was six times more effective per photon than that at 297 nm.

The above data are important for three reasons. The first is the clear indication that UVR can cause transformation in cells in the absence of any confounding immunological, hormonal, or physiological effects encountered in vivo; the conclusion to be drawn is that UVR is directly transforming in hamsters, mice, and human cells of both epidermal and mesenchymal origin. The second is the confirmation that experiments conducted in vitro may be used to extrapolate effects in vivo. The third is that the shorter UV-B wavelengths are more effective in transforming mammalian cells.

As yet, there are no reports of in vitro transformation of melanocytes by either UV or carcinogens. Only recently, however, have techniques been developed that allow the cultivation of melanocytes in vitro (Eisinger and Marko 1982). As noted above, UV-B irradiation in vivo does increase the mitotic activity of murine epidermal melanocytes (Rosdahl and Szabo 1978). In an attempt to gain insight into the possible role of UVR in the induction of human melanoma, the sensitivity of human malignant melanoma cell lines to UV in vitro has been investigated. The finding that some lines are sensitive and some resistant to UVR makes drawing conclusions difficult (Chalmers et al. 1976; Lavin et al. 1981; Howell et al. 1984).

Lethality

In vitro bacterial and mammalian studies have demonstrated that one important effect of irradiation with UV is cytotoxicity. Studies of the action spectrum for this effect suggest that in mammalian cell lines, the action spectra for cytotoxicity and neoplastic transformation are the same (Doniger et al. 1981; Ananthaswamy 1984b) and correlate well with the spectrum for pyrimidine dimer formation (Doniger et al. 1981). The efficiency of both cytotoxicity and transformation goes down with increasing wavelength, however, and one group found that dimer induction alone was not sufficient to account for killing effectiveness at the upper wavelength ranges (Elkind and Han 1978). A possible answer to this apparent discrepancy may lie in the observation that at the higher wavelengths, e.g. 313 nm, lethality in bacteria can be in part attributed to an oxygen dependent DNA-strand breakage (Miguel and Tyrrell 1983). Studies using fibroblasts from XP patients as well as normal controls would tend to confirm the hypothesis that at 313 nm, a mechanism other than pyrimidine dimer formation may be important, for at 313 nm the ratio of thymine dimers to single strand breaks is 9 to 1, whereas at 254 nm it is 5700 to 1 (Cerutti and Netrawali 1979). However, in investigating the repair capabilities of the cells after these radiation treatments, these investigators found that repair mechanisms were much better able to deal with the strand breaks and that it was the unexcised dimers which represented the inhibitory lesions at both wavelengths.

EFFECTS AT THE MOLECULAR LEVEL

Chemical changes and biological damage induced by ultraviolet light require the absorption of light energy (photons) by molecules within the target. The absorption event is specific and unique, because each type of molecule is capable of absorbing radiation only in specific wavelength ranges. Examination of the absorption spectra of molecules in biological systems indicates that a number of biomolecules can absorb radiation in the 220 to 400 nm region and thus may be critical targets for detrimental UV effects (Spikes 1979). These molecules include polynucleotides like DNA and RNA, highly polymerized proteins like keratin and melanin, other proteins which contain chromophoric cofactors or amino acids, and small molecular weight compounds like urocanic acid.

The following subsections review what is known about the interaction of solar radiation with these molecules, tying the information back to events at the cellular level wherever possible, and also review the available mechanisms by which the cell can repair effects on DNA.

Keratins

As indicated in Chapter 3, keratins are a family of polymeric proteins which constitute a major protein product of the keratinocyte and are the principal structural proteins of the epidermis (Fitzpatrick and Soter 1985). Keratins are disulfide-rich proteins which strongly absorb photons in the UV-C and UV-B range (Harber and Bickers 1981). When the epidermis thickens following UV radiation, most of the thickening is due to increased production

of keratinocytes. The additional keratin produced by these cells results in a shift in the absorption maximum of the epidermis from approximately 260 nm to 275-280 nm (Agin et al. 1981).

Melanin

The ultraviolet absorption spectra of major epidermal chromophores including dopa-melanin (a synthetic eumelanin) are given in Figure 3-8. Keratins would absorb principally in the 250 to 300 nm areas of the ultraviolet spectrum because of their content of the amino acids tryptophane (trp) and tyrosine (tyr), with some contribution made by the disulfide bonds contributed by cysteine residues. In contrast, melanin absorbs across a broad range of wavelengths, although more strongly in the shorter wavelengths than the longer (it has twice the absorbance at 200 nm than at 340 nm.)

Urocanic Acid

Urocanic acid (UCA) is a naturally occurring substance found in the stratum corneum of the skin of humans and other mammals and is the major UV-radiation absorbing compound found there. Its UV absorption spectrum lies between 250 and 320 nm and there are indications that it may act as a photoreceptor, albeit not in the usual sense.

Urocanic acid is formed in the stratum corneum by a single-step deamination of histidine catalyzed by the enzyme histidine-ammonia lyase (histidase). It has been proposed that UCA acts as a natural sunscreen protecting the skin from ultraviolet radiation. However, there is evidence that patients with no histidase activity, and thus no UCA in the epidermis, are not unusually sensitive to solar radiation (Zannoni and LaDu 1963). Thus UCA may be involved in a UV-induced process, but other than that of prevention of erythema.

Based on the close fit of the absorption spectrum of UCA to the action spectrum for contact hypersensitivity, its location in the stratum corneum, and its photochemical properties, UCA has been proposed to have an effect in UV-induced local immune suppression. This is supported by experiments involving the removal of the stratum corneum with subsequent prevention of the suppression of DHS (DeFabo and Noonan 1983). However, it is now known that Langerhans cells can be destroyed by high fluences of UV-A, but this does not prevent the development of UV-B-induced suppression of DHS. In addition, UV-induced suppression of DHS can be produced by certain wavelengths that do not affect Langerhans cells (Morison 1984). These observations indicate that a factor other than injury to Langerhans cells is probably responsible for UV-induced local immune suppression. The possibility still exists that Langerhans cells may be involved in the subsequent development of a systemic immune suppression of antigen presentation which plays a role which could in turn promote tumor development.

One of these photoproducts, or a secondary product (formed by interaction between the photoreceptor and the epidermis), might enter the systemic circulation and initiate immunologic suppression. Alteration in the antigen-

presenting ability of cells or the distribution of these cells may direct the production of T suppressor cells specific for a particular antigen (e.g., a chemical contact sensitizer) (Daynes et al. 1977) instead of effector immune cells (DeFabo and Noonan 1983).

For many years the physiological role of UCA has remained obscure, despite the fact that a relatively large amount of this substance (in the trans-configuration) accumulates in mammalian epidermis. A physiological role was postulated for trans-UCA by DeFabo and Noonan (1983) as a UV-B-absorbing skin photoreceptor necessary to regulate against autoimmune attack on sun-damaged skin. Under their hypothesis, trans-UCA is converted to the cis isomer, which is then able to initiate the production of antigen-specific suppressor cells via the induction of an antigen-processing defect. These suppressor cells would be specific for the photoantigens induced on sun-damaged skin cells. UCA might therefore be involved in the outgrowth of UV-induced skin tumors by inadvertently protecting the tumor cells via the production of tumor-specific suppressor cells. These suppressor cells would be formed along with those needed to protect against autoimmune attack on sun-exposed skin.

Alternately, it has been suggested that UCA plays a role in the photoprotection of DNA. The absorption spectrum of UCA significantly overlaps with that of DNA, but UCA absorbs UVR much more efficiently. At wavelengths longer than 290 nm, UCA can be up to 300 times more likely to absorb photons than DNA (DeFabo and Noonan 1983). So, at wavelengths that are involved in photocarcinogenesis, UCA could be expected to protect DNA from some of the adverse effects of ultraviolet radiation by reducing doses which reach sensitive tissues. UCA can directly and efficiently absorb excitation energy in the trans-cis photoisomerization reaction and it is readily triplet sensitized, acting as a low triplet energy sink. Due to its low triplet energy level, UCA is also a very efficient scavenger of singlet oxygen (Morrison 1985).

DNA

As indicated in Figure 3-6, DNA has an absorption maximum at 265 nm (UV-C range). The shorter wavelengths of UV-B radiation are also sufficient to initiate a certain number of direct photoexcitations of DNA; however, as the wavelengths in the UV-B range get longer, the probability that direct photoexcitation events will occur is reduced. Thus, at 320 nm, the probability of damage to DNA via a direct mechanism is significantly less than at 290 nm.

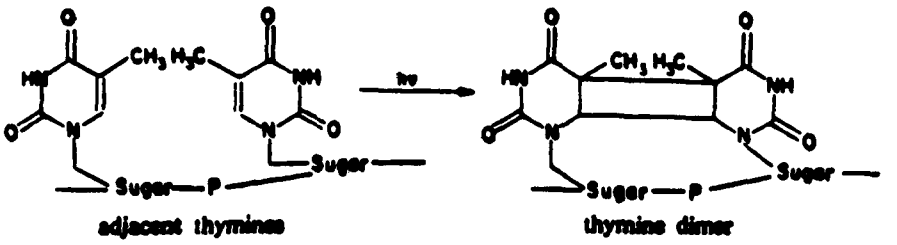
A number of different lesions are induced in DNA by UV irradiation. These include 1) pyrimidine dimers, 2) pyrimidine adducts, 3) single-strand breaks, 4) double-strand breaks, and 5) DNA-protein crosslinks. Different wavelengths have different efficiencies for the production of these lesions and there is also evidence of two possible types of mechanisms--a direct mechanism resulting from absorption of energy by DNA and an indirect mechanism involving reactive oxygen species.

The modifications to DNA by UV-B are thought to be principally by the direct mechanism, whereas those induced by UV-A are thought to be principally indirect and involve the photoactivation of natural endogenous chromophores (i.e., bilirubin, porphyrins, and urocanic acid) or photosensitive agents from cosmetics, tanning oils, or medical preparations. Most of these photosensitizers have absorption peaks in the UV-A range and become excited by UV-A photons. The excited state sensitizers then transfer energy to molecular oxygen, which in turn becomes photoexcited. Photoexcited oxygen can exist in one of several excited states at any given time and interconverts between excited states (singlets, triplets) in a poorly understood fashion (Peak and Peak 1986c). As the reactive species of oxygen decay, they can transfer their energy to cellular components, such as DNA, resulting in damage by an indirect route. The products generated by this indirect route are much the same as those generated directly; thus, the subsequent sections of this chapter discuss these products, indicating the irradiation conditions under which they have been generated.

(1) **Pyrimidine dimers** may be formed by direct absorption of photons in the UV-B wavelength range. Adjacent pyrimidine molecules on the same strand of DNA become linked together by a cyclobutane ring between the 5 and 6 carbon atoms of each residue. Figure 15-2 (taken from Robbins et al. 1974) illustrates a dimer between adjacent thymines. The 5-6 double bond of one pyrimidine molecule absorbs a photon of energy and a radical reaction involving the 5-6 double bond of the adjacent pyrimidine molecule takes place. The excited state of thymine is a much lower energy state than that of cytosine and so thymine dimers are the most likely pyrimidine dimers. Cytosine co-dimers are also possible, as are heterodimers between thymine and cytosine or uracil (Spikes 1983).

The action spectrum for pyrimidine dimer formation in E. coli cells is presented as part of Figure 15-1. As indicated earlier, the action spectra for pyrimidine dimer formation and mutagenesis are very similar. Furthermore, in vitro studies of UVR-treated mammalian cells indicate a similar action spectrum for mutagenesis (Peak et al. 1984) and dimer induction (Doniger et al. 1981) as do experiments performed in vivo in hairless mice (Ley et al. 1983). These action spectra are also in concordance with that of Freeman (1975) for ultraviolet carcinogenesis. This information, in conjunction with the observation that in fish the induction of 254 nm UVR-induced thyroid tumors can be markedly reduced by following the 254 nm treatment with photoreactivating UVR (≥320 nm) (Hart et al. 1977), suggests that pyrimidine dimers may well be important in the carcinogenesis associated with exposure to ultraviolet irradiation below 313 nm.

The induction of pyrimidine dimers of the cyclobutane type by UV-A has been demonstrated in E. coli for 334 and 365 nm radiation (Tyrrell et al. 1973; Peak et al. 1984) and in mammalian cell DNA for 365 nm radiation (Han et al. 1983). However, pyrimidine dimers have not been detected in response to fluences at 405 nm radiation at doses well above the biologically effective dose for other lesions (Han et al. 1983). Endonuclease sensitive sites in DNA have been observed in UV-A-irradiated human skin fibroblasts and keratinocytes (Schothorst et al. 1985) and in intact human skin (Sutherland et al. 1985; Gange et al. 1985).



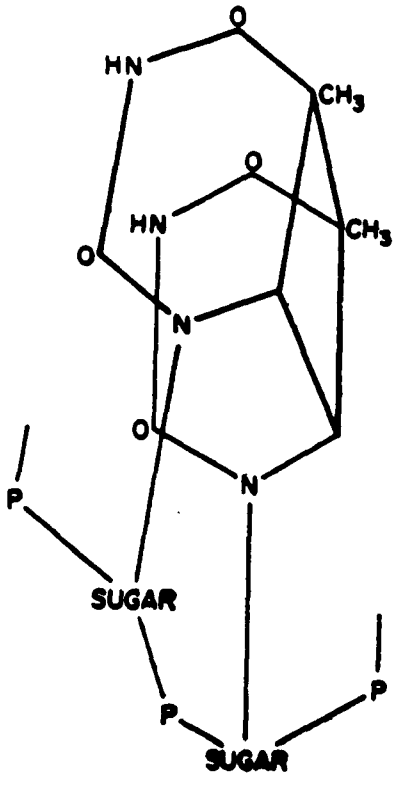


FIGURE 15-2

CYCLOBUTANE PYRIMIDINE DIMER FORMED BY UV LIGHT IN DNA

Top: Adjacent thymines form 5-5 and 5-6 bonds after absorption of UV photons.

Bottom: Approximate structure of dimer in DNA with pyrimidine rings stacked above one another.

Source: Cleaver (1983).

(2) Action spectra for four-membered ring **pyrimidine adduct** formation between two consecutive bases on the same strand of DNA resemble the action spectra for pyrimidine dimer formation (Patrick and Rahn 1976). The efficiency of formation of these photoproducts is about two to ten times lower than for cytosine-cytosine and thymine-thymine dimers. The proportion of these adducts varies according to the base content of DNA and becomes much higher when the ratio of guanine-cytosine/adenine-thymine is greater than or equal to one. The cycloaddition photoproduct that is an adduct of cytosine and thymine is quickly deaminated to form a thyminylpyrimidinone product.

Thymine glycols, another form of pyrimidine adduct, are defined as a group of ring saturated lesions of the 5,6-dihydroxydihydrothymine type and have been detected in the DNA of human cells after irradiation at 254 nm and 313 nm (Hariharan and Cerruti 1977). The formation of these lesions is probably caused by the action of hydroxyl radicals on the 5-6 double bond of thymine. In both the UV-B and UV-A range, thymine glycols may result from the action of reactive oxygen species produced by endogenous sensitizers.

These saturated lesions occur with almost the same frequency as thymine dimers at 313 nm, indicating their possible significance in the UV-B range (Cerruti and Netrawali 1979). Glycol lesions may undergo spontaneous decay to form apyrimidinic sites in a fashion similar to that described for gamma-radiation-produced saturated thymine glycols (Dunlap and Cerrutti 1975). Only about one-third of the thymine glycols are released from the DNA backbone, but there is little evidence to suggest that either the ring saturated thymine or the apyrimidinic decay products are lethal lesions in UV-irradiated DNA.

Pyrimidine hydrates of cytosine result from the addition of a water molecule across the 5-6 double bond. This water molecule is quickly and easily lost (the half-life is 58 minutes in native DNA and 51 minutes in denatured DNA). Cytosine photohydrate may be deaminated during this process, forming uracil, the naturally occurring thymine analog in RNA, and this may lead to a mutation in newly replicated DNA (Helene 1983).

Brash and Haseltine (1982) have shown that there is a linear relationship between base damage incidence and mutation incidence. For shorter wavelengths (UV-B), it seems clear that pyrimidine dimers and 6-4 photoadducts are involved in mutagenesis, but at 365 nm the correlation between dimers/adducts and mutagenesis is not known (Peak et al. 1984).

(3) **DNA single-strand breaks** can be induced directly by UV-B radiation or indirectly by UV-A. Analysis of the relative efficiencies for the induction of single-strand breaks (SSBs) reveals an action spectrum that corresponds with nucleic acid absorption below 313 nm (Peak and Peak 1986a). Relative to thymine dimers, SSBs are induced only to a small extent by 254 nm radiation, but as the wavelength is increased, the proportion of SSBs to thymine dimers increases. At 313 nm, one SSB is induced for every nine thymine dimers (Cerrutti and Netrawali 1979). Some SSBs induced at 313 nm may be due to indirect effects from photosensitizers and oxygen-dependent mechanisms (Miguel and Tyrrell 1983), but the spectral analysis indicates that the majority of SSBs induced at this wavelength are due to direct effects (Peak and Peak 1986a).

Single-strand breaks in the backbone of DNA caused by UV-A radiation deviate significantly from predictions based on a mechanism of direct DNA photoexcitation. Studies utilizing anoxic and anaerobic irradiation of human cells (Peak and Peak 1986c) indicate that oxygen is required to induce most of the DNA damage observed following irradiation at 405 nm. The enhancement of induction of SSBs by 365 and 405 nm radiation in the presence of deuterated water (D2O) shows the involvement of those reactive oxygen species that are longer-lived in D2O than in H2O. The involvement of various reactive oxygen species in the induction of SSBs at UV-A wavelengths is complicated, and several pathways have been implicated. Singlet oxygen, peroxide and hydroxyl radicals, and other reactive species have been identified as being involved in UV-A- and visible light-induced SSBs (Peak and Peak 1982).

Oxygen-dependent SSBs apparently require the participation of non-DNA photosensitizers that initially can absorb the photons of UV-A wavelength radiation, because neither DNA nor molecular oxygen absorb significant energy at these wavelengths. Various endogenous photosensitizers have been suggested, including bilirubin, porphyrins, nicotinamide coenzymes, and riboflavin (Peak and Peak 1986c). For DNA SSBs in human fibroblasts, an absorption maximum near 460 nm is observed. This maximum corresponds well with the absorption spectrum for bilirubin, suggesting that this endogenous chromophore may act as a photosensitive agent in the production of these lesions in human cells (Peak et al. 1985b).

(4) **DNA double-strand breaks** occur about 80 times less frequently than single-strand breaks at 313 nm in bacteria (Tyrrell 1984). Coupled with data indicating that 90 percent of x-ray-induced double-strand breaks in mouse leukemia cells are reannealed within 2 hours (Bradley and Kohn 1979), this indicates that double-strand breaks are likely to have little effect on cell lethality or transformation in mammalian cells. There appears to be a similar fast repair mechanism for double-strand breaks induced by non-ionizing ultraviolet radiation (Ley et al. 1978).

(5) **DNA-protein crosslinks** can be induced by borderline UV-B radiation (290 nm) via a direct photon-absorbing mechanism in human cellular DNA. That the mechanism of DNA-protein crosslinking does not involve photosensitizers and reactive oxygen species can be seen from aerobic/anaerobic experiments in D2O and water, in which no difference was observed in the amount of DNA-protein crosslinking for each of the conditions (Peak et al. 1985a).

DNA-protein crosslinking that results from irradiation at wavelengths above 290 nm is probably due to photodynamic effects involving excited photosensitizers and reactive oxygen species (Peak et al. 1985b). The action spectrum for DNA-protein crosslinking deviates significantly from the DNA spectrum (Figure 15-3), suggesting that crosslinks are induced by an indirect mechanism. Below 320 nm, there are approximately 40 DNA-protein crosslinks per lethal event. As cells can survive 2×10^3 DNA-protein crosslinks induced at longer wavelengths (405 nm), it appears that such a small number of DNA-protein crosslinks is not important in UV-induced cell lethality, assuming that there are no interactions between dimers and DNA-protein crosslinks (Peak et al. 1985b).

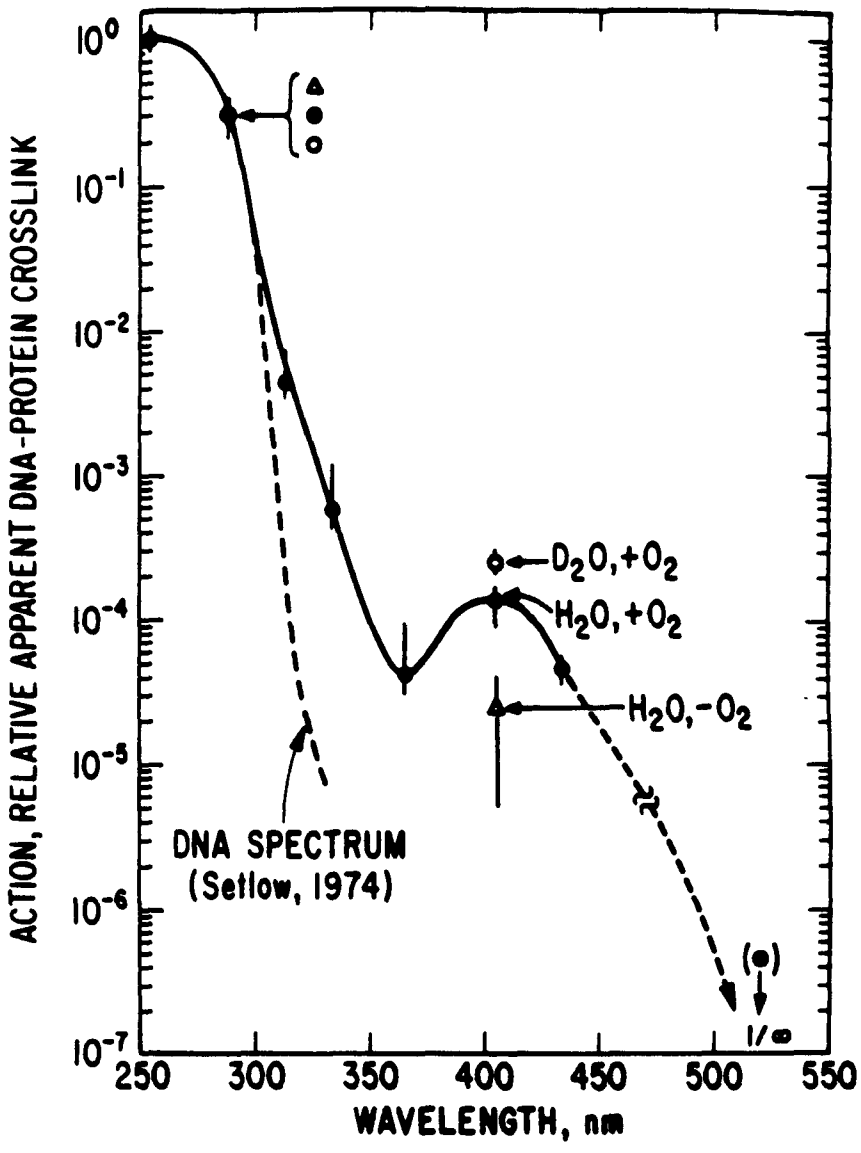


FIGURE 15-3

ACTION SPECTRUM FOR THE INDUCTION OF DNA-TO-PROTEIN CROSSLINKS COMPARED WITH THE SPECTRUM OF DNA

DNA spectrum redrawn from Setlow (1974).

Source: Peak et al. (1985b).

DNA-protein crosslinking is demonstrable in normal human fibroblasts immediately after ultraviolet light irradiation, but this crosslinking is partially reversed after about 12 hours. In fibroblasts from XP patients, crosslinking after UV exposure was not reversed and actually progressed with time, leading to the suggestion that crosslinks might be important to the mechanism of the toxicity of UVR for XP patients. It has also been suggested however, that the observed inability to repair crosslinks is a secondary change due to severe cell damage (Fornace and Kohn 1976). The mechanism of the abnormal sensitivity of XP cells to UV radiation has previously been considered to be due to defective capacities to repair cyclobutylpyrimidine dimers in cellular DNA (Smith and Paterson 1981).

One study (Sugiyama et al. 1984) has shown crosslinking between photoexcited thymine residues on DNA and the lysine ε-amino groups of histones (proteins in the helical interstices of DNA). Although this experiment was conducted using cellular extracts in buffered solution, it would seem reasonable to infer that photocrosslinking of DNA to histones is likely in intact cellular systems, given their proximity in the nucleosome.

DNA-protein crosslinks can also be induced by ultraviolet radiation in the UV-A range via an indirect mechanism that is largely oxygen dependent (Peak et al. 1985a). A minor peak at 405 nm indicates that porphyrins (a class of photosensitizers) may be involved. The action spectrum for DNA-protein crosslinking in the UV-A range indicates an aerobic dependence and a D2O enhancement that is consistent with an indirect photodynamic mechanism involving singlet oxygen. The spectral dependence of the formation of DNA-protein crosslinks in the UV-A region indicates that crosslinks may play a significant role in cell lethality and mutagenicity. It should be noted that at 405 nm the only lesions induced in DNA by irradiation are single-strand breaks and DNA-protein crosslinks. Because single-strand breaks are considered non-mutagenic and their numbers do not correspond well with lethality, it appears that DNA-protein crosslinks may by more likely to play a role in mutagenic and lethal events due to UV-A exposure.

Although the biological significance of DNA-protein crosslinks is not clear, it would seem that these lesions are not lethal to the cell. In normal cells the number of DNA-protein crosslinks per genome per lethal hit is greater than 900 (Peak and Peak 1986a). The conclusion that normal cells have the ability to repair these lesions seems reasonable, as it is unlikely that DNA could be properly replicated with significant amounts of protein covalently bonded to DNA.

RNA

Since the vast majority of organisms carry their genetic information in DNA, photochemically-induced RNA damage is much less biologically significant than damage to DNA. Because RNA is replaceable, photoinduced modification may not be a factor in mutagenesis and lethality. Modification of the properties of messenger RNA could be important, but the occurrence of such changes has not been demonstrated (Tyrrell 1984).

DNA-DNA

Little is known about intramolecular DNA crosslinks, but they are formed in low yields by far ultraviolet radiation (Patrick and Rahn 1976). DNA-DNA crosslinks have not been detected at longer wavelengths, but some chemical compounds are known to induce these lesions (Bradley et al. 1979). The presence of these lesions even in small amounts could lead to serious problems in DNA replication.

Purine damage

Quantum yields for purine damage are typically ten times lower than those for pyrimidines, but this type of damage does exist (Patrick and Rahn 1976), and presumably must be removed from DNA. It seems likely that cellular endonucleases and glycosylases would remove this type of damage (Tyrrell 1984). The low incidence of purine damage also suggests that these are not significant lesions in DNA, thus not major contributors to mutagenesis or cell death.

DNA REPAIR MECHANISMS

When cellular DNA is damaged, the lesions may either have the potential to cause cell death, or may be less severe and merely disturb DNA transcription and replication. Changes in DNA that adversely affect cellular functions and survival need to be repaired in order to assure continuation of a species. Any process that removes lesions from DNA and/or restores a functional DNA molecule is generally called a repair mechanism. Often the repair of a lethal DNA lesion may result in a functional DNA, but with an accompanying modification of the base sequence leading to altered genetic characteristics in the surviving cells. Based on the somatic mutation theory of carcinogenesis discussed earlier, it is these lesions that result in mutations that subsequently result (presumably) in neoplastic transformation.

Modes of repair that generate altered segments of DNA are generally called "error-prone" mechanisms, whereas repair mechanisms that result in unchanged DNA are called "error-free." The occurrence of misrepair may be due to a malfunction in the repair process, or to the presence of certain physiological conditions or cellular enzymatic processes that play a role in the repair of DNA lesions. The inaccuracy of any repair mechanism is likely to result in secondary structural changes in DNA, some of which may lead to mutations.

Many modes of repair are considered constitutive, that is, they are always "turned on." Excision repair and post-replication repair are always operational, although at very low rates, even in the absence of UV light or any other insulting agent. Other mechanisms are activated only in the presence of DNA damage (SOS Repair) or are triggered by the incidence of light at specific wavelengths (photoreactivation).

Photoreactivation

Repair of DNA lesions mediated by light-induced enzymatic process is termed photoreactivation. The usual photoreactivation results from the action of a single cellular enzyme, deoxyribodipyrimidine photolyase (Hall and Mount 1981). This enzyme is present in both bacteria and mammalian cells, but probably constitutes a major pathway for the removal of pyrimidine dimers from DNA only in bacteria. In bacteria, the photoreactivating enzyme (PRE) is activated by light in the range 310-440 nm, with a peak activity around 385 nm (Ikenaga et al. 1970). In mammals, PRE has an action spectrum which extends into the yellow wavelengths (up to 600 nm) and operates at a lower ionic strength than the prokaryotic PRE, leading to the suggestion that the human enzyme may play a different role in the cell (Cleaver 1983).

The photoreactivating enzyme binds very tightly to DNA containing pyrimidine dimers but does not bind to native DNA. Upon absorption of light in the appropriate nm range, the PRE photocatalyzes the splitting of the cyclobutyl ring of pyrimidine dimers, regenerating the original pyrimidine bases (Helene 1983).

A second type of photoreactivation (Type II PR) has been demonstrated in E. coli. Type II PR has a much narrower wavelength range (310-370 nm) than the Type I enzyme, with a peak of activity around 340 nm. Type II PR does not split thymine dimers and apparently has the same mechanism as photoprotection (Ikenaga et al. 1970). Type II PR removes pyrimidine adducts from DNA, but not directly, and has therefore been called indirect photoreactivation.

A third type of photoreactivation in bacteria, Type III PR, has an even narrower wavelength range (310-340 nm), with a peak at about 315 nm (Patrick 1977). This type of photoreactivation removes cytosine-thymine heteroadducts from DNA but the mechanism is unknown.

Studies involving the induction of pyrimidine dimers by 365 nm radiation indicate that these lesions may contribute to lethal damage at this wavelength (Tyrrell 1973). Following the observation that pyrimidine dimers are induced by 365 nm radiation, it was noted that photoreactivation of these lesions was not observed. As pyrimidine dimers induced at 365 nm are normally photo reactivatable, the data suggest that photoreactivating enzyme may be destroyed by high doses of 365 nm radiation (Tyrrell et al. 1973).

Excision Repair

Perhaps the most common mechanism for repairing UV-induced damage to DNA is excision repair. The process has been extensively studied for bacteria. In bacteria, an endonuclease recognizes lesions specific for UV-induced damage and splits the phosphodiester bond near the dimer, usually on the 5' side. Following this "cut," the DNA fragment containing the lesion peels away, and another enzyme, DNA polymerase, uses the complementary undamaged strand as a template to resynthesize the damaged strand, in the 5' to 3' direction. The dimer region is then excised by the exonuclease activity of DNA polymerase. Finally, the newly synthesized DNA and the original DNA strand are joined by

DNA ligase. This process, at least in E. coli, is under the control of a complex system of genes designated UVR A, B, and C. Their gene products (proteins) associate at pyrimidine dimers on UV-irradiated DNA and cleave the DNA chain as indicated above. Excision repair systems have been well characterized in bacterial systems but the comparable mammalian enzymes have not been well studied (Hall and Mount 1981).

The process of excision repair of thymidine dimers in eukaryotic cells does appear to differ significantly from excision repair in bacteria. It had been proposed that the mode of excision repair for mammalian and animal cells is a nick-and-cut method similar to that for bacteria, but evidence from experiments involving human cells indicate that this is not the case. Instead, excision repair in eukaryotic cells involves extensive exonuclease action to make a wide single-strand region before polymerization, removal of an oligonucleotide considerably larger than the pyrimidine dimer, or a combination of both (Cleaver 1984). The distinctive action of eukaryotic polymerases (especially polymerase a, which cannot act on nicked substrates) indicates that excision repair involves a sequence of between 10 and 20 bases. Thus, the mode of excision repair for UV-induced damage in human cells is probably significantly different from the mechanism utilized by E. coli.

Excision repair has also been implicated in the repair of other types of UV-induced DNA damage. Any DNA lesions involving crosslinking of adjacent moieties on the same strand of DNA are subject to excision repair. The excision of cytosine-thymine heteroadducts has been noted in M. radiodurans (Varghese and Day 1970), which has a high concentration of cytosine. This high concentration of cytosine results in more UV-induced cytosine-thymine heteroadducts (and a noticeable rate of repair) than in other organisms that have a lower relative concentration of cytosine in their DNA.

The rate of cytosine-thymine heteroadduct formation in human and animal cells is probably around 5 percent of all thymine-containing lesions. In eukaryotic cells, these lesions are also removed by an excision repair mechanism.

Excision repair is involved in the removal of ring saturated thymine products of the 5,6-dihydroxydihydrothymine type (thymine glycols) from UV-irradiated mammalian cells (Hariharan and Cerrutti 1976). DNA-protein photoinduced crosslinks are also removed by excision repair (Helene 1983).

At least one other type of ultraviolet radiation-induced lesion is removed from DNA by excision repair. Photoinduced complexes between furocoumarins and DNA have been shown to be excised from E. coli by the action of the UVR A, B, C complex. Psoralens, a type of furocoumarin, are used in phototherapy of skin diseases (in conjunction with UV-A for the prophylaxis of psoriasis), in some tanning preparations, and in cosmetics. These psoralen compounds complex with DNA, and upon absorption of UV-A light are covalently bound to DNA (De Mol et al. 1981). These photoinduced covalent bonds between DNA and psoralens can then be removed by the action of an excision repair mechanism.

The removal of psoralens covalently linked to DNA is important because, not only are the psoralen-DNA adducts likely to represent premutagenic or precytotoxic lesions, the furocoumarins can also act as photosensitizing agents, producing singlet oxygen in the presence of UV-A. De Mol et al. (1984) have shown that while psoralens which are not complexed to DNA produce some singlet oxygen, covalently bound psoralens produce more than three times as many singlet oxygen molecules. Thus excision of psoralen covalently bound to DNA is important in the prevention of mutagenicity and cell lethality both because of the direct effect of the adduct and because of possible indirect effects of ultraviolet radiation mediated by singlet oxygen formation.

Post-Replication Repair

When DNA synthesis occurs in UV-irradiated cells, the newly synthesized DNA has been found to have a lower molecular weight than newly synthesized DNA from unirradiated cells. The low molecular weight is due to gaps in the DNA daughter strand that arise because replication is blocked at pyrimidine dimers and other lesions, and then resumes at some site past the lesion. Repair of these gaps has been called post-replication repair or daughter-strand gap repair. It should be noted that post-replication repair is not a repair process removing damage from DNA, such as occurs in excision repair and photoreactivation, but rather a process enabling cells to replicate damaged chromosomes (Hall and Mount 1981). It may not accurately repair the damaged DNA and is thus sometimes referred to as error-prone repair.

During this type of repair the gaps are filled and the discontinuous strands are joined into molecules of high molecular weight. The mechanism by which this occurs involves recombinational strand exchange, resulting in stretches of parental DNA covalently bound to daughter strands (Walker et al. 1985). After the transfer of DNA, via a series of complex rearrangements, any new gaps created in the second daughter strand can be filled by DNA polymerase using the correct information on the original undamaged parent strand.

In E. coli, this process is under control of the recA gene, whose product plays a fundamental role in the recombination step. The final fate of the damage may be removal by excision repair, or it may be "diluted out" by being transmitted to only one of the daughter cells (Helene 1983). Post-replication repair in bacterial systems results in 50 percent of thymine dimers being transferred from parental to newly synthesized strands of DNA.

In UV-irradiated human fibroblasts there are conflicting data concerning recombination as a mechanism for gap-filling. The action of UV-specific endonucleases indicates that pyrimidine transfer may occur at a low rate (5 to 15 percent of total pyrimidine dimers) but some pulse-labeling studies indicate that this may not be the case. Other pulse-labeling studies (label introduced 2 hours after UV treatment) indicate that pyrimidine dimers can be detected in newly synthesized DNA (Hall and Mount 1981).

Although the possibility of pyrimidine dimer transfer from parental to newly synthesized DNA may not be great, there are other mechanisms that indicate genetic recombination could still be involved in gap-filling. It is

conceivable that only short fragments of DNA (compared to the average distance between dimers) might be exchanged, thereby reducing the chance of dimer transfer to newly synthesized DNA. Additionally, SV-40 virus probably utilizes host-cell functions to undergo UV-induced recombination, and so these same processes might also act on UV-damaged cellular DNA (Hall and Mount 1981).

Convincing evidence that either supports or denies a recombinational repair method in UV-irradiated mammalian cells is lacking. Even though DNA replication is temporarily blocked at the sites of pyrimidine dimers, it is difficult to say how different mammalian cell types react subsequently. There are conflicting data on gap formation, DNA synthesis re-initiation, and genetic recombination in the repair of gaps opposite UV-induced lesions; thus, a clear picture of post-replication repair in mammalian cells is not yet available.

Constitutive expression of DNA polymerase may account for repair of some UV-induced lesions. Peak and Peak (1982) have shown that an oxygen-dependent mechanism is involved in the production of single-strand breaks at longer wavelengths in both wild type and mutant strains of bacteria. Single-strand breaks induced in E. coli by 365 nm UVR can be repaired by a fast mechanism in wild-type cells, with up to 80 percent of lesions repaired in 10 minutes (Ley et al. 1978). In DNA-polymerase-I-deficient mutant strains of E. coli, repair of 365 nm-induced single strand breaks is not observed.

The rate of induction of single-strand breaks in DNA polymerase I-proficient cells may be lower in vivo than in vitro due to the immediate action of pre-existing polymerase. Because DNA polymerase apparently is responsible for the resealing of single-strand breaks in DNA, intact cells may repair single-strand breaks during the course of irradiation, thereby producing fewer breaks than would be expected based on studies of cell-free isolates of DNA.

DNA polymerases also play a role in the elongation of daughter strand DNA. Lesions on parental strands of DNA are known to at least temporarily inhibit elongation of DNA daughter strands (Tyrrell 1984). One such lesion is the apyrimidinic site formed by the spontaneous release of damaged bases from UV-irradiated DNA. Thymine dimers and thymine glycols are examples of lesions induced in UV-irradiated DNA that can be spontaneously released by the action of glycosylases from the DNA backbone leaving apyrimidinic sites (Dunlap and Cerrutti 1975). DNA polymerases have been shown to incorporate nucleotides into apyrimidinic sites (Walker 1985) using the opposite strand as a template.

The repair of pyrimidine hydrates is extremely difficult to measure both in vivo and in vitro. Although there are no known photoenzymatic or direct photolytic removal processes for pyrimidine hydrates (Tyrrell 1984), a mechanism for repair has been postulated. Cytosine hydrates, their deaminated products (uracil and uracil hydrates), and rare thymine hydrates are susceptible to recognition and removal by glycolytic activity, leaving an apyrimidinic site. This would be followed by the usual response to apyrimidinic sites.

CELLULAR AND MOLECULAR MECHANISMS IN MELANOMA

The relevance of the foregoing discussion to melanoma induction is dependent on the demonstration that UVR can cause mutagenesis and transformation of melanocytes. Unfortunately, the conditions required to obtain proliferating cultures of melanocytes have just recently been defined and experiments in which UVR has been used to transform melanocytes have not yet been published. There is some information on melanoma cells maintained in vitro, however, which indicates that some cell lines are particularly resistant to cell killing following irradiation with 254 nm UVR, whereas others are not (Chalmers et al. 1976; Lavin et al. 1981). The differences were not thought to involve the pyrimidine dimer excision repair process.

Research from another laboratory (Konishi 1981) examined not only excision repair but also caffeine-sensitive (post-replication) repair in melanoma cell lines. This report also concluded that the difference did not lie in the excision repair process, and noted that the data suggest that melanoma cell lines demonstrate a more rapid post-replication repair process which is also more caffeine sensitive than that seen in the comparison (HeLa) cells. This report has not been confirmed, and so must be viewed with caution. It does, however, suggest an interesting hypothesis, which is presented below.

Given that UV is clearly mutagenic for both fibroblasts and epidermal cells, with the most active wavelengths for this effect in the UV-B range, it is reasonable to conclude that UV-B will be mutagenic for melanocytes. Differences in the relative efficiency of mutagenesis as compared to keratinocytes may occur because the melanin produced by melanocytes may protect the nuclear material in a manner which is dose dependent but has a threshold such that small doses never reach the DNA but large doses either saturate the ability of the melanin to absorb them or saturate the ability of the melanocyte repair processes to repair them. Alternatively, or perhaps in conjunction with the protection to the DNA provided by melanin, a more effective post-replication repair mechanism may contribute to the apparently different responsiveness of melanoma and the non-melanoma skin cancers to solar radiation.

FINDINGS

The material reviewed above leads to the following findings:

15.1 UVR is the most active portion of solar radiation in the induction of adverse effects; it has been shown in vivo and in vitro to induce transformation of mamalian epidermal cells. It is also mutagenic. All of these effects are thought to occur via a mechanism that involves DNA damage.

15.2 UV-B is the most active waveband for these effects and for the induction of pyrimidine dimers, which are thought to be important to skin cancer development, e.g., in XP patients.

15.3 UVR and in particular UV-B is active in the induction of melanogenesis and beratinocyte proliferation--two mechanisms which provide protection from solar radiation to the basal layer.

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CHAPTER 16

UV RADIATION CAN CAUSE SKIN CANCER IN ANIMALS

The presence of melanoma and other skin cancers in animals offers the theoretical possibility that these animals can be used as models for discovering the role of sunlight and ultraviolet B radiation (UV-B) as an agent in the development of melanoma. This chapter reviews information on the natural occurrence of melanoma in animals, potential animal models of melanoma, attempts to induce melanoma in animals in the laboratory, and induction of non-melanoma skin cancer in laboratory animals. There are two important lines of analysis that are pursued: the direct evidence for a UV-B/melanoma relationship by the induction of melanoma under experimental conditions, and an analysis of the potential of ultraviolet radiation (UVR) and in particular UV-B to cause melanomas by examining its capacity to directly induce other epidermal cell neoplasms.

ANIMAL MODELS OF MELANOMA

The investigation of animal models of melanoma has proceeded along two lines: (1) evaluation of the development of spontaneous melanomas in domestic animals, and (2) evaluation of melanomas induced in laboratory animals. The following section briefly discusses the occurrence of melanomas in domestic animals, and then discusses in greater detail the induction of melanocytic tumors in laboratory animals.

Although melanomas do occur spontaneously in domestic animals, the incidence is too low to serve as a potential model for the effect of UV on cutaneous melanoma, with the exception of the high melanoma incidence of Duroc and Sinclair swine.

The histopathologic correlation of the biological behavior of melanoma in domestic animals has been studied and has some similarities to melanoma in man. Benign tumors with junctional activity and dermal melanomas ("blue nevi") have been identified. In dogs, malignant melanomas composed of epithelioid cells or spindle cells or both have been identified. The epithelioid type of malignant melanoma carries the worst prognosis, especially if there are areas with a high mitotic index. These melanomas have been reported to metastasize widely, mainly to lymph nodes and lung.

Occurrence of cutaneous melanomas in domestic animals has been reported in a wide variety of species, including dogs, cats, horses, mules, donkeys, cows, pigs, sheep, Indian water buffalos, gerbils, hamsters, rabbits, and chickens (rev. in Garma-Avina et al. 1981). With the exception of dogs, the incidence of melanoma is rare in domestic animals. The reported frequency of melanomas in dogs ranges from 2.3 percent of all tumors studied to 19.6 percent of cutaneous tumors studied. Purebred dogs, including boxers and cocker spaniels, were overrepresented in more than one study. Larger tumors which appear late in a dog's life (mean 9.5 years) were more apt to be malignant than ones that occur at an earlier age.

In grey horses, incidence of melanoma may reach 80 percent if animals survive to old age (Garma-Avina et al. 1981), but in other horses, only 1.6 to 4.8 percent of all tumors have been reported to be melanomas. The different types of melanomas identified in dogs have not been recognized in horses. Melanomas are rare in cattle (Garma-Avina et al. 1981), constituting less than 1 percent of tumors. Unlike dogs, melanomas in cattle are found in nearly equal numbers in young and old animals and most are considered benign. Melanomas are also rare in cats, with an overall reported frequency of less than 1 percent.

With the exception of Duroc-Jersey and Sinclair swine, melanomas are also rare in pigs (Garma-Avina et al. 1981). In Sinclair swine, selective breeding has increased the prevalence of cutaneous melanoma from the 11 percent reported in 1968 to as high as 54 percent at birth in the progeny of two affected pigs (Hook et al. 1979). The Sinclair swine were frequently born with melanoma, although most tumors appeared in the first year of life. This is an interesting system, in that melanomas, including any metastases present, usually regress (Hook et al. 1982). Only rarely does the melanoma kill the host. Although direct proof is lacking, the tumor regression is probably immunologically mediated since the host inflammatory response in regressing tumors is characteristic of cell-mediated immunity. This is also supported by the observation that lymphocytes from swine with melanoma are highly toxic to melanoma cells in vitro, with patterns of leukocyte reactivity that for the most part paralleled the patterns of in vivo tumor growth and regression (Berkelhammer et al. 1982a). The histopathology of these tumors is similar to human tumors and, likewise, metastatic disease is correlated with deeply invasive tumors. Melanocytic tumors in Duroc swine also demonstrate spontaneous regression and rare metastases, and the occurence is as high as 50 percent of offspring of two affected pigs (Hordinsky 1985). However, no studies have been reported examining the effects of UVR or of sunlight on the growth of these tumors.

The experimental induction of melanomas was first reported in the late 1930's and early 1940's, when a great many studies were done examining the effects of carcinogenic tars and purified polycyclic aromatic hydrocarbons in laboratory animals. In 1938, Passey reported the induction of three tumors, all melanomas (one was histologically malignant), in the skin of dogs after six to seven years of tarring. However, the latent period of the tumors was extremely long and this did not prove to be a valuable animal model for the induction of melanomas. Further work concentrated on three animal species, all of which are susceptible to induction of melanoma: the hamster, the guinea pig, and the mouse. The following section discusses melanoma induction in these three species, beginning with the hamster.

Experimental induction of melanomas in hamsters was reported in 1956 by Della Porta et al. who investigated the production of melanotic lesions by a single dose of 7,12-dimethylbenzanthracene (DMBA) painted on the skin of Syrian golden hamsters. These tumors were located in the dermis and subcutaneous tissues and were sharply demarcated from surrounding lesions. The tumors were not considered malignant because there were no signs of invasion or metastasis even when tumors reached a diameter of 4 cm and even

though efforts to transplant the tumor as fragments were successful in two cases. Repeated application of DMBA, rather than a single dose, gave rise to papillomas and carcinomas rather than melanomas.

Although the original studies were done in brown hamsters, Rappaport et al. (1961) and Nakai and Rappaport (1963) produced tumors in white hamsters. Tumors in white hamsters were sometimes amelanotic, were reported to contain neural elements, and were clinically benign, in contrast to spontaneous hamster melanomas, which are malignant and do not contain neural elements.

Bernfeld and Hamburger (1983) published a comprehensive study detailing the kinetics of the appearance of DMBA-induced melanocytic tumors in genetically defined hamsters. Most of the work was done in F10 Alexander hybrids. They reported that hamsters were susceptible to the induction of melanocytic tumors with DMBA but that benzo(a)pyrene and 3-methylcholanthrene did not induce melanocytic tumors. Promotion of DMBA-induced melanocytic lesions with TPA was not reported to increase the number or decrease the latent period of melanocytic tumors induced in hamsters. It was stated that DMBA-induced tumors greater than 2 mm in diameter were usually malignant melanomas which "occasionally" metastasized, although no systematic autopsies were reported. The number of weeks required for 95 to 100 percent of the hamsters to develop melanomas was dose dependent, reaching a plateau of 9 to 10 weeks at 100 mg/hamster. At 10 mg, the time required to develop melanomas was 14 weeks, and at 3.33 mg, 26 weeks. The average number of melanomas per hamster was also dose dependent, reaching a plateau at 3.33 mg DMBA per hamster. There were wide variations in susceptibility of various strains of hamsters to DMBA induction of melanomas; however, differences were not related to coat color. Different strains of white hamsters and agouti hamsters were among both the most and the least sensitive.

Melanocytic tumors can also be produced by a single intragastric dose of DMBA (Goerttler et al. 1982). The yield of melanocytic tumors could be approximately doubled by painting with TPA. Histopathology of the tumors in this study was not reported.

Another carcinogen, urethan (ethyl carbamate), which is not a polycyclicaromatic hydrocarbon (PAH), also induces melanocytic tumors in hamsters (Pietra and Shubik 1960; Toth et al. 1961) when introduced into the drinking water but not following cutaneous application. Non-melanoma tumors also appeared in the forestomach of animals treated both topically and systemically with urethan.

Vesselinovitch et al. (1970) induced malignant melanomas in Syrian white hamsters with urethan injected intraperitoneally in neonates. Treated animals developed melanomas in 62 percent of males and 40 percent of females. Unlike the melanocytic tumors induced by skin painting with DMBA, these tumors were much more metastatic. Fifty percent of tumor-bearing animals of both sexes had lymph node metastases and 82 percent of males and 25 percent of females had distant metastases. No systematic description is given of the histopathology of the primary tumors but it is evident that those which

metastasized were clearly malignant. No information is given on the number of melanomas per animal.

Therefore, melanocytic tumors induced in hamsters by topical application of DMBA are usually not malignant by the criteria of metastasis. However, the tumors are usually multiple and can sometimes be transplanted into suitable recipients. Therefore, as a model for human malignant melanoma, this system has severe limitations. Malignant melanomas induced with urethan in hamsters seem to be biologically more relevant to human studies in that the tumors are malignant and do metastasize. However, there are no reported studies on the developmental biology of these tumors and thus the similarity to human melanomas is not known.

Melanocytic tumors produced by DMBA in guinea pigs have been reported to be more frequently malignant than those similarly induced in hamsters. Berenblum (1949) reported one of ten spotted guinea pigs painted with DMBA developed a melanoma on pigmented (brown) skin which invaded extensively and had lymph node metastases. Animals injected, rather than painted, with DMBA did not develop melanoma, a finding which is identical in all the species which are susceptible to induction of melanocytic tumors via cutaneous application of DMBA. Edgcomb and Mitchelich (1963) also painted guinea pigs of various colors and reported that 4 of 20 female guinea pigs developed invasive melanomas, 3 of which metastasized widely. The melanomas were said to be surrounded by nevi but no histological description is given of the nevi.

Pawlowski et al. (1976) produced junctional and compound nevi in albino guinea pigs by painting with DMBA. Pigmented spots appeared in 40 of 70 animals and the number of spots per animal increased over time. None regressed but no signs of malignancy such as invasion or metastases were reported. Focal incontinuities were seen in the dermoepidermal junction in nevi excised 6 months after their appearance (at the end of the study), and it is possible that if the experiment had been carried further, invasion and/or metastasis would have occurred.

In another sequential study, Clark et al. (1976) chose the Weiser-Maple guinea pig, a pigmented animal with a uniform coat color. Lesions were excised or biopsied periodically from the 5th to the 130th week of painting. The results showed that the lesions progressed from focal, small, well-demarcated melanocytic tumors, through increasing size and cellular atypias, to a stage Clark et al. call a malignant melanoma with "intralesional transformation," deep invasion, and frequent and progressive lymph node metastasis. Intralesional transformation was described as showing clusters of cells which were nearly pigment free and which upon occasion showed pleomorphism and mitotic figures. Stages having small, non-progressively growing lymph node metastases were not termed malignant. Only 4 to 5 percent of animals bearing melanotic lesions demonstrated intralesional transformation. The authors stated that the developmental biology of the early stages of human and guinea pig melanomas is quite different but both go through well-defined histological stages.

Thus skin painting of guinea pigs with DMBA does lead to the induction of malignant melanomas, albeit with low incidence. However, although sequential painting of hamsters resulted in the induction of carcinomas and papillomas rather than melanocytic tumors, melanoma induction in guinea pigs is reportedly increased by repeated skin painting. There are no literature reports on investigations of the effect of UV-B on melanocytic tumors in the guinea pig.

One of the first laboratory animals in which melanomas were induced was the mouse. As early as 1940, Badger et al. reported the production of melanomas in an undefined strain of mice by the repeated application of 5,9,10-trimethyl- 1,2-benzanthracene (TMBA) in benzene. Hartwell and Stewart (1942) painted DBA, C57 Black, I, C57BLxDBA, and DBAxC57BL mice with TMBA in benzene twice weekly for 10 months. There were more non-melanoma tumors than melanomas in all groups, and none of the albino mice (I) developed melanomas. However, the pigmented mice developed melanomas and the susceptibility was strain dependent, with C57BL x DBA and DBA x C57BL mice the most susceptible, followed by C57 and then DBA. The pigmented foci induced by the TMBA appeared to be benign collections of melanocytes in the subcutaneous tissue near the epidermis, and were not considered malignant. Burgoyne et al. (1949) also painted C57BL, DBA, and their F1-hybrids with TMBA twice weekly up to 16 months. Although the incidence of pigmented foci was somewhat less than observed by Hartwell and Stewart (1942), the same relative susceptibility of the strains was observed. Only one invasive malignant melanoma was found in a female DBA after 221 days of painting.

Klaus and Winkelmann (1965) painted Mayo pigmented hairless mice with DMBA. Those hairless mice which were more pigmented (called "dark" in the study) developed numerous pigmented lesions in seven of ten animals, beginning 8 to 10 weeks after the initial application of carcinogen. The tumors were in mid-dermis, no metastases were seen, and there was no cytological or clinical evidence of malignancy.

Recently two groups have repeated some of the work of Hartwell and Stewart (1942) and have induced pigmented lesions on C57BL mice with DMBA. Berkelhammer et al. (1982b) used a single application of DMBA to the scapular area of newborn C57BL/6 mice followed by applications of croton oil. Two melanomas appeared in female littermates, JB/MS and JB/RH. Both have exhibited metastases upon transplantation. Takizawa et al. (1985) painted 7-week-old female C57BL/6, DBA/2, BALB/c x DBA (BDF1) and C57BL x DBA (BDF1) mice once with DMBA and thereafter with croton oil thrice weekly for 2 years. Small black macules appeared in C57BL, BDF1, and CDF1 mice after about 25 weeks. Macules over 2 mm were called malignant melanomas, and in addition 125 of 206 lesions were examined histologically. Again, the BDF1 mice, were more susceptible to induction of melanocytic tumors than CDF1 and C57 mice, respectively. Pulmonary metastases were noted from one BDF1 tumor, although lymph node metastases were not mentioned.

Thus melanocytic tumors and malignant melanomas can be induced by skin painting with DMBA in mice, although the susceptibility is highly strain dependent and appears not to occur in albino mice.

Herlyn et al. (1986) transplanted human cutaneous nevi onto nude mice. Over a period of 2 to 3 months the nevi were found to change such that the number of nevomelanocytes and the tendency of the nevic cells to form nests decreased. When transplanted human nevi were treated with DMBA, most nevomelanocytes showed signs of hypertrophy, and in four of the nine specimens treated with DMBA for longer than 80 days, there were atypical enlarged nuclei with mitotic figures. Therefore, DMBA is capable of affecting the growth and differentiation of human melanocytes as well as melanocytes of laboratory animals.

Occurrence of Ultraviolet Light-Induced Melanomas

The interaction of UVR and melanomas has only rarely been investigated in animal studies. UVR of mice in the absence of previous chemical induction results in papillomas, squamous cell carcinomas, and spindle cell sarcomas rather than melanocytic tumors. Melanomas are extremely rare if they occur at all.

However, there is some evidence from animal studies that UVR can influence the growth and progression of melanocytic tumors in mice. Benign blue nevi were produced on the backs of hairless mice by Epstein et al. (1967) with a single application of DMBA. Thirteen months after DMBA application, mice were irradiated with a lamp, most of whose UVR was in the UV-B range. In 5 of 11 mice surviving to 5 months after irradiation, invasive melanomas developed. There were apparent lymph node metastases but no evidence of distant metastases. Transplantation was unsuccessful; however, the mice were not inbred. Mice receiving DMBA alone, UV alone, or no treatment did not develop melanomas. The conclusion reached was that UV-B resulted in the production of melanomas from the benign melanocytic tumors.

Ultraviolet light was also implicated in the production of a single melanoma in one of 40 C3H mice given ten UVR treatments over a 2-week period, followed by twice weekly painting with croton oil (Kripke 1979). The tumor arose in the 92nd week and was named K1735. Bilateral metastases were seen in the lymph nodes, although no distant metastases were found. The tumor was transplantable and a lung metastasis was found in the third transplant generation in an immunosuppressed mouse. The original tumor arose in an area of hyperpigmentation; interestingly, there are no reports in the literature of spontaneous melanomas in C3H mice. Tumors induced in haired mice by UVR are usually squamous cell carcinomas and fibrosarcomas.

The relationship of spontaneous and induced melanocytic tumors in animals to melanoma in humans is unclear. In most animal models, the rate at which metastasizing tumors of melanocyte origin are induced is quite low. For example, 1 mouse in 90 (Takizawa et al. 1985), 2 mice in 20 (Berkelhammer et al. 1982b), and 4 to 5 percent of treated guinea pigs (Clark et al. 1976) developed metastatic tumors of melanocytic orgin. The rate of metastatic

melanomas produced by urethan in white Syrian hamsters is much higher, but no attempt has been made to examine the developmental biology of these tumors. Additional difficulty is caused by the lack of agreement on terminology in the animal tumors. For example, authors frequently neglect to state clearly by what criteria a tumor is deemed malignant. Some authors designate well-circumscribed groups of melanocytes melanomas, whereas others others consider tumors to be malignant if they are invasive, and others consider only call tumors with a relatively heavy metastatic load malignant. This adds to the confusion and makes comparison of studies difficult, but it is clear that melanomas can be induced by chemicals (DMBA, TMBA, urethane) in hamsters, guinea pigs, and mice, both by skin painting (DMBA, TMBA) and by systemic administration (urethane, DMBA).

The relationship of UV light to the development of melanomas has apparently been addressed in two studies. Epstein et al. (1967) clearly induced growth and progression of chemically-induced nevi by treating those nevi with UVR. In addition, UVR is also strongly implicated in the induction of the K1735 melanoma in C3H mice.

Therefore, although the effect of UVR on the majority of animal models of melanoma has not been measured, two studies suggest that UVR may play a role in melanoma induction under the right experimental circumstances. Because they focus primarily on chemical carcinogens, most studies on melanoma in animals neither support nor refute the hypothesis that UVR is at least partially responsible for induction of human melanoma. Studies showing that UVR can cause progression of chemically-induced melanocytic tumors lead to speculation that a similar process may occur in humans. However, there is no direct evidence that this occurs in humans and only limited data from animal studies.

UV-INDUCED CARCINOGENESIS IN RODENTS

The association of sunlight with human skin cancer has been discussed since the beginning of the 20th century. The observation that men who had outdoor occupations seemed to suffer more skin cancer prompted Findlay to look experimentally for evidence that UVR was carcinogenic. In 1928, Findlay reported that not only did UVR alone induce skin tumors in mice, but tumors induced by tar appeared more rapidly if those mice were subsequently exposed to UVR. The tumors induced in mice by UVR are primarily squamous cell carcinomas and fibrosarcomas (Epstein and Epstein 1962; Hsu et al. 1975; Kligman and Kligman 1981; Kripke 1977; Spikes et al. 1977; Stenback 1975; Strickland et al. 1979; Winkelman et al. 1963) and are mostly monoclonal in origin (Burnham et al. 1986). The following section discusses the action spectrum of UVR in tumorigenesis in laboratory animals, strain and genetic differences in susceptibility, and some other factors found to affect the induction by UVR of tumors in laboratory animals.

Subsequent studies expressed interest in determining which wavelengths were responsible for the carcinogenicity of UVR. Unfortunately, there is a lack of agreement among many of the studies. Early studies used filters to remove shorter wavelengths from broadband UVR so that the effect of different

wavelengths could be studied. In one of the original studies on the carcinogenic action spectrum of UVR, Rusch et al. (1943) reported that the carcinogenic wavelengths lay between 290 nm and 334 nm; wavelengths greater than 334 nm and those at 254 nm were not found to be carcinogenic. However, a germicidal lamp, which emits at least 90 percent of its UVR at 254 nm, was found to be carcinogenic in mice (Lill 1983) and rats (Strickland et al. 1979). A potential explanation for this difference in results is that the dose of UVR to mice in the second experiment was 3 x 10^4 J/m^2/wk, whereas in that of Rusch et al. (1943) it was approximately 2 x 10^3 J/m^2/wk, a 15-fold difference.

Blum (1943) reported that nearly comparable doses of broadband UVR were less effective in producing tumors when wavelengths of less than 297 nm were removed by filters. A dose of 8.8 x 10^4 J/m^2 from the unfiltered lamp resulted in a median tumor latent period of 167 days, whereas filtration to remove wavelengths of less than 297 nm reduced the dose to 8.0 x 10^4 J/m^2 and increased the median latent period to 300 days. Upon calculation of the dose which penetrated below the epidermis, the discrepency is even greater. However, removal of wavelengths below 265 nm, which reduced the incident dose to 4.1 x 10^4 J/m^2 but only reduced the UVR which reached below the epidermis from 1.3 x 10^4 J/m^2 to 1.0 x 10^4 J/m^2, resulted in a median latent period of 187 days, not appreciably different than the unfiltered lamp. Therefore, he concluded that the most effective wavelengths in producing tumors in mice lay in the region between 260 nm and 300 nm. Strickland et al. (1979) also compared the tumor yield from UVR at 254 nm to that of a lamp emitting UV-A+UV-B and found that the UV-A+B lamp was much more effective in producing tumors. However, if the dose of UVR was corrected for penetration of the statum corneum, then the two lamps were very similar.

Additional experimentation was done using monochromatic UVR by Freeman (1975). He compared doses of UVR with an equivalent minimal erythemal dose (MED), using data from human skin as a guide. Therefore, the ears of albino mice were exposed to a weekly dose of 420 J/m^2 at 290 nm, 600 J/m^2 at 300 nm, 7500 J/m^2 at 310 nm, and 49,500 J/m^2 at 320 nm. Using these doses, the mice receiving UVR at 300 and 310 nm developed tumors with the same median latent period. Only 2 of 5 mice receiving radiation at 320 nm developed tumors, and no mice irradiated at 290 nm developed tumors. When mice were given the same incident radiation at 300 and 310 nm, no mice given radiation at 310 nm developed tumors. Therefore, the carcinogenic effectiveness of UVR at 300 nm is greater than at 310 nm. This finding is also paralleled by in vitro studies which show that above a peak at about 260-265 nm, the shorter the wavelength, the greater the effectiveness of cell transformation (Suzuki et al. 1981). However, the relative lack of effectiveness at 290 nm is somewhat surprising and does not correlate with in vitro findings. But Cole (1981) has published extensive studies on the action spectrum of acute skin damage to mouse skin and has found that UVR at 290 nm is <u>less</u> effective in producing acute skin damage than UVR at 300 nm. In other words, there is a peak in the erythema action spectrum at 300 nm. Given this information, to use an equivalent MED in these experiments, Freeman would have had to use UVR at 290 nm, at a higher dose than at 300 nm, rather than the lower dose which he did use. This may explain why, if the hypothesis is correct that tumorigenicity

is proportional to erythemal effectiveness, no tumors were produced at 290 nm, and would explain the discrepancy between this report and that of Blum discussed above. This is substantiated by a recent report from the same laboratory (discussed below) (Cole et al. 1986).

Forbes et al. (1982) addressed the question of the carcinogenic action spectrum with a study designed specifically to test the effect of simulated stratospheric ozone depletion on photocarcinogenesis in hairless mice. They used filters to remove increasing amounts of UVR so that the effects of varying the dose-rate on photocarcinogenesis could be determined. However, this also has the effect of incrementally removing shorter wavelengths of UVR. They also tested the ability of the R-B sunburn meter to predict tumorigenicity. Results of the experiments showed that the tumorigenicity of UVR could be correlated with its erythemal effectiveness. More important for this discussion is the finding that the R-B sunburn meter underestimated the carcinogenic effectiveness of the shorter wavelengths of UVR. This is particularly important for the decision to regulate CFs, since it is the shorter wavelengths of UVR which will increase most with decreasing stratospheric ozone.

Cole et al. (1986) reported on determination of the carcinogenic action spectrum using three sources of UVR and a series of filters to further produce source spectra. The tumorigenic effects of these sources were then analyzed mathematically using an equation which incorporated the spectral source description and a weighting function dependent on the action spectrum for acute skin edema in hairless mice. The equation assumed no effectiveness from wavelengths greater than 330 nm, and the results supported the conclusion than the relative carcinogenic effectiveness of radiation greater than 330 nm was less than 0.02 percent of that at 297 nm. There was no evidence for wavelength interaction in the spectral range of from 260 to 400 nm. The group examined their data using several weighting functions. Using an averaged DNA action spectrum in the plotting of data of tumorigenesis resulted in overweighting of the importance of the shorter wavelengths; use of the R-B sunburn meter to weight the relative importance of the wavelengths underestimated the contribution of the shorter wavelengths; the relative effectiveness of UVR in inducing edema 48 hours after a single acute dose of UV (MEE48) proved to be the best of the three tested predictors of source effectiveness in tumorigenesis. The investigators state that their results are consistent with many previously reported papers but are specific for certain parameters, such as the strain of animal used, irradiation geometry, and time-dose reciprocity. In addition, the mathematical relationship does not hold in linear fashion for low doses of UVR. It would predict a 50 percent tumor incidence at 0 dose in 70 weeks. The relationship for predicting 50 percent tumor incidence fails at approximately 110 J/m^2 (MEE48 weighted dose). Thus, the mathematical relationships described here will not serve to predict tumor yield in all cases, but supply valuable insights into the relative donation of efficacy of the various wavelengths found in UV sources.

UV-A has also been reported to cause tumors in mice, albeit in very large doses. For example, van Weelden et al. (1983) reported that it required approximately 3,000 times greater incident energy for UV-A compared to UV-B,

to produce tumors with approximately the same median latent period. More important for this discussion, there is one report in the literature that UV-A augments the carcinogenic effects of UV-B (Willis et al. 1981) both when a constant daily dose of UVR is given and when doses which escalate weekly are used. In addition, Staberg et al. (1983) reported that mice irradiated with UV-B for 3 months, followed by irradiation with UV-A had greatly increased tumor incidence. Therefore, although UV-A is, in and of itself, a poor carcinogen, it is reported here to interact with UV-B in an as yet undefined manner to increase the carcinogenic effects of UV-B (although these results are not in agreement with those of Cole et al. [1986]).

There are significant genetic differences in susceptibility to UV-induced carcinogenesis, both among different strains of the same species and among different species. Of the experimental animals tested, mice are the most sensitive to the carcinogenic effects of UV-B. Stenback (1975) compared the effects of UVR in mice, rats, guinea pigs, and hamsters. He found that, using the same protocol of repeated UV exposure, 40 percent of rats and 50 percent of mice developed tumors, whereas 35 percent of hamsters but only 12.5 percent of guinea pigs did so. However, in the mouse, 70 percent of the tumors were malignant, whereas in the rat only 24 percent were malignant, in the hamster only 3 percent, and in the guinea pig none were malignant. Therefore, although mice, hamsters, and rats are similarly sensitive to the tumorigenic effects of UV-B, mice develop more malignant tumors than the other species. Tumors can be induced in both mice (Hsu et al. 1975) and rats (Strickland et al. 1979) following a single dose of UV-B, although most of the tumors induced were benign. In addition, in mice 21 percent of the tumors spontaneously regressed, whereas in rats only about 5 percent regressed.

It is difficult to compare the induction of tumors from one laboratory to another since lamps vary and the method of measuring the UVR may vary. However, from doses published in the literature, the hairless mouse (Kligman and Kligman 1981; Winkelmann et al. 1963) seems to be equally sensitive to the carcinogenic effects of UV light as the haired mouse (Kripke 1977; Spikes et al. 1977). There are strain differences; among three inbred strains of mice, BALB/c mice were more sensitive to UVR that either C3H or C57BL (Kripke 1977), but the median tumor latent period is not influenced by the major histocompatibility complex (Roberts et al. 1984). Sencar mice, which are extremely susceptible to two-stage skin carcinogenesis by chemical carcinogens, are also hypersensitive to UVR (Strickland 1982). Huepner (1941) reported that hairless rats were less susceptible to UV carcinogenesis than their haired littermates.

Although the yield of tumors is directly related to the cumulative dose (de Gruijl et al. 1983), there has been a great deal of experimentation to determine if there is dose-rate reciprocity in UV carcinogenesis. Blum et al. (1942) studied the effect of the intensity of the dose on the tumor latent period and reported that for a 10 fold dose range of between 4.3 $J/m^2/sec$ and 0.42 $J/m^2/sec$, no significant differences were found. In a second study using a wider range of intensities and greater numbers of animals, he reported that above 0.4 $J/m^2/sec$ the effectiveness of UVR in inducing tumors is almost independent of dose-rate, but below that the effectiveness falls off

rapidly with intensity. Strickland et al. (1979) reported that the UVR dose-rate dependence of tumor yield in hairless rats was linear for 254 nm. By comparison, exposure from a lamp emitting both UV-A and UV-B resulted in more tumors per unit exposure at lower intensities than at higher intensities. These authors found that the total dose of UVR to produce a tumor in hairless rats was less at low doses than at high doses of UVR, and suggested that oncogenesis and cell lethality might be competing events at high doses. When the tumor yield per dose of UVR was corrected for lethality by measuring survival of follicles, the dose-response curve for tumorigenesis for the UV-A+B lamps increased its linearity. Additional correction for penetration of the epidermis resulted in the dose-response curves for UV-C and UV-A+B becoming nearly coincident.

Forbes et al. (1981) examined the effect of dose fractionation on tumor induction and reported that increasing the fractionation of the dose (more exposures to yield the same total dose) increased the effectiveness of the protocol. He reported that the effectiveness was related directly to the number of exposures per week, assuming that the total delivered dose per week is kept constant (Forbes 1981).

One can also calculate the amount of energy to produce tumors in 50 percent of animals to determine if the dose rate affects tumor development. De Gruijl et al. (1983) stated that the total dose delivered to hairless mice to induce tumors must be greater if a high daily dose is given than if a low daily dose is given. The greatest dose given was 9.4×10^3 J/m^2/wk, total output of lamps. The same trend was reported by Spikes et al. (1977) in C3H mice. They calculated the average tumor latency as dose of UVR received by the mice at the time that 50 percent of the irradiated mice had developed tumors. For mice receiving UV doses three times per week of 60 seconds (2220 J/m^2), the average tumor latency was reached at 29×10^4 J/m^2, whereas for mice receiving doses three times per week of 2 seconds (74 J/m^2),the average tumor latency was obtained at 2.1×10^4 J/m^2. Therefore, the amount of energy required to produce tumors was much less at low doses than at high doses.

There are many factors which serve to modify the carcinogenic response to UVR. One factor is the immune status of the irradiated animal. Unfortunately there are no simple trends, and one cannot state that immunosuppressed animals will be more susceptible to photocarcinogenesis than animals with normal immune functions. Immunsuppression by administration of rabbit anti-mouse lymphocyte serum enhanced photocarcinogenesis,where administration of 6-mecatopurine appeared to inhibit photocarcinogenesis (Nathanson et al. 1976). Treatment of mice with silica, known to decrease the number of peritoneal macrophages, increased the susceptibility of mice to UV-induced carcinogenesis when the dose of UV was abbreviated (Norbury and Kripke 1979) but not when a full course of UV treatment was given. Conversely, pyran copolymer, which increased the number of peritoneal macrophages and increased resistance to a transplated tumor, also afforded protection against photo-carcinogenesis using an abbreviated dose of UVR. Norbury and Kripke (1978) also studied the effect of T-cell-depletion on UVR carcinogenesis. Although mice which were T-cell-depleted by adult thymectomy, lethal X-irradiation, and

reconstitution with neonatal liver cells were more susceptible to UVR than control mice, the picture is complicated by the finding that the T-cell-depleted mice, when reconstituted with thymic grafts, were even more susceptible than T-cell-depleted mice to photocarcinogenesis. In addition, there were differences in the proportions of squamous cell carcinomas and fibrosarcomas in the two groups. Their finding of increased numbers of squamous cell carcinomas following whole-body radiation is interesting in the light of the reports of increased risk for skin carcinomas in psoriasis patients undergoing PUV-A (psoralen-UV-A) treatment only in those patients who had received whole body radiation (Stern et al. 1979). The ability of UVR itself to alter the immune response to a tumor, particulary UV-induced tumors, has been discussed in a separate section in this chapter.

The age of animals has also been investigated as a factor in ultraviolet carcinogenesis, particularly since sunlight-induced tumors in man usually appear in older persons. However, when both young and old mice are treated with a constant dose of UVR, young mice are more sensitive to the effects of UVR than old mice (Blum et al. 1942; Forbes et al. 1981). Ebbesen and Kripke (1982), using skin grafting as a method for separating the effects of the age of the skin and the age of the host, found that when skin was grafted and then UV irradiated, tumors developed on skin when it was grafted onto younger mice more readily than onto older mice, regardless of the age of the skin donor mice. Therefore, the finding that sunlight-induced tumors in humans usually occur in older persons may be due to accumulated dose rather than increased susceptibility of the aged.

The actual dose of UVR required to reduce tumors in 50 percent of irradiated mice varies tremendously from one report to the next. Obviously there are differences in genetic backgrounds of the animals, dose-rates of UVR employed, schedules of UVR used (daily versus three times per week), and the spectral power distribution of the lamps used. We have seen that all these factors play a role in determining the tumorigenicity of UVR in laboratory animals. Therefore, making comparisons in an attempt to arrive at a generalized dose-response is not productive. For example, Swiss albino mice developed no back tumors after 67 weeks of irradiation with a total dose of 1.3×10^4 J/m^2 (Epstein and Epstein 1962), but albino mice developed ear tumors in 50 percent of the group in 46 weeks after 1.76×10^6 J/m^2 of UVR (Blum et al. 1942), and Kripke (1977) reported a 50 percent tumor incidence after 20 weeks of UVR with a cumulative UV dose of 6×10^5 J/m^2 in BALB/c mice.

FINDINGS

None of the extensive information available on photocarcinogenesis in laboratory animals has any direct bearing on the question of the role of UVR in human melanoma. However, there are certain findings which may be used to develop predictions and hypotheses.

16.1 It is clear that UVR is carcinogenic and that UV-B wavelengths are most effective. Although the tumors induced by UV-B in laboratory animals are not melanomas, UV-B is clearly capable of causing malignant change in both fibroblasts and epithelial cells in vivo.

16.2 It is also clear that the shorter wavelengths of UV-B, those that would be increased by decreasing levels of ozone in the atmosphere, are more carcinogenic than the longer wavelengths.

16.3 There are great genetic differences in the susceptibility to photocarcinogenesis, not all of which can be ascribed to differences in pigmentation.

16.4 There are a wide variety of factors which can influence UV carcinogenesis, including dose rate, humidity, and temperature.

16.5 There is as yet no appropriate animal model in which UVR has consistently produced melanoma.

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CHAPTER 17

EFFECT OF ULTRAVIOLET RADIATION ON THE IMMUNE RESPONSE AND ITS RELATIONSHIP TO CUTANEOUS MELANOMA

Ultraviolet radiation (UVR) has a variety of effects on the immune system, many of which could affect the incidence or morbidity of melanoma. This chapter reviews information about the relevant UVR-induced effects on the immune response (IMR), and explores the impact that UVR might have on melanoma incidence and mortality mediated via the immune response. (For a more general discussion of the immune effects of UVR, refer to Chapter 9 of the document entitled Risk Assessment of Stratospheric Ozone Depletion.

The chapter first reviews the theory according to which effects on the immune system could have an impact on the carcinogenic process, and then briefly discusses the cell types relevant to the theory. Subsequent sections present information on the experimental systems used to explore the role of UVR on the IMR; this is followed by information from studies in humans. A last section discusses the relevance of this information to melanoma development.

Most studies have investigated the relationship between the effects of UVR in the induction and growth of squamous cell carcinomas and fibrosarcomas in mice, since these tumor types are the ones most frequently induced in mice by UVR. However, there is information available which relates the impact of UVR on the immune system to its potential effects on the development of melanomas.

IMMUNE SURVEILLANCE: A PROPOSED ROLE FOR THE IMMUNE SYSTEM IN CARCINOGENESIS

The most widely quoted theory which discusses the impact that the immune system may have on carcinogenesis is that of immune surveillance (Burnet 1970). Burnet proposed that throughout life cells are transformed to a malignant potential which is manifested via the expression of new antigens. Furthermore, Burnet proposed that there exists a certain population of lymphocytes which routinely "surveys" the body and kills those cells with newly-expressed tumor antigens. This theory was the outgrowth of two experimental findings. The first was that tumors bear antigens on their surfaces which were not normally expressed on the cells of an adult. The second was that there existed a population of lymphocytes which, when properly immunized, were capable of killing tumor cells. These lymphocytes were found to mature in the thymus and thus were named thymus-derived lymphocytes or T lymphocytes, frequently shortened to T cells. The immune surveillance theory provided the stimulus for a great deal of research directed at proving or disproving its validity. What has emerged is an understanding that the interaction of the immune system with neoplastic cells, although having elements of Burnet's idea, is not as simple as originally proposed.

CYTOTOXIC LYMPHOCYTES--T CELLS AND OTHERS

Although there are T cells which can kill tumors both in vivo and in vitro, the relationship between depression of T cell function and resistance to tumorigenesis is complicated. For example, "nude" mice, which are genetically deficient in T cells, are no more susceptible to chemical induction of tumors and have no more spontaneous tumors than littermates with normal levels of T cell activity (Stutman 1975). Moreover, there are cells of the immune system other than T cells which are also capable of killing tumor cells. Two such other cell types are natural killer cells (NK cells) and natural cytotoxic cells (NC cells). Both are lymphocytes which lack either B or T cell markers and can kill tumor cells nonspecifically in the absence of antibody. Killing by these cells is not immunologically specific since tumor cells can be killed without prior immune sensitization of the effector cells. It is sometimes difficult to distinguish the activities of these two cells; as a consequence some authors refer to natural cell-mediated cellular cytotoxicity (NCMC) which includes activities of both cell types. Also, macrophages, if their intracellular killing mechanisms have been activated by any of a variety of agents, can non-specifically kill tumor cells but do not kill normal cells. To complicate matters, it has been found that the precise mechanism of tumor cell control (i.e., the cell or cells which are responsible for control of tumor growth in vivo) differs widely from one tumor system to another.

EXPERIMENTAL SYSTEMS

There are practical problems in directly assessing the effects of immune alterations on tumor growth, especially in humans, since one may not transplant tumors into humans to see if they grow. However, researchers have found that there is some relationship between the ability of an animal to develop cell mediated immunity (contact hypersensitivity) such as is involved in poison ivy reactions, and the ability of the animal to develop cellular immunity to a tumor. The correlations are not perfect and there are exceptions, but the concept has allowed immunologists to examine closely many of the mechanisms of the immune response which are necessary to the rejection of a tumor.

A note should be made on the sources of UV radiation used for the experiments to be discussed. Much of the research reported here on the effects of UV-B on the immune response has been performed with fluorescent sun lamps such as the Westinghouse FS40 or FS20. These lamps emit about 60 percent of their energy in the UV-B range but also emit small amounts of UV-C and significant amounts of UV-A and visible light. Therefore, unless control experiments are done with filtered light or a monochromatic source, one cannot be certain that the effects are due specifically to UV-B (Spikes 1983). In fact, most experiments are performed with polychromatic light sources, and one should assume, unless specifically noted otherwise in the discussion, that the results may not be due solely to the effects of UV-B irradiation.

CHARACTERISTICS OF IMMUNOSUPPRESSION IN UVR-TREATED ANIMALS

One of the first reports which discussed the potential effects of UVR on the immune response to UVR-induced primary tumors was that of Kripke (1974), who reported that most murine tumors induced by UVR were highly antigenic and were rejected when transplanted into normal syngeneic recipients, whereas the same tumors grew progressively in syngeneic mice immunosuppressed by X-ray or UVR (Fisher and Kripke 1977). This was found to hold true in three inbred strains of mice (Kripke 1977) and was thus not a strain-specific phenomenon. Therefore, the question was raised: why, if the tumors are antigenic and are rejected when transplanted into normal mice, do they develop and grow progressively in the autochthonous (original) hosts, which is opposite to what is predicted by the immune surveillance theory? One of the first hypotheses examined was that UV irradiation of mice leads to a generalized immunosuppression. Tests of immune function performed by Kripke et al. (1977) included allogeneic tumor rejection, rejection of H-2 compatible skin grafts, antibody production, ability to a mount a graft-versus-host reaction, ability to function as a recipient in graft-versus-host reaction, and ability to exhibit delayed-type hypersensitivity (DTH) to dinitrochlorobenzene (DNCB). However, after 3 to 4 months of UVR, at the time when UV-irradiated mice were uniformly susceptible to challenge with UV-induced tumors and well before any primary tumors develop, all other immune functions had returned to normal (Kripke et al. 1977). In a different laboratory, Spellman et al. (1977a) obtained similar results. Mice were UV-irradiated for 5 weeks and it was found that after such treatment none of the following measures of immunity differed between normal and UV-irradiated mice: 1) the mitogenic response of spleen cells to Concanavalin A (Con A) and lipopolysaccharide (LPS); 2) the plaque-forming cell response to sheep red blood cells (SRBC) and polyvinylpyrrolidone; 3) the percent of B cells, T cells, and macrophages in spleens; 4) the in vitro proliferative response by spleen cells to allogeneic spleen cells; and 5) the in vitro cytotoxic response to allogeneic spleen cells or trinitrophenyl-modified syngeneic spleen cells. Naturally occurring cell-mediated cytotoxic activity in UV-irradiated mice: was found to be transiently suppressed 6 days after UV radiation but had returned to normal after 5 to 10 weeks of UVR (Lynch and Daynes 1983; Noonan et al. 1981a). Norbury et al. (1977) examined further immune responses of UV-irradiated mice from 2 weeks to 6 months of UVR treatment. The in vitro mitogenic responses of spleen cells and lymph node cells to Con A, LPS; and phytohemagglutinin (PHA) did not differ; neither did the number of peritoneal exudate cells elicited by thioglycollate, macrophage phagocytosis, or activation of macrophages by xenogeneic lymphokines or endotoxins.

In summary, mice which have been chronically irradiated with UV radiation, although they are unable to reject UV-induced tumors, are not generally immunosuppressed but have normal immune functions when tested by a very wide number of assays. Thus one would expect that they should have the capability to respond immunologically to tumors. In fact, it was found that UV-irradiated mice respond normally to methylcholanthrene-induced tumors, spontaneous tumors, and virus-induced tumors (Kripke et al. 1979). Interestingly, the only tumor not thought to originate in UV-irradiated mice

which was found to grow preferentially in UV-irradiated mice was the B16 melanoma. B16, a melanoma which arose as a spontaneous tumor in C57BL/6 mice, was found to grow in a greater percentage of UV-irradiated mice than normal control mice (Kripke et al. 1979). These results were confirmed by Bowen and Brody (1983), who reported increased percentage of successful transplants and decreased latency in mice which were UV-irradiated. However, the immune response of UV-irradiated mice to UV-induced tumors is clearly deficient, since UV-induced tumors which are immunologically rejected in normal mice grow progressively in UV-irradiated mice (Fortner and Kripke 1977; Fisher and Kripke 1977; Lill and Fortner 1978). Those tumors which are rejected in normal, non-UV-irradiated mice are termed regressor tumors, although they do grow progressively in UV-irradiated mice. The ability of a transplanted UV-induced regressor tumor to grow progressively in UV-irradiated mice is paralleled by a depressed inflammatory infiltrate of T cells in and around the tumor, compared to that which develops when a UV-induced tumor is transplanted into normal mice (Lill and Fortner 1978). Also, UV-irradiated mice do not develop significant cytotoxicity to transplanted UV-induced regressor tumors, although non-UV-irradiated mice do (Fisher and Kripke 1978; Fortner and Kripke 1977). Thus UV irradiation renders a mouse susceptible to the growth of a UV-induced tumor without significantly affecting its ability to reject transplanted tumors induced by most other agents. This effectively circumvents immune surveillance to those tumors which are induced by UVR, and - also apparently upon occasion to other tumors such as the B16 melanoma.

IDENTIFICATION OF T SUPPRESSOR CELLS SPECIFIC FOR UVR-INDUCED TUMORS

Passive transfer experiments showed that the mechanism for the lack of tumor rejection of UV-induced tumor by UV-irradiated mice is a radiosensitive, Ia positive, Lyt-1+2- (Ullrich and Kripke 1984) T suppressor cell (Spellman and Daynes 1977, 1978; Fisher and Kripke 1977, 1978; Daynes et al. 1979) which is specific for UV-induced tumors. This suppressor cell prevents the mouse from rejecting a syngeneic UV-induced tumor. The T suppressor cell apparently acts at the induction phase of immunity and not on the action of cytotoxic effector cells since if the mouse is sensitized to a UV-induced tumor prior to UV irradiation, it can reject that specific tumor to which it was immunized but is susceptible to all other UV-induced tumors (Kripke and Fisher 1976). There is preliminary evidence that UV-irradiated mice develop helper cells which are sensitized to specific UV-induced tumors but that the suppressor cell acts to prevent the helper cell from inducing cytotoxic effector cells (Romerdahl and Kripke 1986). This is consistent with the data of Roberts et al. (1983), who cloned a T cell line which could suppress antitumor responses in vivo and which could also suppress the differentiation of cytotoxic T cells from the lymph nodes of mice which had been sensitized to a UV-induced tumor. Therefore, the suppressor cell apparently does not prevent sensitization to a UV-induced tumor nor does it prevent the effector action of cytotoxic T cells. Its mode of interfering with immune surveillance is apparently to prevent the effective development of cytotoxic T cells capable of killing the emerging tumor cells in vivo.

All of the above experiments were performed with artificial polychromatic UV sources which do not provide an exact simulation of sunlight. However, Morison and Kelley (1985) reported that irradiation of mice with sunlight also rendered them susceptible to challenge with UV-induced tumors and that filtration of sunlight through filters to remove UV-B abrogated this effect. The susceptibility was also transferable to immunosuppressed recipients. Thus, one can achieve the same effects on the transplantation immunity to UV-induced tumors with sunlight as with the artificial sources of UV radiation used in experimentation, and in both cases it is the UV-B which has the most detrimental effects. This finding is very important when attempting to relate the experimental evidence on the effects of UV irradiation to potential harmful effects on human tumor growth.

ROLE OF IMMUNOSUPPRESSION IN TUMOR DEVELOPMENT

A second, and more important, question about the impact of UVR on immune surveillance is whether the presence of UVR-induced suppressor cells alters the latent period for appearance of tumors or the number of tumors which develop? There is evidence that in certain circumstances UVR may enhance the appearance of autochthonous non-UV-induced tumors. Roberts and Daynes (1980) found that when ventral skin painting with benzo(a)pyrene (BaP) was preceded 3 weeks by dorsal UVR, the latent period of BaP-induced tumors was significantly-shortened. Although in a similar experiment the latent period of methylcholanthrene (MCA)-induced tumors was not significantly shortened in animals pretreated with UVR, MCA-induced tumors from UVR-irradiated mice more frequently showed enhanced growth when transplanted into UV-irradiated mice compared to normal mice. Ebbesen (1981) also reported an enhanced incidence of lymphomas in BALB/c mice which had been UV-irradiated. Thus, under these two experimental conditions, UV irradiation of mice rendered those mice more susceptible to the induction of tumors induced by a carcinogen other than UVR. The exact mechanism is not understood, but it is entirely possible that it may be due to interference with normal immune surveillance mechanisms.

De Gruijl and Van Der Leun (1983) reported that ultraviolet irradiation of ventral skin of mice enhanced subsequent UV tumorigenesis in previously unexposed dorsal skin. The mechanism of this effect was investigated by Fisher and Kripke (1982). Mice were lethally x-irradiated and reconstituted with lymphoid cells from either normal or UV-irradiated mice. These mice were then skin grafted with UV-irradiated skin to provide a source of transformed cells. The latent period was decreased and the percent of animals developing tumors in the transplanted skin was enhanced in those animals which had been reconstituted with lymphocytes from UV-irradiated mice. In a second experiment, normal mice received an injection of T-cell-enriched lymphoid cells from UV-irradiated or normal mice, and were then UV-irradiated. Transfer of T-cell-enriched lymphoid cells from UV-irradiated mice rendered the recipients more susceptible to UV tumorigenesis than transfer of T cells from normal mice. Thus it was concluded that the presence of the T suppressor cell is of great importance in determining if a tumor will appear. Additional evidence for this conclusion comes from the work of Strickland et al. (1985), who showed that ventral UV-B irradiation greatly enhanced the susceptibility

of mice to dorsal two-stage carcinogenesis consisting of initiation of dorsal skin with UVR followed by promotion of dorsal skin with TPA. One may then postulate that the development of the T suppressor cell is the mechanism by which immune surveillance is circumvented. Once mice have developed cells which suppress an effective immune response against UV-induced tumors, then those transformed cells which bear appropriate antigens will be able to grow progressively into grossly visible tumors without interference from the immune response.

Thus, mice that are given UVR are not generally immunosuppressed but do develop T suppressor cells which are generally specific for UV-induced tumors and whose presence has been shown to be directly related to tumor development. Although it is clear that tumor development in UVR-treated mice is at least in part due to the development of UV-tumor-specific suppressor cells, the mechanism by which UVR interacts with the immune response to induce the generation of such suppressor cells is far from clear. Although trauma such as mild thermal burns and phototoxic damage to skin is also transiently immunosuppressive, suppressor cells to UV-induced tumors do not develop (Morison et al. 1985).

ANTIGEN PRESENTATION

An additional effect of UV irradiation, that of suppression of antigen presentation, may help to explain how UV irradiation of mice may lead to the generation of suppressor cells. It had been discovered earlier (Shevach and Rosenthal 1973) that certain cells in the spleen and lymph nodes were required to present antigen to T cells in order to elicit an immune response. When T cells encounter antigen without the aid of antigen presentation by these adherent cells, they respond poorly or not at all. An additional concept which is important to the following discussion is the idea that immunization leads to an immune response, but that the response may be the induction of suppressor cells rather than the induction of effector cells. Therefore, although one cannot directly measure a suppressed immune response since the animal did not generate effector cells, there was a negative response to the antigen. This is not the same as the lack of a response, in which the animal fails to recognize a particular antigen and results from a switching on of T suppressor cells which regulate the lack of measurable response. Thus an animal may not respond to an immunization procedure for a variety of reasons, but if suppressor cells develop, that is an active immune response.

The antigen-presenting capability of cells from UV-irradiated mice is depressed when tested in UV-irradiated mice under certain circumstances. Much of the recent work in the field assesses antigen presentation by measuring the immune response to syngeneic cells to which a hapten has been covalently linked. A hapten is a molecule which is not by itself immunogenic, but when linked to another and larger molecule (or to a cell) can induce an immune response to itself. Thus the cells "present" the hapten to responder cells and the immune response to the hapten is subsequently measured. A second method is to measure the ability of an animal to be sensitized to a chemical which is painted on the skin (contact hypersensitivity).

CONTACT HYPERSENSITIVITY AND LOCAL IMMUNITY

The effect of UV radiation on cell-mediated immunity can be separated into two effects, suppression of local immunity and systemic suppression. Suppression of local immunity occurs when antigen is administered through UV irradiated skin shortly after treatment. Relatively low doses of UVR are required and the effect is not long-lasting. However, systemic suppression of contact hypersensitivity also occurs so that animals are hyporesponsive even when immunized through skin which was not exposed to UVR. Systemic hyporesponsiveness requires larger doses of UVR and is longer-lasting. In both cases the type of immune response affected is delayed-type hypersensitivity (antibody production is not affected) and an antigen-specific T suppressor cell develops.

In an example of a systemic effect, splenic adherent cells or peritoneal exudate cells from UV-treated donor mice which were trinitrophenyl (TNP)-derivatized could not induce hapten-specific delayed/type hypersensitivity when injected into UV-irradiated mice, whereas TNP-derivatized adherent cells from normal mice were able to induce DTH in UV-treated mice (Greene et al. 1979; Noonan et al. 1981b). Thus the cells from UV-treated mice were unable to present the antigen TNP appropriately to induce the production of cytotoxic effector cells although the UV-irradiated mice were capable of responding to TNP when it was presented by cells from normal mice. The hyposensitivity could be passively transferred by lymphocytes into a second recipient and a T suppressor cell was shown to be responsible. Thus presentation of an antigen by cells from UV-irradiated mice induced suppressor cells specific for that antigen. UV radiation was also found to suppress contact hypersensitivity in a second species, guinea pigs (Morison and Kripke 1984); thus the observation is not species specific.

One can also measure the response to a contact allergen such as DNCB which, when painted on skin, normally induces an immune response similar to that which develops in response to poison ivy. If the mice are exposed to an antigen such as DNCB through UV-B-irradiated body wall skin, a state of unresponsiveness develops that is maintained at least in part by an Lyt-1+ T suppressor cell. This cell was found to act on the induction phase of immunity (Elmets et al. 1983a). The suppression of the immune response to antigens presented through UV-irradiated skin is short-lived. The animals have normal or elevated responses as early as 3 days after irradiation of the skin (Lynch et al 1983). It was suggested that UV impairs the antigen-presenting potential of Langerhans cells, and in the absence of that ability hapten-derivatized keratinocytes are able to deliver a tolerogenic signal.

The great majority of the experimentation has been done with lamps which simulate sunlight. However, it is important to note that is was also reported that sunlight itself could suppress contact hypersensitivity in both mice and guinea pigs and that the wavelengths responsible were in the UV-B range (Morison et al. 1985).

Granstein (1985a, b) has reported that when mice are immunized subcutaneously with hapten-coupled UV-irradiated epidermal cells, they are

hyporesponsive when contact hypersensitivity to the hapten is measured, and that hapten-specific T suppressor cells are present in the immunized mice. However, depletion of cells which bear the antigen I-J from the epidermal cell suspension prior to UVR and haptenation prevents the appearance of these suppressor cells. Non-UVR-treated epidermal cells which are I-J depleted and haptenated can induce contact hypersensitivity. Therefore, there seems to be a separate cell in the epidermis which is UV-resistant and which apparently presents antigen in a tolerogenic fashion and thus preferentially induces suppressor cells.

ACTION SPECTRA OF IMMUNE SUPPRESSION

Experimentation on the photobiology of the phenomenon has provided a great deal of information on the relative effectiveness of various wavelengths and on reciprocity. The wavelengths which most effectively suppress contact hypersensitivity and which also lead to the production of tumor specific suppressor cells lie in the UV-B range. It was found that the ability of UVR to induce susceptibility to transplanted UV-induced tumors in mice lies in wavelengths below 315 nm (i.e., UV-B) and appears to show reciprocity (dose rate independence)(De Fabo and Kripke 1979, 1980). This is in contrast to tumorigenesis by UVR, which does not appear to show dose/rate reciprocity (Forbes et al. 1978) but which is also primarily caused by UV-B.

In a study of the photobiology of the suppression of contact hypersensitivity by UVR (Noonan et al. 1981a), it was reported that a Mylar filter, which removes wavelengths less than 315 nm, abrogated the suppressive effect. Thus it was concluded that depression of contact hypersensitivity was due to UV-B. Elmets et al. (1983b) also studied the wavelength dependence of the local suppressive effect of UVR on contact hypersensitivity and determined that the greatest effect was at 297 nm. Wavelengths of 290 nm or greater than 315 nm were less effective. De Fabo and Noonan (1983) constructed a detail in vivo action spectrum using 10 different narrow wavebands (2-3 nm) and found peak suppression of contact hypersensitivity between 260 nm and 270 nm. They found a shoulder at 280 to 285 nm and then a steady decline in effectiveness to about 3 percent of maximum at 320 nm.

The great majority of the experimentation has been done with lamps which simulate sunlight, but it has also shown that sunlight itself could suppress contact hypersensitivity in both mice and guinea pigs (Morison et al. 1985). In the latter experiment, the wavelengths responsible were reported to be in the UV-B range. The data for all experiments described are quite consistent in showing that UV-A wavelengths are ineffective in suppressing contact hypersensitivity. The wavelengths reported to cause the greatest depression of contact hypersensitivity depend somewhat on the UVR source used. For example, in sunlight, UV-B is apparently the most effective. However, when one compares a broad range of wavelengths, there is a general trend that the shorter the UV-B, the greater the suppression. However, the most effective wavelengths lie in the longer wavelengths of UV-C. Since reduction of ozone in the stratosphere would increase the penetration of the shorter wavelengths of UV-B more than that of the longer UV-B, this is an important consideration.

POSSIBLE ROLE OF UROCANIC ACID IN IMMUNE SUPPRESSION BY UVR

Noonan et al. (1981a) found a clear differential in wavelength effectiveness in suppression of contact hypersensitivity, and they suggest that this indicates the existence of a unique photoreceptor mediating UV-induced immunosuppression. However, the action spectra which they constructed for suppression of contact hypersensitivity are not congruent with the absorption spectrum of DNA proposed by Setlow (1974). Because their action spectrum closely matches the absorption spectrum of urocanic acid, and urocanic acid is found in the epidermis, they conclude that there is a strong possibility that this compound is the photoreceptor. Evidence supporting this hypothesis is given by studies of Noonan et al. (1985). Trans urocanic acid, a derivative of histidine, accumulates in the stratum corneum to as much as 0.5 percent of the wet weight of the epidermis (De Fabo and Noonan 1983) and undergoes isomerization to the cis form when exposed to UVR (Morrison et al. 1980, 1984). Removal of the stratum corneum by tape stripping prior to UVR abrogated the induction of suppression of contact hypersensitivity by UVR (De Fabo and Noonan 1983). In addition, UV-irradiated urocanic acid was reported to suppress delayed-type hypersensitivity in mice (Ross et al. 1986). Thus these results suggest that absorption of UVR by DNA, although generally considered of greatest importance for carcinogenesis, might not mediate the suppression of the immune response.

UVR-INDUCED ANTIGENS ON UV-IRRADIATED SKIN

Spellman and Daynes (1984) have reported that in mice there are antigens present on UV-irradiated skin that are cross-reactive with UV-induced tumors. Mice were irradiated 30 minutes per day for 6 weeks, which is well under the time of radiation required to produce tumors in that system. Skin from these animals was then transplanted as 1 cm grafts to normal mice. Twenty days later a second graft of UV-irradiated skin was made. When the mice that had received the skin grafts of UV-irradiated skin were challenged with a UV-induced tumor 15 days later, the animals did not succumb to the tumor, i.e., they were protected from the challenge. Since the grafting of UV-irradiated skin protected against a challenge with UV-induced tumors, the conclusion was drawn that antigens existed on UV-irradiated skin that were not normally present on skin and which were also present on UV-induced tumors. Therefore, if UVR causes the expression of neoantigens on skin and at the same time facilitates the induction of suppressor cells to antigens, then the immune response against those tumors might take the form of induction of suppression rather than induction of cytotoxic cells. This would effectively circumvent immune surveillance.

HUMAN STUDIES

There have been very few studies of the effects of in vivo UVR on the immune response in humans. Morison et al. (1979) UV-irradiated human volunteers with 1.5 minimal erythemal doses (MED) to produce what they termed asymptomatic erythema, or 3 MED, which they termed symptomatic erythema. Post-irradiation, all subjects showed a significant increase in the proportion of circulating polymorphonuclear leukocytes and a corresponding decrease in

the proportion of circulating lymphocytes. Subjects who received 3 MED also had a significant decrease in the proportion of circulating E-rosette-forming cells (i.e. T cells), and an increase in the proportion of null cells (cells which lack surface markers for T or B cells). The changes in the absolute numbers of these cells were not significant. Thirty minutes and 4 hours after UV irradiation, the response of lymphocytes to PHA was increased; it then decreased to a minimum 12 hours after UVR, and returned to a normal range 72 hours post-exposure. This experiment demonstrates that in vivo UV irradiation of humans can affect the function of lymphocytes as measured in vitro, although the relationship of these experiments to those in mice is not quite clear.

Hersey et al. studied the effects of UVR on humans after solarium exposure (1983a) and after exposure to 10 days of sunlight for 1 hour per day (1983b). In both studies there was a marked increase in the ratio of suppressor cells to cytotoxic/helper cells which had not returned to normal 2 weeks after UV irradiation. Also, there was a decrease in NK activity and an increase in the in vitro activity of a gamma radiation-sensitive suppressor T cell activity against nonspecific (pokeweed mitogen-induced) IgG and IgM production. Although immunoglobulin production in vitro had too wide a range for statistical analysis of these small numbers of patients to be of value, Hersey et al. (1983a,b) found that gamma irradiation of T cells prior to culture increased the amount of immunoglobulin produced in patients exposed to sunlight but not in controls. O'Dell et al. (1980) reported that there was a diminished immune response in sun-damaged skin. The concentration of DNCB required to elicit a positive patch test was greater in sun-damaged skin than in normal skin. In addition, the delayed-type hypersensitivity to intradermal injection of Candida, mumps, and PPD antigens was decreased in sun-damaged skin so that the differences were not due to a difference in percutaneous absorption of antigen through sun-damaged skin. The inflammatory response to a primary irritant was the same in both sun-damaged skin and normal skin and there was no difference in the two tested sites (back of the neck and the back) in volunteers without sun-damaged skin at the back of the neck. Therefore, there is apparently a local suppression of contact hypersensitivity in sun-damaged skin. These reports suggest strongly that UVR can suppress certain parameters of the immune response in humans as well as in laboratory animals and further suggests that UV irradiation of humans could interfere with immune surveillance of UV-induced tumors in a fashion similar to that observed in mice. A very recent publication from this same group carried this investigation one step further and asked the question would the use of sunscreens prevent the decrease in NK activity (Hersey et al. 1987)? They found to their surprise that use of a sunscreen did not prevent the increase in NK activity, leading them to urge caution in the use of these agents until their effectiveness in preventing the systemic impact of UVR on the immune system can be clearly established. Otherwise, use of such agents while presenting erythemal responses could lead to longer exposures and greater damage.

CONCLUSIONS

Very little of the research done is related directly to melanoma. However, there is evidence that, although UVR does not seem to affect the ability of a mouse to reject most transplanted tumors (those not induced by UVR) (Kripke et al. 1979), there are reports that UVR of mice does enhance the development of spontaneous (Ebbesen 1981) and chemically induced (Roberts and Daynes 1980) autochthonous tumors. There is, then, circumstantial evidence that UVR may potentially facilitate the growth of melanomas in humans. First, there are cross-reacting antigens on melanomas among mouse (Gersten and Marchalonis 1982) and among human melanomas (Houghton et al. 1982), and there are similarities in antigens found on both human and mouse melanomas (Tomecki et al. 1980). Humans bearing melanomas make an immune response to that tumor but the response is ineffective in at least those patients who develop progressive melanomas, and the tumor is able to grow and kill the host. Any effect on the immune response which interferes with that immune response can potentially increase the growth rate of that tumor or allow it to escape from immune surveillance. The experimentation with animals has shown that UVR induces the production of suppressor cells which not only facilitate the growth of UV-induced tumors, but also the B16 melanoma. Similar experimentation with other melanomas has not been reported and no such experimentation is possible with human melanomas. However, the potential exists that the same events may take place in humans. If so, then UVR might facilitate the growth of melanomas in a fashion similar to what is seen in mice.

Finally, the experiments of Hersey et al. (1983 a,b) and O'Dell (1980) demonstrate that the immune system of humans can be adversely affected by UVR. All of this information in toto implies that UVR may permit the growth of human melanomas. There is no direct evidence that this does occur but there is certainly experimental evidence that it is a possibility. It is clear that there is a real and pressing need for more research in this area to directly address, to the extent possible, the question of the effect of UVR on the growth of melanomas as well as the induction of melanomas.

FINDINGS

In conclusion, ultraviolet radiation has been shown to have a variety of effects on the functioning of the immune system.

17.1 UVR, specifically UV-B, can result in the generation of T suppressor cells which specifically suppress the immune response to UV-induced tumors. The suppressor cells have been shown to be capable of shortening the latent period of tumors induced by UVR. UV-B-treated animals also appear to have increased susceptibility to one form of melanoma in experiments with transplanted tumors.

17.2 The wavelengths most effective in causing the production of tumor-specific suppressor cells in mice appear to be in the UV-B range.

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SECTION IV

DOSE-RESPONSE RELATIONSHIPS AND CONCLUSIONS

CHAPTER 18

MELANOMA DOSE-RESPONSE

This chapter reviews the recent literature relevant to assessing dose-response relationships between ultraviolet radiation, particularly ultraviolet radiation-B (UV-B), and cutaneous melanoma skin cancer (CMM). Dose-response relationships for CMM have been estimated in several epidemiologic studies; at present, there is no animal model for CMM dose-response relationships. The focus of this chapter is on evaluating the epidemiologic studies for their usefulness in estimating how future melanoma incidence and mortality rates would respond to potential future modifications in total column ozone that, in turn, alter the flux of UV-B reaching the earth's surface.

DATA BASES AVAILABLE FOR DOSE-RESPONSE MODELING

Estimation of the changes in melanoma incidence or mortality that would be associated with variations in UV flux could be performed in a variety of ways. Information from animal models could be used, in which the responses of animals to large doses are assumed to be relevant to the responses of humans to small doses. Human epidemiologic data could be used, in which UV-B measurements taken at different locations are related to melanoma incidence and mortality at these locations. Each approach has strengths and weaknesses.

The use of animal data to extrapolate to human risk has several generic weaknesses, the principal ones being that extrapolation is required from high to low doses and from one species to another. In addition, animal data generally come from a very homogeneous population, both genetically and in terms of exposure, whereas humans are genetically very heterogeneous and have very different exposure patterns. In the case of CMM there is one additional major weakness; the availability of an appropriate animal model. There is an animal model for non-melanoma skin cancer, and is most risk assessments, e.g., for those performed for chemicals, that would be used to estimate risk to human populations. In the case of melanoma, however, given the great differences in the biologic behavior of CMM and non-melanoma skin cancer, it does not seem appropriate to use the animal data on NMSC to estimate human risk from CMM.

Use of epidemiologic studies avoids some of the problems associated with the use of animal studies but has other, different weaknesses. The advantages of epidemiologic studies include (1) the ability to control for environmental factors that could influence the effectiveness of dose; (2) the analysis of UV-B doses that are often within the range of predictive concern; and (3) obviously, a focus on human beings--the species of predictive concern. The cost of this "realism," however, is high. Many genetic and environmental factors that are believed to influence melanoma incidence and mortality cannot be measured accurately in epidemiologic studies. Furthermore, human exposure to UV-B rarely varies systematically, making it difficult to find appropriate

test and control populations. Nonetheless, a number of ecologically oriented epidemiologic studies have been performed (Fears et al. 1976, 1977; Scotto and Fears 1986; Pitcher 1987), and are evaluated in this chapter.

Sources of Unexplained Variation

In using epidemiologic data bases of melanoma incidence and mortality in order to derive dose-response relationships, researchers must make a number of assumptions about the variables that can potentially influence both UV-B dose and response. Ambient UV-B varies substantially in the environment, with gradients of peak and cumulative UV-B existing for latitude. UV-B also varies with altitude, cloudiness, albedo, and the time of day. Another factor causing UV-B variations is the climatology of ozone transport and abundance (Angell and Kofshover 1983). Available measurements of UV-B show that these factors cause variations of UV-B (Scotto and Fears 1986; Reinsel et al. 1983). Consequently, whether one is using modeled UV-B data (Green and Siskind 1983), a combination of modeled and measured* data (Serafino and Frederick 1986), or measured data alone (Scotto and Fears 1986), the exposure data used in ecological studies will only approximate the actual potential exposure of individuals over a long period of time. Some amount of unexplained variation in UV-B affects any ecological analysis, decreasing the ability of any model to explain variations in CMM incidence or mortality.

In addition, a number of factors affect the actual dose a person receives. Skin color in the absence of tanning and the ability to tan or to have skin thicken can affect the amount of UV-B that reaches the basal layer of the skin. Individual behavior can vary across locations. People have different patterns of dress, work exposure, recreation, eating, and even medical care and intervention. All of these factors can be expected, in varying degrees, to introduce variations in CMM incidence or mortality that are unexplained in epidemiologic studies. For example, Crombie (1981) concludes that differences in ethnicity and skin color make the observation of a latitudinal gradient of incidence across European countries impossible. Within England, however, where variation in skin color and tanning capability is relatively small, changes in solar radiation appear to be highly related to variations in melanoma incidence rates (Crombie 1981). In other countries e.g., Italy, where skin color varies north to south, the influence of skin color variability and behavior on incidence and mortality may overwhelm the impact of variations in UV-B (Crombie 1981). Finally, little is known about genetic factors that affect melanoma incidence and mortality but are unrelated to solar exposure. Chapters 2 and 3 of this review discuss the many factors that potentially can influence the dose of UV-B received in a particular location.

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* Measured UVR data usually comprise a few locational sample points collected over a short time period.

DISCUSSION OF EPIDEMIOLOGIC STUDIES USEFUL FOR EVALUATING DOSE-RESPONSE

A variety of case-control epidemiologic studies have identified risk factors for CMM. Unfortunately none of the case-control studies focused specifically on UV-B, so these efforts cannot be used to estimate a dose-response relationship between melanoma and UV-B. For example, studies of the relationship between "sunshine hours" and CMM were not evaluated in this chapter because the relationship between "sunshine hours" and UV-B dose will vary with individual. The ecological studies evaluated in this chapter do not fully control individual UV-B dose but do focus specifically on how variations in UV-B exposures explain variations in melanoma incidence and mortality.

The number of countries in which ecological studies appropriate to assessing the relationship between UV-B and CMM can be performed is limited. Ideally, such studies should use data from a country that spans a wide range of latitudes, thus allowing the use of UV-B data that reflect a significant range of exposures. However, the studies must control for differences in skin coloration across latitudes, requiring either (1) data from a country that has a population with a predominant single skin color (e.g., Norway, Sweden, or England) or countries in which skin color does not vary with latitude, such as the so-called immigrant countries (the U.S., Australia, or New Zealand); or (2) data on population characteristics that would enable researchers to control for differences in skin coloration (Fears and Scotto 1983). Ruling out ecological studies that do not meet these requirements, only a few epidemiologic studies remain.

One study which is potentially useful for estimating a dose-response relationship between UV-B and CMM in the United States is that performed by Fears et al. (1976). These authors use two types of data to represent UV-B exposure: (1) latitude--latitude and UV-B radiation weighted for erythema effectiveness correlate at 0.97; and (2) monthly totals of erythema-producing UV radiation--expressed as Biologically Effective Units (BEUs) and derived from Schultze (1974). Both types of data were correlated with CMM mortality and incidence data. The incidence data were for four cities included in the Third National Cancer Survey (TNCS) (1975). Mortality data were from the U.S. Cancer Mortality by county data base (Mason and McKay 1973).

Table 18-1 shows the results of the simple correlation model based on latitude:

$$\log R = \alpha + \beta L$$

where R is the age-adjusted rate of incidence or mortality, α and β are constants, and L is latitude.

Table 18-2 shows the results estimated using BEUs. These estimates were based on an exponential model and represent the percentage changes in incidence and mortality estimated to occur with increases in UV radiation of between 10 and 30 percent. Note that the use of an exponential model leads to higher dose-response relationships for higher base exposures.

TABLE 18-1

SUMMARY STATISTICS FOR REGRESSIONS OF
SKIN CANCER INCIDENCE AND MORTALITY ON LATITUDE

	MALES			FEMALES		
	Correlation Coefficient[a]/	Regression Slope ± S.D.	Doubling Latitude (degrees)	Correlation Coefficient[a]/	Regression Slope ± S.D.	Doubling Latitude (degrees)
Melanoma Incidence	-.86	-.037 ± .007	-9.8	-.83	-.038 ± .007	-10.7
Melanoma Mortality	-.81	-.017 ± .002	-19.9	-.71	-.014 ± .002	-22.2

a/ Simple correlation coefficient between log of incidence or mortality rate and latitude. Model coefficients were statistically significant at $p<0.01$.

Source: Fears et al. (1976).

TABLE 18-2

ESTIMATED PERCENTAGE INCREASES IN MELANOMA SKIN CANCER INCIDENCE AND MORTALITY ASSOCIATED WITH CHANGES IN ERYTHEMA DOSE a/
(figures in parentheses are 95 percent confidence intervals)

	Base BEU	MALES Increase in Total Dose 10%	20%	30%	FEMALES Increase in Total Dose 10%	20%	30%
Melanoma incidence							
	650	15%(7-24)	32%	52%	13%	29%	46%
	850	20	44(18-75)	72	18	39	64
	1050	25	57	96(37-180) b/	22	50	84 b/
Melanoma mortality							
	650	8(6-10)	16	26	6	13	21
	850	10	22(16-28)	35	9	18	28
	1050	13	28	45(33-58)	11	22	36

a/ A sample computation is outlined:
A 10% increase in total dose at 48.25'N, where exposure is 650 BEU, equals 65 BEU.
A change of 65 BEU is equivalent to a reduction in latitude of 1.93'.
A change of 1.93' at 48.25'N is associated with an 18% increase in non-melanoma incidence.

b/ These estimates require extrapolation well beyond the range of the data.

Source: Fears et al. (1976).

There are several limitations in this work. In particular, only four cities were used for melanoma incidence. With a sample this small, variations in behavior, skin pigmentation, and cloud cover may bias estimates of the coefficients. Thus, caution must be used in evaluating the error of the estimate.

In another study, the same authors estimate a dose-response relationship for melanoma incidence using a power model (Fears et al. 1977):

$$P_{ij} = b\,(U_i)^c\,(A_j)^k$$

where P_{ij} = probability of developing melanoma for jth age group at location i;

U_i = annual UV count at ith location;

A_j = midrange of jth age group; and

b, c, k are constants.

They assume that melanoma skin cancer incidence for the jth age group at location (denoted by R_{ij}) is binomally distributed. They argue that because R_{ij}'s are small and population size is large, then $\ln(R_{ij})$ can be regarded as normally distributed with variance equal to the inverse of the expected number of cases $(W_{ij})^{-1}$. Using least squares regression, parameters were estimated by fitting a log form of the model (for $\ln R_{ij} = a + c \ln U_i + k \ln A_j + E_{ij}$) after weighting by the observed number of cases. Annual counts from Robertson-Berger meters were used for UV-B. Incidence data were from the TNCS (1975). This measure differs from the erythema spectrum by weighting more heavily towards longer wavelengths.

Table 18-3 presents the regression coefficients and statistics. A one percent relative increase in UV radiation results in an estimated $100*(1.01^c - 1)$ percentage increase in melanoma incidence, or 2.47 for females and 2.24 for males. The authors stress, however, that these estimates may be biased by the omission of location-specific demographic and environmental variables.

In applying the authors' 1976 and 1977 studies to a risk assessment of ozone depletion, notice should be paid to how two factors, the biological

TABLE 18-3

SUMMARY OF FEARS ET AL. (1977) REGRESSION ANALYSIS OF MELANOMA INCIDENCE VERSUS ULTRAVIOLET a/

Sex	Percent Variation Explained	t-statistic (UV Coefficient)	α + SD (Constant)	κ + SD (Age Coefficent)	c + SD (UV Coefficient)
Males	74	5.4	-35.6 $\pm$ 6.5	.80 $\pm$ .31	2.45 $\pm$ .45
Females	62	4.6	-30.5 $\pm$ 6.9	.29 $\pm$ .34	2.23 $\pm$ .48

a/ $\ln R_{ij} = \alpha + c \ln U_i + \kappa \ln A_j + E_{ij}$

$p \leq .01$

Source: Fears et al. (1977).

amplification factor (BAF) and radiation amplification factor (RAF), interact. A BAF is a number that indicates the percentage change in incidence or mortality associated with a given percentage change in UV-B. The RAF relates percentage changes in ozone levels to percentage changes in UV-B. Fears et al. (1976) used the erythema action spectrum to weight wavelengths in the UV-B. Because erythema varies more with latitude compared to other action spectra, a lower BAF was estimated. At the same time, erythema is more sensitive to ozone depletion; it has a higher RAF.

Scotto and Fears (1986) estimated a dose-response relationship for melanoma incidence using an expanded data base about populations in a greater number of cities. They (1986) also included a new term (VAR) to adjust for the presence of some host or environmental characteristics:

$$\underset{ij}{\text{Ln } R} = a + b \ln (\text{Age}_i) + c \ln \underset{j}{\text{UV-B}} + d\underset{ij}{\text{VAR}} + \underset{ij}{e}$$

Seven areas are included in the data base: Detroit, Seattle, Iowa, Utah, San Francisco, Atlanta, and New Mexico. Again, counts obtained from Robertson-Berger meters were used for UV-B.

Separate estimates were made for: (1) different anatomical sites--FHN (face, hands, neck); UE (upper extremity); and LE (truck and lower extremity); and (2) age groups--20-39; 40-54; 55-64; and 65-74. Non-whites and Hispanics in New Mexico were excluded. For most categories, Scotto and Fears found that, after controlling for confounding variables, each 1 percent increase in UV-B increases incidence by less than 1 percent. Table 18-4 shows the results for different anatomical sites. The dose-response estimates are statistically significant ($p \leq 0.1$). Table 18-5 shows the effects of introducing different constitutional and environmental variables. These factors were analyzed using stepwise multiple regressions. The analysis showed statistically significant biological amplification factors ($p \leq 0.5$) for ethnic groups that spent some time outside, with particular risk associated with weekend sun exposure.

Pitcher (1987) used data on melanoma death rates by county for a 30-year period and exposure data from a satellite data based National Air and Space Administration model (the NASA Model) to estimate the relationship between CMM death rates and several alternative estimates of UV-B dosed. These were either peak (a clear day in June) or mean annual dose estimates using weighting functions derived either from the average DNA damage action spectrum proposed by Setlow (1974) or an erythema action spectrum.

Data on melanoma mortality by county were obtained from an EPA/NCI data base (Riggan et al. 1983) for the period 1950 to 1979. The NASA Model estimated UV exposures in these counties by using modeling relationships based on latitude, longitude, altitude, surface albedo, total column ozone, and cloud cover to estimate the amount of UV delivered. Weighting functions derived with various biological action spectra were then applied to those total UV energy estimates to get estimates of "effective" UV energy estimates termed "weighted UV doses". An extensive effort to validate the exposure data

TABLE 18-4

BIOLOGICAL AMPLIFICATION FACTORS FOR SKIN MELANOMA BY SEX AND ANATOMICAL SITE GROUPS, ADJUSTING FOR AGE AND SELECTED CONSTITUTIONAL AND EXPOSURE VARIABLES a

Variable	Male		Female	
	Trunk/LE b/	FHN/UE c/	Trunk/LE b/	FHN/UE c/
Age	6%	8%	5%	10%
Sunburn	4	8	5	10
Freckles	5	7	5	10
Scandinavian ancestry	5	9	5	10
Light hair color	5	8	5	10
Scot/Irish ancestry	6	6	4	8
Moles	6	7	5	11
Light eye color	6	8	4	9
Fair skin	6	8	4	9
Sunscreen use	4	7	4	10
Suntan lotion use	5	8	4	10
Radiation protection	5	8	6	10
Protective clothes	8	10	5	10
Hours outdoors on weekdays	7	9	5	10
Hours outdoors on weekends	5	7	8	13

a/ The biological amplification factor indicates the percentage change in melanoma incidence associated with a 10 percent relative increase in UV-B.

b/ Trunk and lower extramities.

c/ Face, head, neck and upper extremities.

Source: Scotto and Fears (1986).

TABLE 18-5

BIOLOGICAL AMPLIFICATION FACTORS FOR SKIN MELANOMA BY SEX AND ANATOMICAL SITE GROUPS, ADJUSTING FOR AGE AND COMBINATIONS OF SELECTED CONSTITUTIONAL AND EXPOSURE VARIABLES a

Anatomical Site	MALE	FEMALE
Trunk/LE b/	3 Percent	4 Percent
Variables included in model	Suntan lotion use Scandinavian Lt hair color UV-B INDEX Hours outdoors, weekdays	Suntan lotion use Scandinavian Lt hair color UV-B INDEX Hours outdoors, weekends
FHN/UE c/	5 Percent	6 Percent
Variables included in model	Scot/Irish ancestry Suntan lotion use Fair skin UV-B INDEX Hours outdoors, weekends	Scot/Irish ancestry Suntan lotion use Fair skin UV-B INDEX

a/ A biological amplification factor is a number that indicates the percentage change in melanoma incidence for a 10 percent percentage increase in UV-B.

b/ Trunk and lower extramities.

c/ Face, head, neck and upper extremities.

Source: Scotto and Fears (1986).

obtained from the UV model using ground based measurements from Robertson-Berger meters has been made and will be reported in a subsequent report. Figure 18-1 presents a comparison drawn from that effort:

An examination of Pitcher's data in Figure 18-2 and 18-3 shows that the relationship between age and melanoma death rates is approximately exponential. Further, the rates for males and females are different. These observations led Pitcher to fit a power and an exponential model data for each sex group. For either model DRM_{ijk} is defined then the exponential model can be expressed as the death rate for the ith cohort in the jth location in the kth time period.

$$DRM_{ijk} = \exp(a_0 + a_1 AGE_{ik} + a_2 a_2 WUV_j) + e_{ijk} \qquad \text{(Model 1)}$$

and the power model can be expressed:

$$DRM_{ijk} = \exp(b_0 + b_{1i} AGE_{ik} + b_2 \log(WUV_j) + e_{ijk}) \text{ or,}$$

$$DRM_{ijk} = (WUV_j)^{b2} \exp(b_0 + b_{1i} AGE_{ik}) + e_{ijk}. \qquad \text{(Model 2)}$$

where AGE_{ik} is the age of ith cohort in the kth time period, WUV_j is the UV dose in the jth location (SMA) and e_{ijk} is the error term.

In model 1, the percentage change in melanoma mortality associated with variations in UV flux is higher the greater the baseline exposure. Model 2 differs from the first only in the use of the log of the exposure variable. In it, a 1 percent increase in UV dose generates the same percentage increase in melanoma death rates regardless of the baseline death rate.

Pitcher (1987) found that many of the birth cohorts had zero deaths in any given 5-year period, especially in smaller cities. Further, because rates differed significantly across cohorts, the variances of the cohort death rates varied under the assumption that the probability of death had a binomial distribution. The different population sizes within cohorts also caused variation in the variance of the cohort death rate. These issues made the use of normal linear regression techniques unfeasible. Normal weighting techniques could not be used because zero rates for some cohorts prevented computation of weights. Therefore, weights were computed using expected rates rather than actual rates.

Using both the power and the exponential models, Pitcher (1987a) estimated the empirical relationships between melanoma mortality and a variety of different estimates of UV dose derived through the combination of two exposure scenarios (peak dose versus annual dose) and two different weighting functions

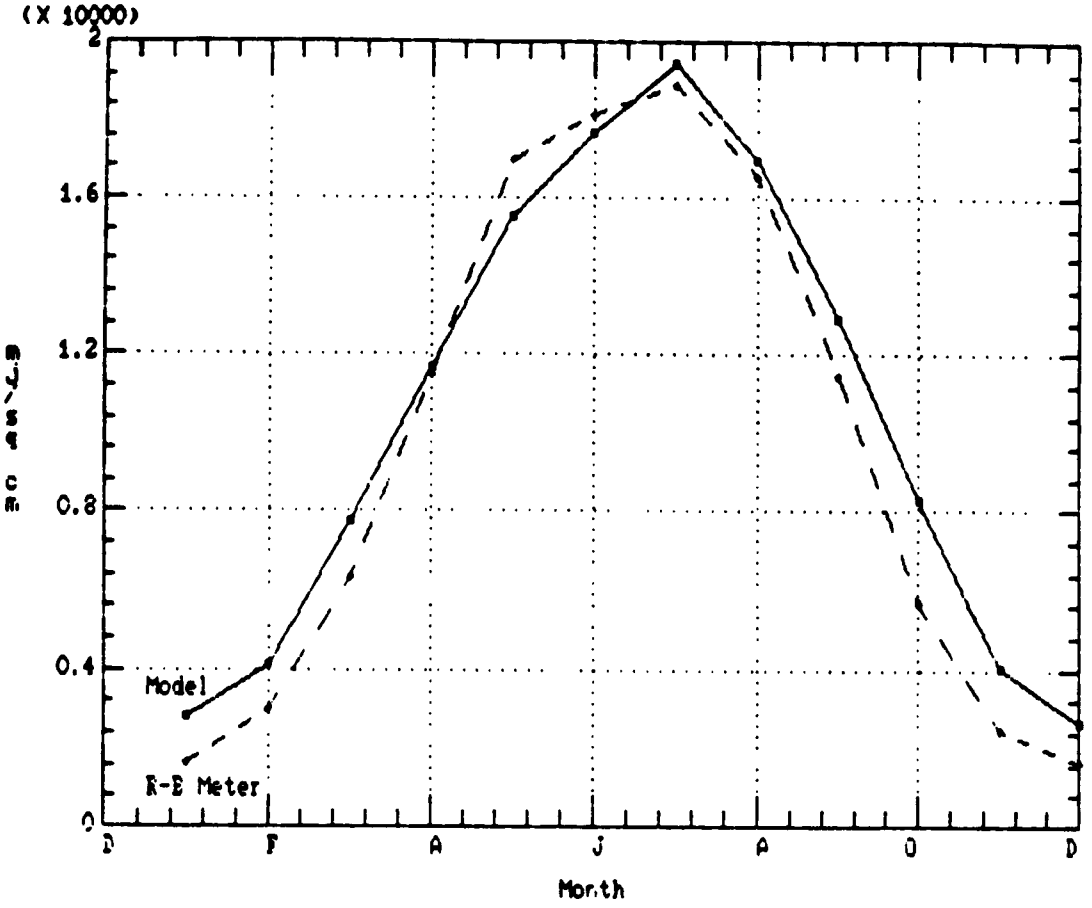

FIGURE 18-1

COMPARISON OF MONTHLY WEIGHTED-ENERGY LEVELS RECORDED BY THE R-B METER AND PREDICTED BY THE NASA MODEL FOR SAN FRANCISCO, CALIFORNIA

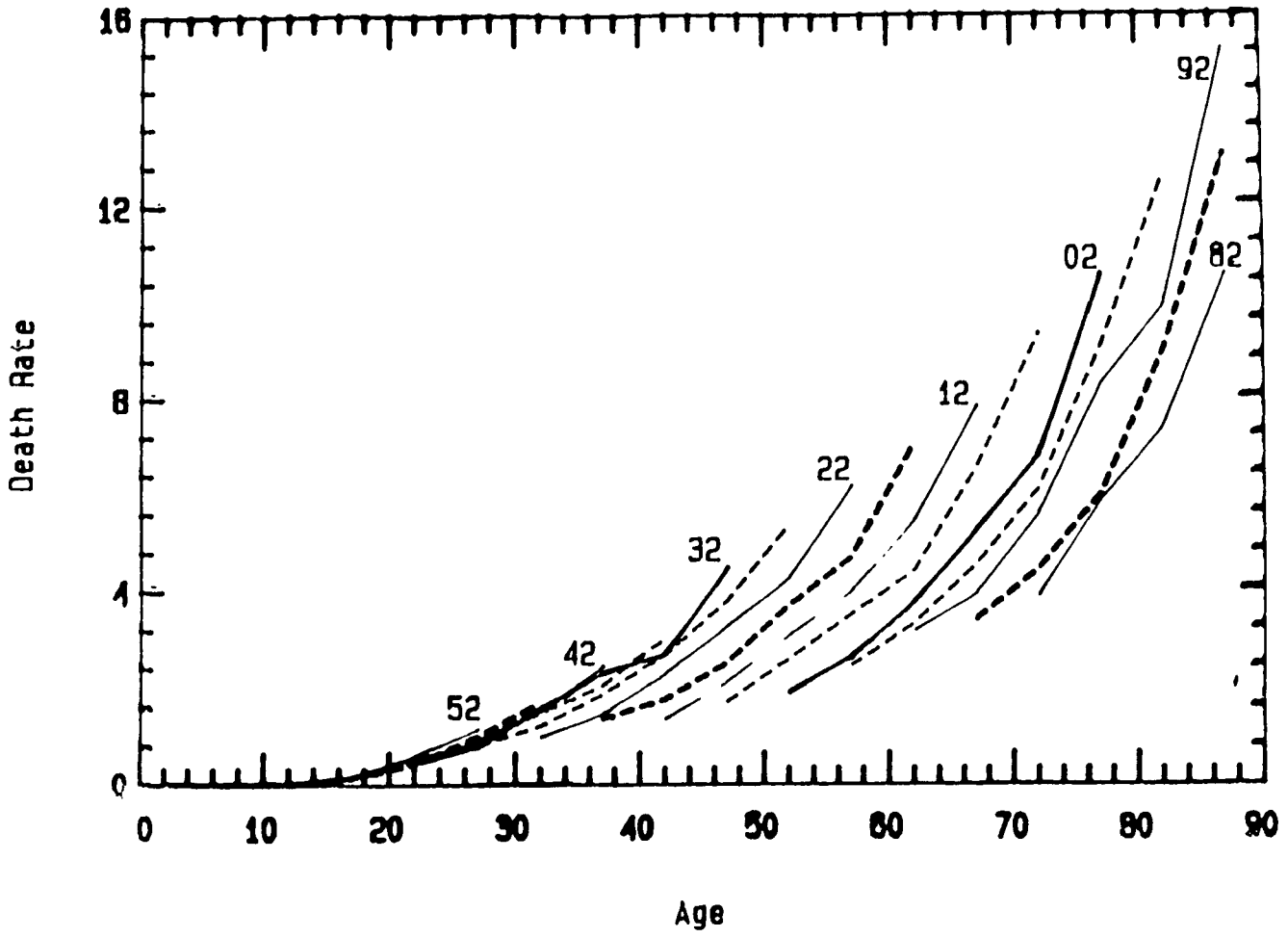

FIGURE 18-2

COHORT DEATH RATES 1950 TO 1979 (PER 100,000) FOR MALES BORN BETWEEN 1880 AND 1960

Solid lines indicate plots of the death rates occurring between 1950 to 1979 in five years cohorts with a median birth year ending in 3, i.e., the cohort born between 1880 and 1885 is designated "82" in the figure; the death rates observed in this cohort have been plotted as the first solid line on the right in the figure. Dashed lines indicate plots of cohort death rates for cohorts with a median birth year ending in 7, i.e., the first dashed line on the right of the figure is for the cohort born between 1885 and 1890.

Source: Pitcher (1987).

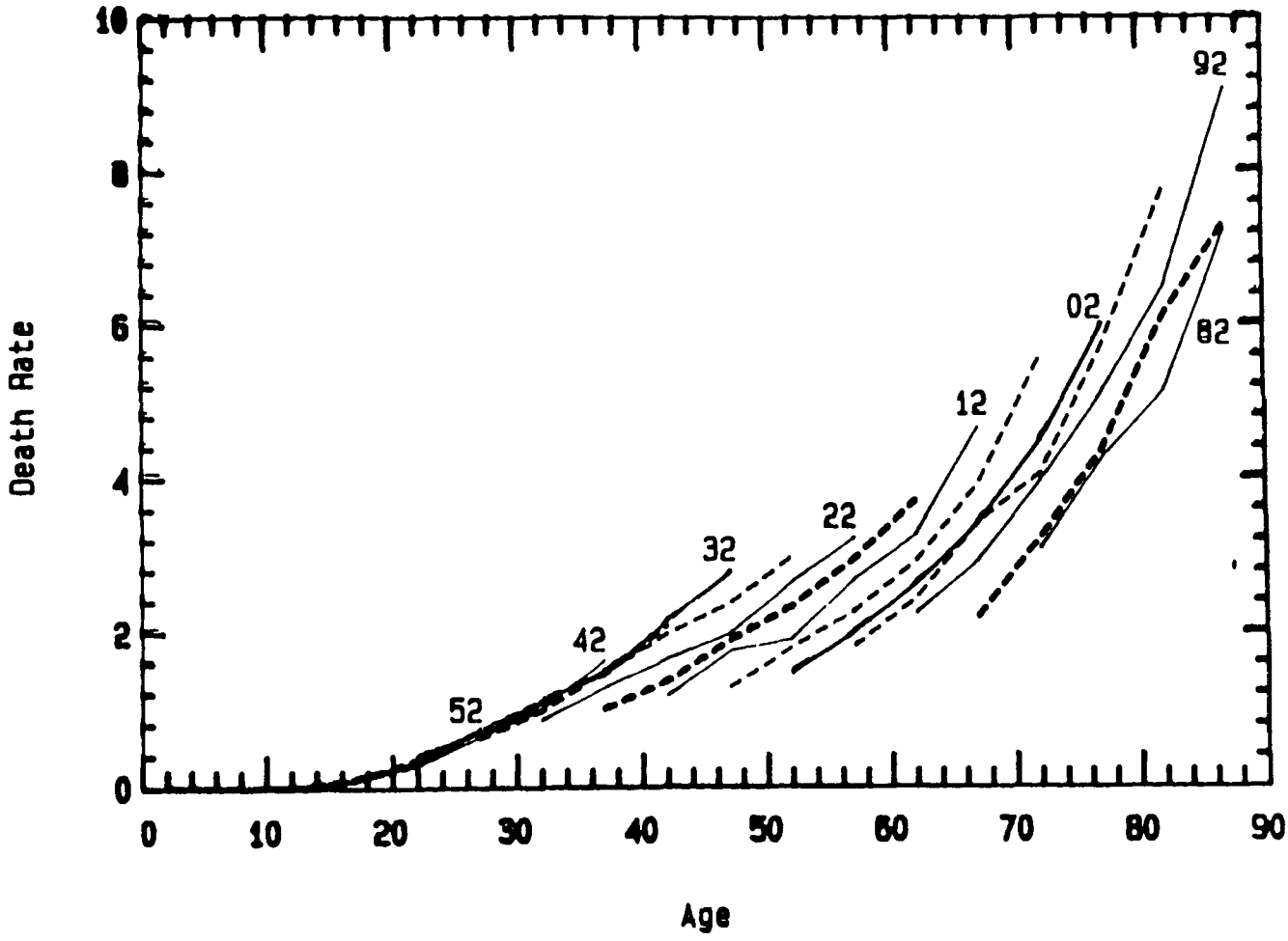

FIGURE 18-3

COHORT DEATH RATES 1950 TO 1979 (PER 100,000) FOR FEMALES BORN BETWEEN 1880 AND 1960

Solid lines indicate plots of the death rates occurring between 1950 to 1979 in five years cohorts with a median birth year ending in 2, i.e., the cohort born between 1880 and 1885 is designated "82" in the figure; the death rates observed in this cohort have been plotted as the first solid line on the right in the figure. Dashed lines indicate plots of cohort death rates for cohorts with a median birth year ending in 7, i.e., the first dashed line on the right of the figure is for the cohort born between 1885 and 1890.

Source: Pitcher (1987a).

TABLE 18-6

BIOLOGICAL AMPLIFICATION FACTORS (AND THEIR STANDARD ERRORS) FOR ERYTHEMA- AND DNA-WEIGHTED DOSES FOR BOTH MODELS USING THE ALL (216) CITIES DATASET

	DNA-Weighted		Erythema-Weighted	
	Peak	Annual	Peak	Annual
EXPONENTIAL MODEL*				
Males	.7911	.3445	.9194	.3815
	(.0647)	(.0300)	(.0764)	(.0332)
Females	.5185	.2209	.6161	.2511
	(.0763)	(.0352)	(.0901)	(.0388)
POWER MODEL				
Males	.8516	.4220	.9786	.4591
	(.0670)	(.0332)	(.0786)	(.0365)
Females	.5779	.2913	.6741	.3216
	(.0784)	(.0385)	(.0923)	(.0424)

*Standard errors for BAF's in the exponential model were computed using linear model results. Since the model is nearly linear in the vicinity of the solution, these are reasonably good measures of the statistical precision of the results.

(based on the DNA damage or erythema action spectra). Table 18-6 presents the biological amplification factors (percent change in death rates associated with a 1 percent change in UV dose derived from that exercise when data from all 216 cities were evaluauted. Based on those BAF's, Table 18-7 presents the percentage increase in melanoma death rates predicted for a one percent decline in stratospheric ozone using the two models four different dose estimates (DNA-weighted peak, DNA weighted annual, erythema-weighted peak and erythema weighted annual) for males and females. Clearly choice of the dose estimate, particularly between annual or peak exposure durations, will make large differences in the prediction of increases in melanoma death rate. Unfortunately, the strength of the statistical association between any of these dose estimates and mealnoma mortality are approximately the same so that a choice cannot be made on that basis. Furthermore, the mechanism of melanoma induction-particularly the role of UV, is sufficiently unclear, that a choice between the various options is difficult. Further investigations are planned in this area (Pitcher 1987b).

PROBLEMS IN USING RESULTS OF EPIDEMIOLOGIC STUDIES

There are a variety of problems in applying the results of the epidemiologic studies to estimate the changes in incidence and mortality rates that would occur with ozone depletion. Ethnic shares in the population may not be maintained over time. Depending on the future population mix, this issue could under- or overestimate future rates. Migration was not considered in the studies; if southern cities have large future population increases, the sensitivity of the overall U.S. population to UV-B will be underestimated. Individuals might also change their personal behaviors that influence UV dose, such as the use of sunscreens or the propensity to work outdoors.

The dose-response relationships developed in epidemiologic studies also omit other important variables that could influence melanoma incidence and mortality. For example, to the extent that the dose of UV-B relates to income and sunny vacations, risks could be biased. In addition, some seasonal components of UV-B are more important than others, so that the independent variables used in the dose-response estimates could over- or underestimate responses. Because of these and other unresolved uncertainties, dose-response relationships continue to be developed.

FINDINGS

18.1 There are currently no animal data which are applicable to the evaluation of dose-response relationships between CMM and UV-B; there is no animal model for CMM induction by UV-B, and animal data on the relationship between non-melanoma skin cancer (NMSC) and UV-B are probably not appropriate given the large differences in biologic behavior between CMM and NMSC in human populations.

18.2 Studies of the relationship between changes in UV-B radiation and melanoma incidence and mortality continue to be developed. Nevertheless, recent efforts suggest a significant correlation.

TABLE 18-7

PERCENTAGE INCREASE IN MELANOMA DEATH RATES FOR A ONE PERCENT DECLINE IN OZONE

	MALES			
	Peak		Annual	
	Exponential	Power	Exponential	Power
El Paso				
DNA	1.99	1.65	1.18	.82
Erythema	1.90	1.60	1.07	.75
San Francisco				
DNA	1.59	1.64	.82	.82
Erythema	1.54	1.63	.76	.75
Minneapolis				
DNA	1.40	1.72	.52	.86
Erythema	1.34	1.77	.50	.77

	FEMALES			
	Peak		Annual	
	Exponential	Power	Exponential	Power
El Paso				
DNA	1.30	1.11	.76	.56
Erythema	1.27	1.10	.70	.53
San Francisco				
DNA	1.04	1.10	.53	.57
Erythema	1.03	1.09	.50	.53
Minneapolis				
DNA	.90	1.20	.34	.59
Erythema	.92	1.12	.33	.54

18.2a Scotto and Fears (1986) found that each 10 percent increase in UV-B would be associated with a 3 to 5 percent increase in melanoma incidence after controlling for confounding host or environmental characteristics. This range reflects differences in (1) anatomical site--trunk and lower extremities were found to respond less to changes in UV radiation than face, head, neck, and lower extremities; (2) sex; and (3) the constitutional and exposure variables included in the estimates.

18.2b Pitcher (1987) derived a variety of estimates of the relationship between UV-B radiation and melanoma mortality under different exposure scenarios (i.e., power or exponential model, peak or mean annual exposure measure and DNA-damage or erythema action spectra as weighting functions) For a 10 percent change in UV-B these estimates in males ranged from a high of a 9.8 percent increase in CMM mortality to a low of 3.4. In females the range was 6.7 to 2.2.

18.3 Because the strength of the associations between UV radiation and melanoma incidence and mortality appears sensitive to the choice of action spectrum, assessing the risks of melanoma skin cancer due to ozone modification requires using an appropriate action spectrum when estimating (1) the relationship between ozone depletion and UV radiation, and (2) how melanoma incidence and mortality respond to changes in UV radiation.

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CHAPTER 19

CONCLUSIONS

This concluding chapter evaluates whether the weight of evidence presented in this document supports the conclusion that it may be reasonably anticipated that a change in ambient ultraviolet radiation caused by modification of in the concentration column ozone would increase the incidence or mortality of cutaneous malignant melanoma (CMM). An affirmative judgment must be based on weighing and balancing all the evidence, not on whether the evidence provides absolute proof or certainty that increases in UV-B will be associated with increases in CMM.

In order to address the issue of whether ozone depletion can be reasonably anticipated to increase CMM, this review has been designed to address three questions:

1. **Does the evidence support the hypothesis that, for susceptible populations, solar radiation is a cause of melanoma?**

2. **Does the evidence support the hypothesis that UV-B is a major component of solar radiation which causes melanoma?**

3. **What dose-response relationships between melanoma and UV-B are consistent with the epidemiologic and experimental data?**

There are certain points which must be recognized before addressing the questions presented above. In our review, we found no perfect studies nor any single overwhelming piece of evidence that answered any of these questions. In fact, as indicated in Table 19-1, we found a number of serious limitations to the current data base.

TABLE 19-1

LIMITATIONS TO THE DATA BASE

1. There is no experimental animal model for CMM.

2. There is no experimental in vitro model for malignant transformation of melanocytes.

3. There are no epidemiologic studies of CMM where individual human UV-B exposures have been adequately assessed.

Consequently, the review has had to build on many diverse pieces of evidence from many different disciplines. Most of the evidence appears to support a clear response to these questions, but some appears contradictory. Consequently, we have had to focus on the weight of the evidence, the likelihood of various answers, and the best approximations of the dose-response relationship, not on finding absolutely definitive answers to any of the questions.

BACKGROUND

Chapters 2 and 3 summarized important information about ambient solar radiation, the skin, and the nature of CMM relevant to understanding the epidemiologic and experimental evidence reviewed in this document. Table 19-2 summarizes key points from these chapters. The central implication of all these summary points is that uncertainty exists about how to determine both the appropriate dose of solar radiation and the appropriate response--dose will be one thing if the important wavelengths are UV-B, another if UV-A. The etiologic relationships between UVR and the various histological types of melanoma may differ. Studies that focus on sun-exposed hours and lump all melanoma types together suffer from aggregating what may be very different things.

IS SOLAR RADIATION A CAUSE OF MELANOMA?

The first question addressed is:

> **Does the evidence support the hypothesis that, for susceptible populations, solar radiation is a cause of melanoma?**

Table 19-3 presents a list of findings that can be interpreted as supporting the conclusion that solar radiation is one of the causes of cutaneous melanoma.

The first three points in Table 19-3 all suggest that the risk of developing CMM is somehow inversely associated with degree of pigmentation. Thus Blacks have less risk than Whites, and Whites with darker pigmentation, either constitutional or acquired via tanning, are at less risk than light-skinned Whites. This information, in view of the fact that melanin, the major skin pigment, is a strong absorber of solar radiation, lends support to the belief that solar radiation plays a role in CMM development, in that it suggests that the presence of melanin by reducing the effective dose of solar radiation penetrating through the skin reduces the likelihood of CMM induction. Alternative explanations are possible; for example, melanin in the skin could act as an anticarcinogen in general, but such explanations are less straightforward and have a weaker factual basis.

TABLE 19-2

SUMMARY POINTS RELEVANT TO ASSESSING THE EPIDEMIOLOGIC AND EXPERIMENTAL EVIDENCE

- Ozone differentially removes wavelengths of UV-B between 295-320 nm; UV-A (320-400 nm) in wavelengths above 350 is not removed nor visible light (400-900 nm). Ozone removes all UV-C (i.e., wavelengths less than 295 nm).

- Wavelengths between 295 nm and 300 nm are generally much more biologically effective (damage target molecules in the skin including DNA) than other wavelengths in UV-B and even more so than UV-A radiation.

- Latitudinal variations exist in solar radiation; model predictions indicate that the greatest variability is seen in cumulative UV-B (e.g., monthly doses), followed by cumulative UV-A and then peak UV-B (highest one-day doses). Peak UV-A varies very little across latitude up to 60°N. Greater ambient variation also exists in UV-B than UV-A by time of day.

- The biologically effective dose that actually reaches target molecules in the skin depends on the duration of exposure at particular locations, time of day, time of year, behavior (i.e., in terms of clothes and sunscreens), and on pigmentation and other characteristics of the skin, including temporary variations (e.g., changes in pigmentation due to tanning).

- Cloudiness and albedo, although causing large variations in the amount of UV-B and UV-A, do not greatly change the ratio of UV-B to UV-A.

- Ozone depletion is predicted to cause the largest increases in the 295-300 nm UV-B range, less in the 300-320 nm range, and UV-A is virtually unaffected.

- Cutaneous malignant melanoma has a number of different histologic types which vary in their relationship to sunlight, their site and racial distribution, and possibly in their precursor lesions; assessment of incidence by type is not consistent among registries, thus complicating attempts to evaluate associations between CMM and solar radiation.

- Melanin is the principal pigment in skin that gives it color; melanin effectively absorbs UV radiation; the darker the skin, the more the basal layer is protected from UV radiation.

TABLE 19-3

INFORMATION THAT HAS BEEN INTERPRETED AS SUPPORTING THE CONCLUSION THAT SOLAR RADIATION IS ONE OF THE CAUSES OF CUTANEOUS MALIGNANT MELANOMA (CMM)

- Whites whose skin contains less protective melanin have higher CMM incidence and mortality rates from CMM than Blacks.
- Whites, who are unable to tan or who tan poorly, get more CMM than darker-skinned Whites.
- Sun exposure leading to sunburn apparently induces melanocytic nevi.
- Individuals who have more melanocytic nevi, develop more CMM; the greatest risk is associated with a particular type of nevus--the dysplastic nevus.
- Sunlight induces freckling, and freckling is an important risk factor for CMM.
- Incidence has been increasing in cohorts in a manner consistent with changes in patterns of sun exposure, particularly with respect to increasing intermittent exposure of certain anatomical sites.
- Immigrants who move to sunnier climates have higher rates of CMM than populations who remain in their country of origin. Immigrants develop rates approaching those of prior (but native born) immigrants to the adopted country; this is particularly accentuated in individuals arriving at or just before the age of puberty (10-14 years).
- It has been suggested that CMM risk may be associated with childhood sunburn; however, other evidence suggests that childhood sunburn may reflect an individual's pigmentary characteristics or may be related to nevus development, rather than being a separate risk factor.
- Most studies that have used latitude as a surrogate for sunlight or UV-B exposure have found increases in the incidence or mortality of CMM correlated to increasing latitude. A recent study of incidence being measured UV-B and CMM survey data found a strong relationship between UV-B and incidence of CMM. Another study that used modeled UV-B data and an expanded database on CMM mortality found a strong UV-B/mortality relationship.
- Patients with xeroderma pigmentosum who cannot repair UV-B-induced lesions in skin DNA have a 2,000-fold increased risk of CMM by the age of 20.
- One form of CMM, Hutchinson's melanotic freckle melanoma, appears almost invariably on the chronically sun-damaged skin of older people.

Further reinforcing the solar radiation hypothesis is the fact that the development of nevi and freckles appears to be a response to solar radiation and that there is a positive association between these conditions and the risk of CMM. Some argue that the development of nevi, possibly dysplastic nevi, may be a step in CMM related to solar exposure.

The rise in CMM rates during this century has been cited as both supporting an involvement of solar radiation in CMM and as not supporting it. Those who argue it does not support an association of CMM with solar radiation point out that ozone depletion has not occurred, to our knowledge, in this century. Those who argue the rising rates are positive evidence point out that shifts have occurred in patterns of dress and recreational sun exposure, thus increasing intermittent solar exposure to those sites showing the greatest increase.

Immigrant studies provide further support to the solar radiation hypothesis because they show that CMM rates rise in immigrants who move to countries with more solar radiation than in their lands of origin. Furthermore, the longer an immigrant resides in such a high exposure country, the more the risk increases. Part of this increased risk may be due to exposure during some critical event in childhood; there is some indication that arrival before the age of 10-14 is associated with increased risk. An alternative explanation, however, is that childhood is a better time to influence behavior patterns of high sun exposure.

Many ecological epidemiology studies show that increasing incidence or mortality of CMM is inversely correlated with latitude. Latitude is closely correlated with UV-B flux. While these studies do not control for differences in skin pigmentation, for the ratio of indoor and outdoor workers, or for differences in behavior, these characteristics (at least in the U.S.) are probably randomly distributed with respect to latitude. Thus, the differences in behavior, skin pigmentation, and indoor/outdoor worker ratios could be expected to introduce only a small amount of noise into the analyses, reducing the amount of variation in CMM incidence or mortality that can be explained by UV-B dose, but not enough to obscure the fundamental relationship. The fact that a number of studies have found a relationship, and that the best studies have done so, lends support to the solar hypothesis.

The presence of high rates of CMM in xeroderma pigmentosum patients indicates that a component of solar radiation, UV-B, could be important in CMM etiology, and again adds another, different kind of evidence to the array of evidence supporting the conclusion that solar radiation is etiologically related to CMM.

Table 19-4 presents information that has been interpreted as not supporting, being in conflict with, or refuting the solar radiation hypothesis. The points discussed here are, in fact, the fundamental conundrum of this issue.

The failure to find latitudinal gradients of CMM incidence or mortality in some ecological studies (most particularly in Europe) has been interpreted by some to introduce uncertainty into the relationship between solar radiation and CMM. In contrast, many of the original researchers and others have suggested that the failure to find a correlation between latitude and CMM was a product of an inverse gradient of skin pigmentation (i.e., dark-skinned whites in the south, and fair-skinned whites in the north) or a lack of a UV-B gradient north to south in the study area.

Although it would have reinforced the solar hypothesis greatly to have all latitudinal studies in agreement, the main conclusion to be drawn is the need to control for skin pigmentation, behavior, and actual doses of solar radiation by wavelength in such studies.

The difference in CMM rates between indoor and outdoor workers is probably the most difficult information with which to reconcile the solar radiation hypothesis. If solar radiation is a key factor, how is it possible that outdoor workers, who presumably get a larger total dose of solar radiation than indoor workers, have lower incidence rates? This may be a question of definition. For example, one study, which looked only at highly exposed sites, found that outdoor workers had higher CMM rates than indoor workers. Another study, which separated indoor workers into professionals and "others," showed no difference between the indoor "other" classification and outdoor workers, suggesting the hypothesis that greater exposure due to opportunities associated with higher socioeconomic status may explain this issue. Unfortunately, no studies have computed the biologically effective dose of solar radiation, and it is uncertain how much UV-B indoor and outdoor workers receive and how their skin pigmentation differs when they are exposed. Consequently, the only conclusion that can be reached with certainty about the differences between indoor and outdoor workers is that an estimate of UV-B dose based on total hours of solar exposure does not correlate well with CMM incidence. Until epidemiologic studies are done which derive biologically effective doses as opposed to hours of solar exposure, very little more can be said with certainty.

In comparison to basal cell (BCC) and squamous cell cancers (SCC), CMM occurs more frequently on intermittently exposed than continuously exposed sites; this clearly indicates that CMM is related to solar radiation exposure in a way different from BCC and SCC. Many hypotheses have been put forward to explain this difference in behavior of CMM, ranging from a requirement for early childhood exposures, to the need for intermittent or excess exposures, e.g., large doses prior to tanning, or sunburns. Unfortunately, at this time the epidemiologic and experimental data bases do not allow us to determine which, if any, of these hypotheses is correct. Thus, this observation weakens the case for solar exposure, at least as it is now being measured (sunlit hours).

TABLE 19-4

INFORMATION THAT CREATES UNCERTAINTY ABOUT THE CONCLUSION THAT SOLAR RADIATION IS ONE OF THE CAUSES OF CUTANEOUS MELANOMA

- Some ecological epidemiology studies, primarily in Europe or close to the equator, have failed to find a latitudinal gradient for CMM.
- Outdoor workers generally have lower incidence and mortality rates for CMM than indoor workers which appears incompatible with the hypothesis that the cumulative dose of solar radiation is important to CMM causation.
- Unlike basal cell and squamous cell carcinomas, most CMM occurs on sites that are not habitually exposed to sunlight; this contrast also suggests that cumulative dose of solar radiation or UV-B is not solely responsible for variations in CMM.

This finding indicates that CMM, if it is etiologically linked to solar radiation, must be influenced not by total hours exposed to solar radiation but by some other dose parameter. In essence, the evidence that adds uncertainty to the role of solar radiation in the induction of CMM suggests a relationship between induction and a biologically effective dose rather than between induction and a simple measure of cumulative exposure. Thus, it might be possible to resolve this inconsistency if one could compare the UV-B exposures of indoor and outdoor workers through time. Research must focus on determining the UV-B energy actually received at the surface of the skin and, if possible, the penetration of that radiation as tanning takes place.

BALANCING THE EVIDENCE

The supporting evidence that solar radiation is a causal factor in CMM is not indisputable. One must admit that a possibility exists that CMM is not related to solar radiation. On balance, however, the web of evidence taken as a whole supports solar radiation as at least one of the causes of CMM. One can find a number of alternative explanations for each piece of evidence, but in general these do not fit together to provide a meaningful alternative explanation to solar radiation. The likelihood that the array of evidence pointing to solar radiation is either all wrong or is completely explained by a series of other unknown factors is low.

The evidence that fails to support or apparently contradicts the issue does not refute the solar radiation hypothesis. Rather, it supports the view that CMM is a complex disease. On balance, the evidence seems to support solar radiation as a cause of CMM, but does not support the hypothesis that the appropriate measure of dose is cumulative hours of sun exposure.

IS UV-B A WAVEBAND OF SOLAR RADIATION THAT CAUSES CMM?

The second question addressed is:

Does the evidence support the hypothesis that UV-B is a major component of sunlight which causes melanoma?

In Table 19-5, we present summary points which we believe support the hypothesis that UV-B is most likely to be the major component of solar radiation which causes cutaneous melanoma, whereas information which has been considered in contradiction to this hypothesis, e.g., the lack of an animal model, has been discussed in the text principally as flaws in the data base.

Information on patients with xeroderma pigmentosum is perhaps the strongest evidence that we have on a role for solar radiation, and in particular UV-B, in the etiology of CMM. These individuals comprise a susceptible population that is at considerably increased risk for melanoma. The major defect associated with this condition is an inability to repair pyrimidine dimers--a lesion in DNA whose action spectrum principally spans the UV-B region. There is little information addressing the issue of whether it is appropriate to extrapolate from this susceptible population to the general

TABLE 19-5

INFORMATION THAT SUGGESTS THAT UV-B IS THE MAJOR COMPONENT OF SOLAR RADIATION WHICH CAUSES MELANOMA

- Xeroderma pigmentosum patients who fail to repair UV-B-induced pyrimidine dimers in their DNA have a 2,000-fold excess rate of CMM by the time they are 20.
- UV-B is the most active part of the solar spectrum in the induction of mutagenesis and transformation in vitro.
- UV-B is the most active part of the solar spectrum in the induction of carcinogenesis in experimental animals and is considered to be a causative agent of non-melanoma skin cancer in humans.
- UV-B is the most active portion of the solar spectrum in inducing immunosuppression, which may have a role in melanoma development.
- The limitations in the epidemiologic and experimental database leave some doubt as to the effectiveness of UV-B wavelengths in causing CMM.

population; nevertheless we believe that the fact that there is a human population known to be extremely sensitive to UV-B which is also extremely susceptible to melanoma strongly supports a role for UV-B in CMM.

The second and third points of Table 19-5 are similar; one states the evidence which supports the conclusion on the basis of in vitro experiments, and the other is based on information derived from in vivo experiments. The point to be made is that UV-B is the most active portion of the solar spectrum in inducing adverse effects that are related to carcinogenesis. It is true that other portions of the spectrum, in particular UV-A, can cause adverse effects, but these wavelengths are several orders of magnitude less effective at inducing most types of damage. The final point is that UV-B is the most active waveband at inducing UV-R-induced tumor-specific immunosuppression, thus further adding credence to the hypothesis that UV-B is the most likely candidate waveband in solar radiation to be the cause of CMM.

There are several points derived from the experimental literature which are often cited as evidence which does not support a role for solar radiation in CMM, and which we have called weaknesses in the data base. The two key ones relevant to this issue are the lack of an animal model and the lack of an in vitro correlate of malignant transformation. The lack of positive evidence certainly is a weakness in the data base. Efforts have been expended to develop an animal model in mice, but have only been partially successful; those which have partially succeeded have required treatment of animals with a carcinogen, followed by UVR treatment. In several experiments such treatments induced nevi that later became melanomas. This suggests that a possible reason for the lack of an animal model is that we do not yet fully understand the role of precursor lesions in the disease and thus we cannot develop an adequate animal model.

The lack of an in vitro correlate may be due to a similar sort of technical problem. Melanocytes are difficult cells to grow in culture and it is only recently that the growth in vitro has become routine. It is likely that this difficulty has impeded the development of an in vitro system for melanocyte transformation by UV-B. Of course, most data from negative experiments are never published, so it is not possible to judge if adequate experiments have been carried out and not reported, or if technical difficulties have precluded the design and performance of adequate experiments.

BALANCING THE EVIDENCE

The evidence that UV-B is a major component of solar radiation which could cause cutaneous melanoma is not absolute. Clearly the evidence has limitations, as indicated by the lack of either in vivo or in vitro evidence that UV-B can cause transformation of melanocytes. However, there is no evidence which would suggest any alternative hypothesis, and the available experimental evidence indicates quite strongly that UV-B is the waveband most likely to be carcinogenic, not only in animals but also (as evidenced by what is known about non-melanoma skin cancer in general, and melanoma in xeroderma pigmentosum patients in particular) in humans. Given this conclusion, it is reasonable and prudent to examine possible dose-response relationships for UV-B and melanoma.

WHAT DOSE-RESPONSE RELATIONSHIPS ARE CONSISTENT WITH THE DATA?

The last question to be addressed is:

What dose-response relationships between melanoma and UV-B are consistent with the epidemiologic and experimental data?

Table 19-6 summarizes information relevant to evaluating this question.

In evaluating dose-response relationships for risk assessment, two types of data might be used: that which comes from animal experiments or that which comes from epidemiologic studies. In the case of CMM, there are no appropriate animal data. There is no animal model for the induction of CMM by UV-B, and the data linking UV-B exposure to non-melanoma skin cancer (NMSC) in animals is probably inappropriate given the differences in biologic behavior between NMSC and CMM in humans.

Among the available epidemiologic studies, there is no perfect study. The available case-control studies which assessed exposure to solar radiation via questionnaire do not provide information with which to assess UV-B exposures and so are not useful for estimating dose-response relationships. There are, however, several ecological studies in which measured or estimated exposures to UV-B at various locations were correlated to CMM incidence or mortality at those locations. Two of the most recent studies took slightly different approaches. In one, actual annual UV-B measurements from Robertson-Berger meters located in seven cities were converted to biologically effective units using a DNA action spectrum, and these estimated doses were correlated to incidence data from those seven cities using a power model to relate incidence to UV units. Also incorporated into this model was a term which provided some adjustment for host or environmental characteristics. The analysis was segregated by anatomic site so that separate estimates were made for trunk and lower extremities (trunk/LE) versus face, head, and neck, and upper extremities (FHN/UE). This analysis predicted that a 10 percent increase in UV-B would result in a 6 and 5 percent increase in CMM of trunk/LE for males and females, respectively, and 8 and 10 percent increases in CMM of FHN/UE in males and females, respectively.

A second study derived UV-B estimates by county based on a NASA satellite model and weighted by a variety of different action spectra. These were then correlated with county-based mortality data using two different model forms. In total, 8 different sets of assumptions were evaluated [two models (power and exponential), two action spectra (DNA damage and erythema) and two UV flux estimates (peak and mean annual)]. For a ten percent change in UV-B, this study found a range of increases in CMM mortality in males of between 3.4 and 9.8 percent. In females the range was between 2.2 and 6.7 percent.

There are still many uncertainties in these estimates of dose-response relationships, particularly as they apply to future populations. As a result, estimates of the appropriate dose-response relationship between UV-B exposure and CMM (incidence and mortality) continue to be developed. In particular, the epidemiologic studies conducted to date do not account for many population

TABLE 19-6

KEY POINTS RELEVANT TO EVALUATING DOSE-RESPONSE RELATIONSHIPS

- There are no animal data appropriate for developing dose-response estimates for CMM; there is no animal model for CMM, and animal non-melanoma skin cancer (NMSC) data are not appropriate given the differences in biologic behavior between CMM and NMSC in humans.

- Among epidemiologic studies, the most promising for estimating dose-response, relationships are ecologic studies in whic measured or estimated exposures to UB-B at various geographic locations are correlated with CMM incidence or mortality at those locations.

- One such recent study by NCI evaluated the relationship between measured levels of UV-B (annual R-B meter counts) in seven cities and CMM incidence rates in those seven cities; this study predicts that a 10 percent change in UV-B will be assciated with about a 7 percent increase in CMM incidence in males and a 7.5 percent increase in females.

- A second study evaluated the relationship of CMM mortality to model-based estimates of either mean annual or peak-day UV-B flux (weighted based on the action spectra for either DNA damage or erythema). Two forms (exponential and power) of the dose-response relationship were evaluated. The CMM mortality data were county-(SMA) based; data from up to 216 SMAs were evaluated. This study estimated that a ten percent change in UV would result in between a 2.5 and 8.5 percent increase in mortality depending on the assumptions chosen.

characteristics that could change in the future. These include geographic shifts in the population, changes in population age, better prognosis, earlier diagnosis and behavior modification to prevent excessive solar exposure. Such changes are difficult to predict and for the purpose of this process, the critical assumption made has been that population characteristiccs will remain equivalent to those observed in the population from which the mortality and incidence data have been drawn, particularly with regard to ethnicity. Also, because of a lack of the appropriate data these studies cannot adequately control for host factors such as pigmentation. For example, if pigmentation varies systematically with latitude, then the inability to control for it would bias the resulting estimates. There are other variables that might show systematic variation by latitude or geographic location (e.g., socioeconomic status). Again, should such variation occur it could bias the estimates. Other problems yet to be solved in epidemiologic studies include 1) selection of the correct functional form to describe dose-response; 2) controlling fully for genetic and host characteristics such as mode of dress and sunscreen use; and 3) the development of an action spectrum specific for CMM which could be used to weigh solar radiation dose estimates in order to derive a better estimate of UV-B dose.

APPENDIX A

PREPARATION OF THE DOCUMENT

APPENDIX A

PREPARATION OF THE DOCUMENT

INTRODUCTION

The goal of this appendix is to provide information as to the manner in which this document has been prepared. Included in it is a description of the process by which the literature in this document was identified, reviewed, organized into topics and incorporated into chapters.

As indicated in the overview of the document, the goal of this document was to critically review the available experimental and epidemiologic evidence pertinent to determining if it can be reasonably anticipated that a change in stratospheric ozone and a resulting change in the amount of UV-B delivered to the earth's surface would result in a change in the incidence or morbidity of cutaneous malignant melanoma (CMM).

The review was designed to be comprehensive but places particular emphasis on information entering the literature after the latest National Academy of Sciences report (NAS 1984). One very recent publication, The Epidemiology of Malignant Melanoma, Volume 102 of Recent Results in Cancer Research, was not available in time to be included systematically, although, where possible, we have included that information in the relevant chapters. The articles of Gallagher et al., Holman et al., Green et al., and Osterlind and Jensen are particularly relevant to the issues discussed in this review; their findings and analyses tend to support the conclusions reached in this document.

LITERATURE RETRIEVAL

The retrieval of literature for this project was performed principally on the National Library of Medicine's Elhill databases: MEDLINE, CANCERLINE, SDILINE and TOXLINE, although some searches on the DIALOG databases were also made. Initially the search strategy consisted of printout of a search based on the keywords melanoma cross-referenced with solar or ultraviolet or light or sun or sunlight. Abstracts from this search were selected and the literature for them was retrieved. Subsequent searches were much more focussed; in all there were more than 100 such searches run. An example - the search strategy used to research the question of animal models for primary (as opposed to transplanted) cutaneous malignant melanoma is presented in Exhibit A1.

The search strategies generally were designed with one of two objectives, either to retrieve as much as was known about a particular area of interest, e.g., animal models for primary melanoma, or to pinpoint the key information or the most current information on a particular point, e.g., the generation of superoxides following irradiation of melanin with UV-B. In some instances, author searches were performed. For example, in reviewing the epidemiologic evidence it was clear that certain authors published heavily in a given area. Some of the authors for whom such searches were made include: C.D.J. Holman, A. Green, M.H. Greene, J.A. Lee, J. Scotto, V. Beral, A. Swerdlow, T. Fitzpatrick, P. Armstrong, A. Houghton, C.M. Balch, I. Crombie, K. Magnus, J. Elwood, D.E. Elder, and W.H. Clark.

With the exception of the very first more or less global searches, all of the searches on the ELHILL databases were performed by the information specialist/project manager in response to questions raised during the review or chapter-drafting processes. In addition to the online searches, new journals in the relevant areas were also checked on a weekly or biweekly basis. A list of the journals that were routinely searched in this manner is presented in Exhibit A2. Also as a way of ensuring that the information reviewed was kept current, ELHILL'S most current month file - SDILINE - was checked on a regular basis for anything relevant to melanoma, ultraviolet radiation and carcinogenesis.

SEARCHABLE BIBLIOGRAPHIC DATA BASE

About midway into the literature identification and retrieval for this project, it became apparent that identifying the relevant reports among the vast amount of literature retrieved might be facilitated by a relational data base of the articles, searchable by keywords. Accordingly, a key wording process was instituted. Exhibit A3 presents the coding sheet used and Exhibit A4, the definitions given each keyword. The data base was designed in DBaseIII® and is searchable principally by keywords but also, to a limited extent, by first author. Keywords can be "ored" or "anded". Originally, the file required DBaseIII® in order to be used, it was subsequently compiled using the program Clipper® and now runs as a "stand-alone". The program requires an IBM-PC/XT or AT but is fairly slow on the XT.

The system proved very useful at identifying the literature already in-house. One problem encountered, however, was that authors in writing their chapters would tree-search to identify new information and those new articles were often delayed in being put on the data base as a consequence the data base is not complete.

THE REVIEW PROCESS

The review process was carried out by the team of contributors indicated on the title page. Initially the review process involved in-depth evaluation of the same key studies by the group as a whole, followed by meetings in which the reviews were discussed and the key findings identified, and verified. The purpose of these reviews and meetings was to ensure that the reviewers who were later to be authors of various chapters in the document would start with the same background information and knowledge of the area, and would approach the analysis in a similar fashion.

Information to be reviewed was divided into chapters and assignments were made to the various contributors. The division into chapters was based on the findings to be examined; as the review process proceeded, the material was reorganized several times in order to develop the final organization presented here.

Much of the new information dealt with a number of new epidemiological studies. Because of the importance of this information, detailed critical reviews of these studies were provided by Dr. Ralph Buncher and David Warschwsky of the University of Cincinnati Medical School, Department of Epidemiology. Those reviews, as well as critical reviews of other important epidemiologic references done by Dr. Buncher and Ms. Sarah Foster are presented in the following Appendix B.

CHAPTER DRAFTING AND REVIEW

First drafts of each chapter were prepared and submitted to the other contributors for review. Chapters reviewing the epidemiologic evidence were written by either Dr. Saftlas, Ms. Knox or Ms. Foster and were critically reviewed principally by Dr. Aparna Koppikar,but also by Dr. Saftlas, Ms. Knox and Ms. Foster. Chapters reviewing the experimental evidence were principally written by Drs. Lill, Longstreth and DeFabo, with internal reviews being provided by contributors other than the author. The introductory chapter on melanoma and the chapter on predisposing lesions which were combinations of experimental and epidemiolgic evidence were written by Dr. Longstreth and were kindly reviewed by Dr. David Elder of the Pigmented Lesion Group in Philadelphia, as well as by the other contributors. The chapters on variations in UV by latitude and altitude and on the dose-response relationships for melanoma were written by Mr. Hugh Pitcher and Dr. Longstreth and reviewed by Dr. Frederick and Mr. Scotto respectively. The document in its entirety was given detailed review by Dr. E.A. Emmett of the Johns Hopkins School of Public Health and Mr. J. Scotto of the National Cancer Institute.

EXHIBIT A1

SEARCH STRATEGY FOR ANIMAL MODELS OF PRIMARY CUTANEOUS MALIGNANT MELANOMA

```
SEARCH FORMULATION BEGINNING AT SS 1 :
 (ALL MELANOMA AND ALL ANIMAL# )  --        4657 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 2 :
  SS  1 AND NOT ALL B16 )  --        3116 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 3 :
 (SS  2 AND NOT ALL CULTURE# )  --        1443 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 4 :
  SS  3 AND NOT ALL VITRO )  --        1099 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 5 :
  SS  4 AND NOT ALL TRANSPLANT: )  --         979 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 6 :
  SS  5 AND NOT ALL DRUG# )  --         815 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 7 :
 (SS  6 AND NOT HUMAN (TW) )  --         819 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 8 :
 (SS  7 AND NOT PATIENT  TW) )  --         388 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 9 :
 (SS  8 AND NOT ALL MODEL# )  --         806 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 10 :
 (SS  9 AND NOT ALL UVEAL OR SS  9 AND NOT ALL EYE#
                          --         802 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 11 :
  SS 10 AND NOT ALL B-16 )  --         722 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 12 :
 (SS 11 AND NOT ALL CLOUDMAN )  --         696 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 13 :
  SS 12 AND ALL ENG (LA) )  --         534 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 14 :
  SS 13 AND NOT ALL PHARMACEUT: )  --         534 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 15 :
 (SS 14 AND NOT ALL EQUINE# OR SS 14 AND NOT ALL HORSE:
                          --         530 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 16 :
 (SS 15 AND NOT ALL COW# OR SS 15 AND NOT ALL NEWT:
                          --         530 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 17 :
 (SS 16 AND NOT ALL OPHTHAL: )  --         580 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 18 :
 (SS 17 AND NOT ALL PROSTAGLANDIN: AND SS 17 AND NOT ALL PLASMINOGE
                          --         584 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 19 :
 (SS 18 AND NOT ALL CHEMO: )  --         514 POSTINGS

SEARCH FORMULATION BEGINNING AT SS 20 :
 (SS 19 AND NOT ALL INTRAOC: )  --         515 POSTINGS
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EXHIBIT A2

CURRENT JOURNALS FOLLOWED

International Journal of Cancer

American Journal of Epidemiology

International Journal of Epidemiology

Cancer Research

Cancer

British Journal of Dermatology

International Journal of Dermatology

Archives of Dermatology

British Journal of Cancer

Journal of Experimental Medicine

The American Journal of Dermatopathology

Journal of American Academy of Dermatology

EXHIBIT A3

KEYWORD CODING FORM

KEYWORD

Citation: _____

10 melanoma
20 non-melanoma
30 economic impact
40 letter/abstract
50 skin/cutaneous (nos)
60 review/editorial
70 action spectrum
80 dose-response
90 neoplasia
91 initiator
92 promoter
100 HUMAN STUDY
110 histopathologic type
120 case report
130 treatment technique
140 pregnancy/estrogen
150 site/racial differences
155 racial/ethnic
160 clinical diagnostic factors
170 genetic factors
175 skin characteristics
180 environmental factors
181 smoking
182 diet/nutrition
200 EPIDEMIOLOGICAL
205 Descriptive
210 case-control
220 cohort study
225 time trends
230 cross-sectional
240 retrospective
250 prospective
260 migrant
265 occupational
270 socioeconomic status
280 age/sex
290 incidence
291 mortality
292 survival
300 ANIMAL STUDY
310 mouse
320 guinea pigs
330 hamster
340 tumor transplant
350 chemical carcinogen
400 CELLULAR (in vitro)
410 transformation
411 differentiation/development
420 melanocyte/melanoblast
430 keratinocyte
440 squamous cell
450 epidermis/epidermal cell
460 nevus/nevus cell/mole
470 basal cell
480 stratum corneum
500 MOLECULAR
510 urocanic acid/histidine
520 DNA damage
530 melanin/tyrosine
540 pigment
550 mechanism/hypothesis
600 IMMUNOLOGIC/lymphocyte (nos)
610 Ia antigens (class II MHC)
620 Langerhans cells
630 T-lymphocytes
640 B-lymphocytes
650 autoimmunity
660 antibody
670 immunosuppression
700 CATARACT/eye (nos)
710 cornea
720 lens
730 retina
800 SUNLIGHT (nos)
810 ultraviolet light
811 UV-A
812 UV-B
820 latitude gradient
830 fluorescent lights
840 erythema/sunburn
850 ionizing radiation
860 exposure characteristics
861 intensity/duration
900 VIRUSES
910 Herpes

EXHIBIT A4

KEYWORD EXPLANATIONS

10 - Melanoma: use for anything that references melanoma.

20 - Non-melanoma: use for any study that refers to non-melanoma skin cancer, either basal or squamous cell.

30 - Economic impact: use for studies which address costs of treatment, costs of disease (hospitalization), loss of work time, etc.

40 - Letter/abstract: any article which is a meeting abstract or a letter to the editor.

50 - Skin/cutaneous (nos): use for studies that mention the skin or cutaneous diseases/eruptions.

60 - Review/editorial: any article that identifies itself as a review article or any article which provides no new data, e.g., an editorial.

70 - Action spectrum: any studies that evaluate several wavelengths of UV light to determine which is the most active at causing an effect.

80 - Dose-response: studies which report a relationship between dose and response; e.g., by investigating the different level of effects of several doses.

90 - Neoplasia carcinogenesis: any studies having to do with benign or malignant tumors or growth. Use also for theories of carcinogenesis.

91 - Initiator: any cancer-causing substance which can initiate a neoplastic event; i.e., which will induce a tumor without subsequent application of a promoter.

92 - Promoter: a substance which is not itself carcinogenic, but which increase the carcinogenic effect of an initiator.

100 - HUMAN (study): any study dealing with humans or human cells except for those studies based on populations; i.e., epidemiological studies.

110 - Histopathologic type: use this if the study differentiates among different types of tumors or cells; e.g., draws different conclusions for superficial spreading melanoma vs. nodular melanoma.

120 - Case report: use for human studies that report results of medical cases; e.g, physician's report of patients presenting with different kinds of melanoma.

EXHIBIT A4

KEYWORD DEFINITIONS (Continued)

130 - Treatment technique: use for reports evaluating various treatments; e.g., cryosurgery, surgery, chemitherapeutics radiation.

140 - Pregnancy/hormone: use for the evaluation of impact of pregnancy, birth control pills, or post-menopausal hormones. Should also be used for hormones (nos).

150 - Anatomical differences: use if report compares or contrasts different rates among anatomical sites.

160 - Clinical/diagnostic factors: use if a report evaluates disease states with regard to staging of disease, or prognostic/diagnostic factors or clinical parameters which help predict disease onset or progression.

170 - Genetic factors: use if report evaluates familial history or genetic factors/markers such as HLA antigens.

180 - Environmental factors: use if report evaluates other environmental factors such as smoking, nutrition, chemicals

190 - Skin characteristics: use for a study that evaluates various skin characteristics; e.g, types I, II, III or freckles or degree of pigmentation. May also be used for studies that deal with abnormalities of the skin such as vitiligo.

200 - EPIDEMIOLOGICAL: use if report is an epidemiologic study or if a review summarizes epidemiologic information.

205 - DESCRIPTIVE: use if study summarizes trends in a data set, such as trends in incidence or mortality with respect to age, site, sex, or occupation. Do not use for a study which analyzes and evaluates potential cause/effect relationships.

210 - Case-control: The individuals in the study are selected based upon whether they have the disease of interest (cases) or not (controls). In general, it is preferable to choose incident rather than prevalent cases within a specified time period. Case-control studies may be retrospective (if exposure or cause information is for a time period preceding the disease occurrence) or nondirectional (if disease and exposure information are from the same time period). Case-control studies can be used for relatively infrequent diseases, although a problem often arises in remembering or documenting exposure (i.e., cause) information.

220 - Cohort: The individuals to be studied (the cohort) are defined based upon characteristics manifest before the appearance of the disease being

EXHIBIT A4

KEYWORD DEFINITIONS (Continued)

studied. The cohort is then followed up to determine the frequency of disease in it. Cohort studies usually measure incidence or mortality. A prospective cohort study is one in which the cases of disease have not occurred at the time the study has begun, but the causes may or may not have occurred. A retrospective cohort study is one in which all causes and effects have already occurred at the time the study is initiated. (Note that retrospective and prospective are, in this terminology, used to describe the time of occurrence of the events being studied relative to the study investigator's place in time.) Prospective cohort studies are only economical when the disease is relatively frequent. For rare diseases, vary large cohorts are needed. In a cohort study, the number of cases in the cohort may be compared with the expected number of cases in a reference population. The reference population should be compared to the cohort with respect to factors other than the exposure of interest.

225 - Time trends: use if a report evaluates trends such as increasing incidence with time or increasing mortality with age of onset. This keyword should also be used if reference is made to relationship of incidence to sunspot activity or other periodic phenomena. Also, use for birth cohort effect.

230 - Cross-sectional: in a cross-sectional study, the measurements of cause and effect have been made at the same point in time. Thus, it is a nondirectional (i.e., neither retrospective nor prospective) study. Cross-sectional studies are usually based on disease prevalence information rather than incidence. In contrast to a cohort study, a cross-sectional study that assesses prevalence data cannot ascertain the direction of the relationship between the study factor and the disease (i.e., cannot determine whether the hypothesized cause was an antecedant or a consequent of the disease). It differs from a case-control study in that the study population is selected from a single target population.

240 - Retrospective: an epidemiologic study that selects its population to be watched on the basis of a known characteristic and then tracks backwards in time to identify any other charactertistics held in common.

250 - Prospective: any epidemiological study that takes a population and watches it for the subsequent appearance of a characteristic; e.g., a disease.

260 - Migrant: epidemiologic studies that evaluate the response of individuals that migrate from a geographic location of relatively low exposure to a location of relatively high exposure.

EXHIBIT A4

KEYWORD DEFINITIONS (Continued)

265 - Occupational: use for studies that evaluate the impact of occupation on incidence, or survival of a disease. This word should be used if a study mentions difference between indoor and outdoor work, or occupational exposures to carcinogens or differences between office workers and factory workers.

270 - Socio-economic status: use if report talks about relationship of disease to socioeconomic status; e.g., years of education, blue-collor/white-collar.

280 - Age/sex differences: use if report deals with differences in response of different age groups or between males and females.

290 - Incidence: use if a study gives incidence rates or ratios or evaluates differences in incidence between different parameters; e.g., anatomical site.

291 - Mortality: use if a report evalutes a mortality parameter; e.g, SMA (standard mortality ratio), or compares and contrasts mortality in different populations based on various characteristics.

292 - Survival: use if a study evaluates the survival of a population after various treatments or based on different characteristics; e.g., smoking habits.

300 - ANIMAL (study): experimental studies in which whole animals are used to determine the impact of an agent at the animal, tissue, or cellular level.

310 - Mouse: use for experimental studies employing mice (or mouse cells).

320 - Guinea pig: use for experimental studies employing guinea pigs (or their cells).

330 - Hamster: use for experimental studies employing hamsters (or their cells).

340 - Tumor transplant: use if study mentions transplantation of tumors.

350 - Chemical carcinogen: use if study mentions the use of a chemical carcinogen to induce a tumor.

EXHIBIT A4

KEYWORD DEFINITIONS (Continued)

400 - CELLULAR (in vitro): experimental studies dealing with the impact of an agent on cells. May be in vivo or in vitro. There may be cross-over with animal studies.

410 - Transformation: any study that evaluates the preneoplastic or neoplastic development of a cell. May be applied to in vivo or in vitro studies.

411 - Differentiation/development: use for any study that evaluates cellular differentiation or growth states, or for a study that looks at developmental changes or stages.

420 - Melanocyte/melanoblast: studies of cells (or their precursors) that synthesize melanin.

430 - Keratinocyte: any information that mentions keratinocytes or epidermal cells that synthesize keratin. These cells eventually become the corneocytes that form the stratus corneum.

440 - Squamous cell: use for any information on squamous cell carcinoma or for any studies that deal with the precursor cell for this lesion.

450 - Epidermis/epidermal cell: use for studies of the epidermis or for cells not otherwise specified (nos) which populate the epidermis. This should track with keratinocyte, melanocyte, basal cell and Langerhans cells.

460 - Nevus/nevus cell/mole: use for any study mentioning nevi, nevus, or moles.

470 - Basal cell: use for basal cell carcinoma and any studies dealing with basal cells in the dermis or epidermis.

480 - Stratum corneum: use for studies which mention or examine the stratum corneum layer of the skin.

500 - MOLECULAR: use for any study designed to investigate the problem at the molecular level; i.e., could be at the biochemical or histochemical level. Could involve urocanic acid or DNA damage.

510 - Urocanic acid/histidine: use for any studies dealing with urocanic acid or the metabolism of histidine.

520 - DNA: any studies dealing with damage to the genetic material, measured biochemically. This should also include oncogene research.

EXHIBIT A4

KEYWORD DEFINITIONS (Continued)

530 - Melanin/tyrosine: use for studies of or tyrosine melanin biochemistry, characterization, synthesis, etc.

540 - Pigment: use for studies evaluating pigment differences not otherwise specified; i.e., could be used for epi studies where darkness of pigmentation was an evaluated parameter.

550 - Mechanism/hypothesis: use for studies which put forth a mechanism or a hypothesis.

600 - IMMUNOLOGIC/lymphocyte (nos): use for anything having to do with the immune system and its responses. Use also for any reference to lymphocytes which does not identify a specific type.

610 - Ia antigens/Class II MHC: use for studies evaluating the role of Ia or Class II MHC antigens in the immune response or as a marker for Langerhans cells.

620 - Langerhans cells: use for studies which mention these cells of the macrophage lineage that normally reside in the skin.

630 - T-lymphocyte: use for studies that mention "thymus derived" lymphocytes. These cells may be "helper" cells, "inducer" cells, "suppressor" cells, or "killer" cells.

640 - B-lymphocyte: use for studies which deal with antibody forming cells and their precursor surface-antibody positive lymphocytes.

650 - Autoimmunity: use for studies evaluating aspects of immune reactions against self. Use for any studies of systemic lupus erythematosus.

660 - Antibody: use for any studies relating to the production of antibodies during disease states. Do not use if antibodies are being used as a diagnostic tool.

670 - Immunosuppression: use for reports indicating lack or depression of normal immune function.

700 - CATARACT/eye (nos): use for studies relating to the etiology of cataract development and for any general studies of the eye.

710 - Cornea: use for studies evaluating the impact of an agent on the cornea.

EXHIBIT A4

KEYWORD DEFINITIONS (Continued)

720 - Lens: use for studies relating to the impact on the lens. All cataract studies are also lens studies but not vice versa.

730 - Retina: use for studies relating to retinal behavior or damage.

800 - SUNLIGHT: use for studies where sunlight is evaluated as a risk factor but where no wavelength is specified.

810 - Ultraviolet light: this should be used when UV is identified but the wavelength is not specified.

811 - UV-A: use for studies that have evaluated the impact of UV in the 320-400 nm range.

812 - UV-B: use for studies that have evalauted the impact of UV in the 280-320 nm range.

820 - Latitude gradient: use for studies which evaluate impact correlated to latitude changes.

830 - Fluorescent light: use for studies which evaluate the role of fluorescent or indoor light on disease development (could be melanoma, cataract, etc.)

840 - Erythema/sunburn: use for studies that evaluate role or amount of sunburn that an individual received, or studies that deal with the erythemal response to ultraviolet irradiation.

850 - Ionizing radiation: use for studies that evaluate the impact of exposure to x-irradiation.

860 - Exposure characteristics: use for studies that evaluate the characteristics of exposure to radiation.

861 - Intensity/duration: use for studies that evalute the intensity or duration of exposure; e.g., differences between acute and chronic exposures, or sunburn versus gradual tanning.

900 - VIRUSES: use for studies which deal with viruses (nos).

910 - Herpes: use for studies of herpes viruses and the diseases they induce.

APPENDIX B

REVIEW OF CRITICAL EPIDEMIOLOGIC STUDIES

GREEN AND COLLEAGUES -- QUEENSLAND MELANOMA DATA

This is a case-control study from Queensland in northeast Australia, an area which has the highest incidence of melanoma in the world. Queensland is unusual in that a predominantly Caucasian population inhabits both tropical and subtropical latitudes.

Cases were those persons first diagnosed with a primary cutaneous melanoma during the year from July 1, 1979 to June 30, 1980. Cases were ascertained from the records of the 24 Queensland pathology laboratories. There were 871 cases diagnosed of which 201 were reported to have an in situ component of Hutchinson's melanotic freckle (HMF). No histological classification was given for 10 cases and age was not stated for an additional 27 leaving 633 cases for the analysis of non-Hutchinson's melanoma. Address at the time of diagnosis was used for geographic correlations.

In a series of seven publications to date, Green and her colleagues have examined several subsets of the Queensland patient series. Three of the articles analyze randomly selected patient subsets. The four other articles present case-control comparisons for randomly selected patient subsets and age-, sex-, and residence-matched controls randomly selected from Queensland electoral rolls.

Three studies deal with the incidence and reporting of CMM in Queensland, the relationship between CMM incidence and latitude, and the diagnosis of HMFM. The case-control studies investigate the effects of cumulative sun exposure, episodes of sunburn, the number of naevi on the left arm, and the presence of nonmelanotic skin tumors on risk of CMM.

For the case-control studies, information obtained on each subject included lifetime sun exposure (occupational or recreational), acute and chronic response to sun exposure, episodes of severe sunburn, complexion (skin, eye and hair color), number of naevi (2 mm or more in diameter) on the left arm, family melanoma history, social class (based on occupation), ethnicity, and nonmelanotic facial skin cancers.

Reference:

Green, A. "Incidence and reporting of cutaneous melanoma in Queensland." Aust. J. Derm. 23:105-109 (1982).

Investigator Results:

1. The incidence rate was still rising, especially of thin tumors. The 1979-1980 crude annual incidence rate was $39.6/10^5$ compared to $32.7/10^5$ in 1977.

2. Of the 871 cases, 455 (52 percent) were in women and 416 (48 percent) were in men. More women than men noticed their own tumors. Among the 236 patients, in females, 68 percent of the lesions were first detected by the patient, 12 percent by other non-medical individuals, and 20 percent by the doctor; in males the numbers were 46 percent, 28 percent, and 26 percent, respectively.

3. Cell types included malignant and nonmalignant tumors; 57 percent were superficial spreading melanoma (SSM). Lentigo maligna (melanoma) (LMM) accounted for 23 percent of all lesions compared to 15 percent in 1977 and 7 percent in 1967. Nodular melanoma comprised 15 percent of the lesions compared to 15 percent in 1977 and 28 percent in 1967. A distribution of anatomic location by cell type was given showing a majority of tumors on the head to be LMM. Most of the SSM and LMM tumors were thin while the nodular tumors tended towards greater thickness.

4. The author commented that "... it is difficult to distinguish between a true rise in disease which may have occurred, e.g. as the result of sun exposure received at increasingly popular beach resorts, and a rise resulting from early reporting in a community which is aware of the disease."

Methodology:

All 871 patients with a first cutaneous melanoma diagnosed in Queensland from 1 July 1979 to 30 June 1980 reported by one of the 24 pathology laboratories were studied. The author interviewed a random sample of 236 patients with a standard questionnaire concerning how they first became aware of the lesion.

Experimental Design and Analysis Issues:

A descriptive analysis of malignant melanoma (MM) information from Queensland, Australia.

Reference:

Green, A. and Siskind, V. "Geographical distribution of cutaneous melanoma in Queensland." Med. J. Australia 1:407-410 (1983).

Investigator Results:

1. A latitude gradient for melanoma incidence in Queensland from 1979-1980 was found. The reported incidence rate for Queensland had, however, doubled from $16.4/10^5$ in 1965 to $32.7/10^5$ in 1977.

2. A significantly increased incidence of melanoma was observed in coastal, compared to inland regions.

3. Authors concluded that one possible explanation of the observed geographical distribution lies in the ready accessibility to beaches which encourages sunbathing in the coastal population.

Methodology:

A cross-sectional analysis of the relationship between melanoma incidence rates and latitude in Queensland. Incidence rates were calculated based on 633 cases of first primary cutaneous melanoma diagnosed and reported at the 24 Queensland pathology laboratories between 1 July 1979 - 30 June 1980, directly age-standardized to 1979 Australian Bureau of Statistics population estimates. Patient information included age, sex, residential address at time of diagnosis, and histologically classified lesion according to Clark method. Patients with HMF and HMFM were treat separately.

Queensland was partitioned into four regions (tropical, subtropical, inland, coastal) as well as into 11 statistical divisions defined by the Australian Bureau of Statistics.

Experimental Design and Analysis Issues:

A cross sectional analysis of the relationship between melanoma incidence and latitude in Queensland.

For Result 1:

Age-standardized incidence rates ranged from $9.4/10^5$ - $41.6/10^5$ in Queensland by statistical division. Differences between divisions and by latitude were not significant.

For Result 2:

Age-standardized incidence rates differed significantly by region (p less than 0.05) with the source of the difference due to inland vs. coastal incidence rates (p less than 0.01) rather than tropical vs. subtropical rates (p greater than 0.5). There was no evidence that the major histological types differed by geographic area. The erythemal UV dose decreases with latitude in July (mid-winter) but this pattern is modified in January (mid-summer) when there is also an increasing gradient as one moves inland.

Comment:

It is uncertain whether the case ascertainment was complete since it is possible that some cases were treated in an individual physician's office from which no material was submitted to one of the pathology laboratories surveyed or from which the material might have been submitted to another laboratory. The address at the time of diagnosis was used in this study; the classic problem of the address when the cancer was "caused" then becomes relevant since we are not assured that the patient resided at the diagnosis address for any particular period of time.

Reference:

Green, A., Little, J.H. and Weedon D., "The diagnosis of Hutchinson's melanotic freckle (lentigo maligna) in Queensland." Pathology 15:33-35 (1983).

Investigator Results:

1. Among a sample of 99 melanoma lesions, 76 had an in-situ component of HMFM type, 12 had in-situ component of SSM type, 4 indeterminant/lack of agreement in-situ component, and 7 were lentigines with insufficient atypical features to warrant a diagnosis of HMFM.

2. The authors comment ... "Our review highlights the potential for misclassification as well as overdiagnosis of HMFM". In Queensland the number of reported cases of primary cutaneous melanoma "rose from 106 in 1977 (15 percent of the year's total of 705) to 224 for the 12 month period from July 1979 (26 percent of 878)".

Methodology:

A descriptive analysis of a sample of 99 lesions from 97 patients (44 percent) out of 224 cases diagnosed in Queensland, Australia from 1 July 1979 to 30 June 1980 which were reviewed by two pathologists.

Comment:

With a strict reproducibility rate of 76/99 = 77 percent, misclassification and overdiagnosis could explain some of the increase in the disease. On the other hand, it is difficult to explain a doubling of the disease by this mechanism.

Reference:

Green, A. "Sun exposure and the risk of melanoma." Br. J. Derm. 25:99-102 (1984).

Investigator Results:

1. In a case-control study the risk of melanoma increased with accumulated solar exposure through life including lifetime occupational and recreational exposures adjusted for residential mobility.

2. Among 183 matched case-control pairs, risk of melanoma increased with number of cumulative hours of sun exposure through life even after adjusting for the effects of exact age, presence of naevi on the arms, hair color, and sunburn propensity in a multivariate model. For less than 2,000 hours, the relative risk (RR) was 1.0. For 2000 to 50,000 hours, the RR was 3.2 (95% C.I. 0.9-12.4) and for more than 50,000 hours, the RR was 5.3 (95% C.I. 0.9-30.8). The unadjusted RRs were 1.0, 2.0, and 3.3, respectively.

3. Cases had significantly more actinic lesions (a three-fold increase) on their faces than controls.

4. The author commented that "These data strongly suggest that melanoma does have an association with high doses of solar UV radiation."

Methodology:

A case-control study of MM patients who reported their first primary MM between 1 July 1979 - 30 June 1980 in Queensland and for whom histological diagnosis and tumor thickness were provided by Statewide pathology libraries. Of 871 total cases diagnosed in the year, 243 were randomly selected and 236 (97 percent) contacted and interviewed. Controls, randomly selected from electoral rolls, were matched by age, sex, and place of residence. Information on cases and controls, obtained by interviewer questionnaire, included all episodes of severe sunburn (48+ hours duration), number of sunburn experiences by age group (0-9, 10-19, 20-29, 30+ with virtually all burns occurring before age 40), lifetime sun exposure (occupational and recreational), eye and hair color, acute and chronic response to sun exposure, nonmelanotic facial skin cancers, and number of naevi (dark brown lesions 2 mm or more in diameter) on left arm. After lentigo maligna and acral lentiginous melanomas were excluded, 183 case-control study pairs from 14 to 81 years of age remained.

Crude unmatched RRs were calculated, as well as matched from RRs unadjusted and using conditional logistic regression (CLR).

Comment:

The relative risks in the multivariate model have the possibility that hours of sun serves as a pseudonym for age and/or presence of nevi especially after these have been included in the multivariate model. It would be important to know the correlation among these predictor variables.

Reference:

Green, A., MacLennan, R., and Siskind, V. "Common acquired naevi and the risk of malignant melanoma." Int. J. Cancer 35:297-300 (1985).

Investigator Results:

1. Among 183 MM patients and 183 sex-, age-, and area of residence-matched controls, there was a strong association between presence of pigmented naevi on arms and MM, with a crude relative risk (RR) of 28.0. After adjusting for hair color, propensity to sunburn, and lifetime sun exposure, the RR was 30.1.

2. Family history did not appear to be a determinant of MM independent of above-mentioned risk factors.

3. The authors commented that "Similar findings regarding the risk of melanoma in sun-sensitive persons ... provide excellent circumstantial evidence that sun exposure has a causal association with disease."

Methodology:

A case-control study of MM patients who reported their first primary MM between 1 July 1979 - 30 June 1980 in Queensland and for whom histological diagnosis and tumor thickness were provided by Statewide pathology libraries. Of 871 total cases diagnosed in the year, 243 were randomly selected and 236 (97 percent) contacted and interviewed. Controls, randomly selected from electoral rolls, were matched by age, sex, and place of residence. Information on cases and controls, obtained by interviewer questionnaire, included all episodes of severe sunburn (48+ hours duration), number of sunburn experiences by age group (0-9, 10-19, 20-29, 30+ with virtually all burns occurring before age 40), lifetime sun exposure (occupational and recreational), eye and hair color, acute and chronic response to sun exposure, nonmelanotic facial skin cancers, and number of naevi (dark brown lesions 2 mm or more in diameter) on left arm. The final 183 case-control pairs included cases with intra-epidermal components of superficial spreading or indeterminate melanoma types, and those with no intra-epidermal component (nodular). LMM and acral lentiginous melanomas were excluded.

Crude associations were estimated with simple matched and unmatched univariate screening; other factors were assessed with Mantel-Haenszel RR estimates and conditional logistic regression (CLR) for matched pairs.

Experimental Design and Analysis Issues:

A well-designed case-control study of the association of a variety of factors and MM.

For Result 1:

The strongest association was between MM and naevi on arms (2-4 naevi vs. none, RR=15.7; 5-10 naevi, RR=14.9; 10+ naevi, RR=20.1). The major effect was presence of any naevi with RR=15.8 (95% confidence interval 9.4-26.5) with unmatched data, RR=28.0 (10.6-106.8) with matched data. Several other factors were crude predictors of MM risk, including propensity to burn then tan, or burn then peel (crude RR=3.6, adjusted for naevi RR=2.5), moderate or no tan tendencies (crude RR=4.5, adjusted RR=3.0), propensity to freckle, light brown/blonde hair color, and red hair color (crude RR=3.6, adjusted RR=2.4).

In a stepwise CLR with all phenotypic characteristics, the major MM determinants were naevi on arms, propensity to sunburn upon acute exposure, and hair color. After adjusting for lifetime sun exposure, propensity to burn and hair color, the RR for presence of naevi was 30.1, for red hair 5.9, for light brown/blond hair 3.5, for black/dark brown hair 1.0, and for the propensity to sunburn 3.5.

For Result 2:

There was no evidence of an association between MM and positive family history of skin and noncutaneous cancer. Significantly more cases than controls had a family history of skin cancer (18% vs. 8%) with crude RR=2.5. When naevi, sunburn and hair color were considered, the RR for family MM history was 0.96.

Reference:

Green, A., Siskind, V., Bain, C., Alexander, J. "Sunburn and malignant melanoma." Br. J. Cancer 51:393-397 (1985).

Investigator Results:

1. Among 183 case-control pairs, 99 percent of sunburn experiences occurred prior to age 40 (median age at diagnosis was 46). Of the 183 cases, 141 (77 percent) had superficial spreading melanoma, 36 (20 percent) had nodular melanoma, and 6 (3 percent) had interdeterminate melanoma.

2. There was an association between multiple sunburns and melanoma (excluding LMM) among the case-control pairs. After controlling for other risk factors, a significant dose response association (p less than 0.05) was evident (RR=1.5 for 2-5 sunburns in life, RR=2.4 for 6+ sunburns).

3. The authors commented that "... sunburn exposure factor is a consequence of the amount of UV received at the skin surface and the degree of pigment protection provided by melanin against UV transmission through the epidermis. Thus regardless of an individual's innate colouring or tanning from previous sun exposure, an experience of painful erythema indicates that acute high-dose UV has been delivered to the level of the melanocyte."

Methodology:

A case-control study of MM patients who reported their first primary MM between 1 July 1979 - 30 June 1980 in Queensland and for whom histological diagnosis and tumor thickness were provided by Statewide pathology libraries. Of 871 total cases diagnosed in the year, 243 were randomly selected and 236 (97 percent) contacted and interviewed. Controls, randomly selected from electoral rolls, were matched by age, sex, and place of residence. Information on cases and controls, obtained by interviewer questionnaire, included all episodes of severe sunburn (48+ hours duration), number of sunburn experiences by age group (0-9, 10-19, 20-29, 30+ with virtually all burns occurring before age 40), lifetime sun exposure (occupational and recreational), eye and hair color, acute and chronic response to sun exposure, nonmelanotic facial skin cancers, and number of naevi (dark brown lesions 2 mm or more in diameter) on left arm. After lentigo maligna and acral lentiginous melanomas were excluded, 183 case-control study pairs from 14 to 81 years of age remained.

Crude unmatched RRs were calculated, as well as matched from RRs unadjusted and using conditional logistic regression (CLR).

Experimental Design and Analysis Issues:

A case-control study among 183 age-, sex-, residence-matched pairs.

Cases generally had more sunburns than controls (p less than 0.01), and when number of sunburns were considered (0-1 controls, 0-1 cases, 2-5 cases, 6+ cases), there were significantly more cases than controls (p less than 0.001) with 2-5 burns, crude RR=2.4 and with 6+ burns, crude RR=3.3.

When number of naevi on arms and age were included in a multivariate model, the adjusted RR was 1.5 (95% C.I. 0.7-3.2) for 2-5 burns and 2.4 (95% C.I. 1.0-6.1) for 6+ burns (p less than 0.05). When presence of skin cancers, migrant status, and social class were included, the RRs remained essentially unchanged. Although small samples limited analysis by histogenic type, a tendency of increasing RRs with number of sunburns, especially for superficial spreading was observed.

Reference:

Green, A. and O'Rourke, M.G.E. "Cutaneous malignant melanoma in association with other skin cancers." JNCI 74(5):977-980 (1985).

Investigator Results:

1. In a case-control study of 232 MM cases and 232 matched controls, a fourfold increase in risk was associated with presence of facial actinic tumors. The risk persisted for melanoma groups: LMM, SSM, and NM.

2. Cases with heavy lifetime sun exposure had higher relative risks than comparable controls, even after adjusting for age, nevi, hair color, and propensity to sunburn.

Methodology:

A case-control study of 232 MM cases (14-86 years old) who had primary melanoma reported between 1 July 1979 - 30 June 1980 in Queensland (randomly selected and stratified by geographic location from 871 eligible cases). Controls randomly selected from the Electoral Roll were matched by age, sex, and area of residence. Interviewer questionnaire (by one of the authors) obtained information on history of lifetime sun exposure (all outdoor occupations of 6+ months and all regular outdoor recreations since 10 years old), complexion (e.g., hair color), sun sensitivity (e.g., propensity to burn), social class based on occupation, country of birth of patient and 2 previous generations, actinic tumors on face and left forearm, and nevi (2 or more mm in diameter). Tumors were classified as superficial spreading (60.8%, SSM), nodular (15.5%, NM), lentigo maligna (21.1%, LMM), and indeterminate (2.6%, IND).

Experimental Design and Analysis Issues:

A case-control study of 232 melanoma patients and 232 age-, sex-, and residence-matched controls in Queensland.

For Result 1:

A significantly greater percentage of facial actinic tumors occurred among cases (41%) than controls (15%, p less than 0.0001), with a crude relative risk (RR) of 4.4. The relative risk when adjusted by age and nevi was 3.6. When other possible risk factors (e.g., social class, ethnic origin) were taken into account, the risks were relatively unchanged. This case-control difference was also observed among LLM, and combined SSM, NM and IND group (p less than 0.001). Results for forearm tumors were similar. The data showed no strong trend of increasing risk with increasing number of facial tumors. Presence of nevi on arms was associated with a 30-fold increase in melanoma risk.

For Result 2:

More cases than controls were in high sun exposure categories (accumulated hours of sun during work and recreation). The crude relative risk (RR) was 2.3 for 50,000+ hours of lifetime exposure compared to less than 2,000 hours exposure. Risks were higher after adjustment for age, nevi, hair color, and sunburn propensity. The adjusted RR was 3.2 for 2,000-50,000 hours exposure and 5.3 for 50,000+ hours exposure.

HOLMAN AND COLLEAGUES -- WESTERN AUSTRALIA MELANOMA STUDY

Holman and his colleagues have presented several studies on cutaneous malignant melanoma incidence and mortality in Australia. In this section, nine of these studies are reviewed.

Of particular importance among these studies are five case-control comparisons based on 1980-1981 data from western Australia. The cases consisted of 511 melanoma patients under 80 years of age (233M, 278F) with histologically diagnosed pre-invasive and invasive melanoma, possible melanoma, and Spitz nevus occurring in western Australia for the first time from 1 January 1980 - 5 November 1981. The cases were identified from histopathology reports issued by public and private medical laboratories. Of the 820 preinvasive and invasive melanomas ascertained, 766 were histologically reviewed by six pathologists for confirmation or rejection of diagnosis, histogenic type (McGovern classification), level of invasion, and tumor thickness. After review and including acceptance of the original diagnosis in 39 primary cases unavailable for review, acceptance of 4 of 9 possible melanoma cases and 1 of 14 Spitz nevi cases, the study series consisted of 815 melanomas arising in 798 patients. Of the 798 patients, 670 were eligible for interview (interviews were not attempted in some rural and remote areas), and permission to interview was granted for 582 cases (87%). The number of individuals approached for interview was 565 (15 were untraceable or had migrated and 2 were in distant rural areas) from which 511 (90%) actually responded. The cases ranged from 10-79 years of age.

Sections from the tumors (except for 14 patients) were classified by a panel of six pathologists into the following histological types: Hutchinson's melanotic freckle (HMFM), superficial spreading melanoma (SSM), unclassifiable melanoma (UCM), or nodular melanoma (NM). Clinical details were obtained from the general practitioner and surgeons who attended the patients.

Of 824 potential controls randomly identified for the study, 511 were selected from the Australian Commonwealth Electoral Roll, and for 10 cases under 18 years, the student rolls of a public school in the case's area of residence. Controls were matched by age ($\pm$5 years), sex, and area of residence. The number of controls actually approached was 740 from which 511 (69%) were interviewed. A selection bias may have been introduced because only 69% of controls approached were interviewed in contrast to 90% of approached cases. The methods used to contact potential participants and to obtain their cooperation were identical for cases and controls.

Subjects were interviewed in their homes (occasionally at their workplace) by trained nurse interviewers. To the extent possible, interviewers were blinded with respect to who were cases and who controls. A highly structured questionnaire was administered. Information collected on each subject by interview consisted of skin, hair, and eye color, number of palpable nevi on the arms, history of sun exposure, harmone use, diet, measurements of weight, height, hairiness, and extent of actinic damage in skin (based on cutaneous

microtopographs), acute and chronic skin reactions to sunlight, ethnicity of grandparents, family history of melanoma or xeroderma pigmentosum, history of mole excisions, and treatment of nonskin cancers. Skin color was measured at the dorsum of the left hand (continuous sun exposure), tip of left shoulder (intermittently exposed), and left upper inner arm (not usually exposed) and was graded according to ranges of reflectance values (%). A voluntary venous blood sample was collected for retinol and cholesterol assays.

In 1983, following a report that melanoma was associated with exposure to fluorescent lighting at work, 337 of the cases and 349 controls were reinterviewed regarding fluorescent light exposure.

The matched case-control data were analyzed according to methods described by Breslow and Day. Empirical odds ratios (ORs) were calculated by conditional maximum likelihood estimation. The significance of trends in the ORs were assessed by the chi-square formula for matched data. Conditional logistic regression was used to analyze two or more risk factors. Four controls reporting history of mole excision and their corresponding cases were excluded from all analyses except that for the history of melanoma.

Reference:

Holman, C.D.J., Mulroney, C.D. and Armstrong, B.K. "Epidemiology of pre-invasive and invasive malignant melanoma in Western Australia." Br. J. Cancer 25:317-323 (1980).

Investigator Results:

1. Annual incidence rates of melanoma in western Australian in 1975-1976 were $4.4/10^5$ (males) and $6.2/10^5$ (females) for pre-invasive lesions and $18.6/10^5$ and $18.8/10^5$ for invasive lesions.

2. Incidence patterns with age indicated a progressive increase beginning about age 40 for HMF and head and neck invasive melanoma, and an early rise at about age 20 with mid-life peak and subsequent stabilization or decline for superficial spreading, non-invasive and invasive lower limb and less frequently trunk and upper limb melanomas.

3. Incidence rates were highest in native-born Australians, followed by British immigrants. Rates among British immigrants were over 2 times higher than rates in the U.K.

4. Incidence was highest in high social class residential areas, and higher in indoor (vs. outdoor) workers.

5. Incidence was highest in the capital city (Perth) and southwest corner of State (vs. north part).

6. Patterns for invasive and pre-invasive lesions were similar.

7. Aspects of the data were inconsistent with the solar hypothesis, but some inconsistencies might be explained if intermittent, intense sun exposure were more relevant to melanoma than continuous exposure.

Methodology:

A descriptive analysis of pre-invasive (PIM) and invasive malignant (IMM) melanoma in western Australia determined retrospectively for 1975-1976 from discharge records for all western Australia hospitals in 1975-1976, and histopathology reports in 1975-1976 from all pathology labs in the State. Each case (120 PIM, 422 IMM) had to be a usual resident of western Australia, have histological verification of diagnosis, have first biopsy between January 1975-December 1976, and have skin as primary lesion site. Information sought on each case included sex, birth date, country of birth, occupation, usual residence, diagnosis date, anatomical site and description of histopathology (categorized only as PIM or IMM, and for PIM, HMF and "other including superficial and spreading, non-invasive (SSM), or in situ melanomas). Age- and sex-specific incidence rates were calculated based on Australian Bureau of Statistics 1976 population estimates.

Experimental Design and Analysis Issues:

A descriptive analysis of 542 PIM and IMM patients in western Australia from 1975-1976.

For Result 1:

No additional information.

For Result 2:

For both PIM and IMM, incidence rates increased progressively with age in males but less regularly in females, with initial peak at 40-49 and, after further rise, apparent decline after 80+ years. The differences between sexes in age-incidence curves were explained by pathologic lesion characteristics. Among PIM, equal number of HMF in men and women $1.3/10^5$) but over 50% more SSM in women than men (incidences $3.1/10^5$ and $4.9/10^5$, respectively). HMF incidence increased progressively with age except for early peak at 60-69, whereas SSM reached peak at 50-59 years and declined thereafter (both sexes similar).

For IMM and SSM, a male trunk and female lower limb predominance was observed. For HMF, 79% occurred on head and neck in both sexes. Head and neck lesions showed progressive incidence rise from about age 40, whereas lower limb lesions (and to lesser extent trunk and upper limb lesions) showed increased from age 20-29 (females) and 30-39 (males), peak at 50-59, and decline thereafter. These different patterns produce irregular IMM pattern as a whole.

No incidence changes were seen in women (or men) 40-49 and 50-59. The pronounced irregularity of PIM at all sites in women between 40-60 was due to high proportion of limb lesions. The female age incidence pattern does not support hypothesis that hormones may be involved in melanoma etiology.

For Result 3:

Incidence rates among PIM and IMM were over 2 times greater among native-born Australians ($5.6/10^5$ males, $6.7/10^5$ females for PIM; $26.1/10^5$ males, $23.7/10^5$ females for IMM) than among immigrants. Rates of IMM in British born ($10/10^5$ males, $13/10^5$ females) were about 2 times greater than all other immigrants combined, and 2-5 times higher than British rates from 1968-1972 ($2\text{-}5/10^5$ age-standardized). Differences in rates were unchanged after adjustment by social class and age.

For Result 4:

An analysis by social class (based on a socio-economic index referencing occupation and education divided into 4 "classes") indicated highest IMM incidence in highest social class with progressive incidence decline in women with decreasing social class. For PIM the pattern was less clear. After controlling by country of birth, proximity to sea, and age, no appreciable changes were observed.

IMM incidence rates were highest among professional workers ($39/10^5$), clerical and sales workers, and administrators and managers, and lowest among farmers and fishermen ($18.5/10^5$), laborers and tradesmen, and transport and communication workers.

For Result 5:

Highes PIM and IMM incidence rates were in Perth or Southwest region (e.g., $5.6/10^5$ PIM and $2.55/10^5$ IMM in males) whereas rates in Central, Pilbara, and Kimberley regions were lower (e.g., $1.9/10^5$ PIM and $18.0/10^5$ IMM in males) in spite of their northerly latitude and higher sun exposure.

For Result 6:

Similarities between PIM and IMM included more common occurrence among females, similar age-incidence curves, similar curve irregularities due to two patterns of incidence change with age (progressive increase beginning in mid-life for HMF and head and neck IMM and rapid increase in early adult life with peak at about 50 and decline thereafter for SSM and lower limb IMM), more common occurrence in native-born Australians, in higher social classes, and in Perth and Southwest of State.

Reference:

Holman, C.D.J., James, I.R., Gattey, P.H., and Armstrong, B.K. "An analysis of trends in mortality from malignant melanoma of the skin in Australia." Int. J. Cancer 26:703-709 (1980).

Investigator Results:

1. Age-standardized Australian MM mortality rates more than quadrupled from $0.8/10^5$ (males) and $0.6/10^5$ (females) in 1931-1934 to $4.2/10^5$ (males) and $2.5/10^5$ (females) in 1975-1977. Approximately parallel increases were found for each of the six Australian states.

2. MM mortality rates decreased from north to south.

3. Increasing mortality rates could be explained by increases in successive birth cohorts, beginning in 1865, and stabilizing around 1925 (females) and 1935 (males). The authors suggested that cohort increases resulted from lifestyle changes in successive generations. They predicted that the trend towards increasing total MM mortality would stabilize over the next 40 years.

Methodology:

A descriptive analysis of MM mortality data for 1931-1977 (in 5-year age groups) obtained from the Australian Bureau of Statistics (subdivided by the 6 Australian States after 1950). Annual mortality rates for each 5-year age group and for 5-year time periods were based on Australian Bureau of Statistic's population estimates. The data were analyzed to separate birth cohort, age, and calendar year of death effects in an additive three-factor model which estimated expected mortality rates.

Experimental Design and Analysis Issues:

A descriptive analysis of MM mortality data and the fit to a birth cohort, age, and calendar year of death dependent additive model.

For Result 1:

Crude and age-standardized MM mortality rates from 1931-1934 to 1975-1977 more than quadrupled in both sexes, although the increase was greater in males (429%) than females (302%).

For Result 2:

Highest mortality rates were in Queensland (latitude 11°-29°S), intermediate rates in Western Australia (14°-35°S), New South Wales (28°-37S), and South Australia (26°-38°S), and lowest rates in Victoria (34°-39°S) and Tasmania (40°-43°S).

For Result 3:

The pattern of mortality rate changes from 1931-1934 to 1975-1977 was more consistent with cohort-based rather than cross-sectional based mortality increases due to a slowing mortality rate increase among 1920-1935 cohorts. The cohort pattern was also evident for each Australian State (except Tasmania and Queensland).

Age, cohort, and time factors from the mortality data fit the three-factor model well. The age factor rose quickly among 10-14 to 30-34 year-olds, and less steeply thereafter. The cohort factor showed increasing trends from 1865-1935 (males) and 1865-1925 (females). Non-linear fluctuations in the time factor were small in comparison to those in age and cohort factors.

When only age and cohort factors were considered in a two-factor model, the fit was poorer than for the three-factor model. However, the age and cohort values were similar for both models.

Reference:

Holman, C.D.J and Armstrong, B.K. RE: "Skin melanoma and seasonal patterns." Am. J. Epi. 113:202 (1981).

Investigator Results:

A seasonal pattern of melanoma incidence with summertime peak was observed for 541 cases in western Australia from 1975-1976. Largest number of diagnosed cases was in early summer, November (females), and December (males), and cyclic trends were significant in males ($p=0.04$) and females ($p=0.02$).

Methodology:

A short letter to the editor summarizing seasonal trends in incident melanoma cases among 541 patients in western Australia from 1975-1976. Cyclic trends were tested by Edward's test.

Reference:

Holman, C.D.J. and Armstrong, B.K. "Hutchinson's melanotic freckle melanoma associated with non-permanent hair dyes." Aust. J. Cancer, 48:599-601 (1983).

Investigator Results:

1. There was no evidence of a relationship between melanoma of the head and neck nor any histologic type and ever use of permanent hair dyes.

2. HMFM was associated with use of nonpermanent dyes with an odds ratio (OR) of 3.4 (95% C.I. 1.1-10.2) for subjects exposed on 10 or more occasions. There was a linear dose-response relationship for HMFM with increasing frequency of use of nonpermanent dyes ($p=0.02$ for trend).

3. The results suggested that nonpermanent hair dyes increase the risk of HMFM. The authors commented that "It was postulated that HMFM results from an accumulation of damage induced by UV radiation in the genome of melanocytes, whereas SMM may develop from initiated cells in pigmented naevi which undergo promotion by intermittent sun exposure and other agents. The results of this study if confirmed by further research would suggest that initiating carcinogens other than ultraviolet radiation, such as one or more of the aromatic compounds present in nonpermanent hair dyes, may also contribute to the causation of HMFM." This study's results, however, require further confirmation in other studies.

Methodology:

A case-control study of 511 melanoma patients and 511 age-, sex-, and residence-matched controls in western Australia (see introduction to this section). Information obtained from cases and controls regarding past exposure to permanent and nonpermanent (i.e., temporary and semipermanent) hair dyes was analyzed in this study. Four case-control pairs were excluded from analysis because of a past history of melanoma in the controls.

Experimental Design and Analysis Issues:

For Result 1:

Permanent hair dyes had been used by 22% of the cases and 21% of controls. Except for an OR of 3.5 (95% C.I. 0.7-24.3) for nodular melanoma (NM) based on 9 discordant case-control pairs, there was no evidence of a relationship between any histologic subtype nor melanoma of the head and neck with ever-use of permanent hair dyes.

For Result 2:

Semipermanent or temporary hair dyes had been used by 34% of cases and 33% of controls. For HMFM, in addition to an OR of 3.4 associated with 10 or more uses of nonpermanent dyes, there was a linear dose-response relationship with ORs of 1.5 and 3.4 for 1-9 uses and 10 or more uses, respectively, of nonpermanent hair dyes ($p=0.02$ for trend). There was no evidence of an association between head and neck melanoma other than HMFM and use of nonpermanent hair dyes. The ORs for 10 or more uses of nonpermanent hair dyes for HMFM of the head and neck and HMFM elsewhere on the body were 3.1 (95% C.I. 0.9-10.7) and 4.8 (95% C.I. 0.4-52.2), respectively.

Reference:

Holman, C.D.J., Evans, P.R., Lumsden, G.J. and Armstrong, B.K. "The determinants of actinic skin damage: Problems of confounding among environmental and constitutional variables." Amer. J. Epi. 120:414-422 (1984).

Investigator Results:

1. Of the total 1,216 individuals studied, 46 percent were male, 53 percent were older than 50 years, 24 percent had fair or red hair, and 39 percent were blue eyed. Of those with actinic skin damage, 59 percent were male, 80 percent were older than 50, 64 percent had fair or red hair, and 61 percent had blue eyes.

2. Individuals aged 50 or more had 3.44 times as much actinic skin damage as those under 50 (95% C.I. 3.05-3.89). Males had 1.21 times the damage of females (95% C.I. 1.09-1.34). Individuals with fair or red hair had 1.27 times the damage of those with black or brown hair (95% C.I. 1.13-1.43) and blue eyes had 1.23 times the damage of other eye colors (95% C.I. 1.11-1.37). Other factors that were statistically significant and their prevalence ratios were longest held outdoor occupation (1.28), outdoor leisure activity once or more per week (0.85), swimming as a preferred activity (0.52), boating as a preferred activity (0.69 -- borderline significance based on only 24 yes answers), maintenance of a suntan (0.67), and use of sunscreens sometimes versus never (0.73). Studied but not statistically significant were number of Celtic grandparents, skin reaction to sunlight, and skin color of forearm.

3. When all of the above-mentioned factors were combined in a multiple logistic regression, male sex, age, the square of age, burn reaction to sunlight, and outdoor occupation were the only statistically significant factors.

4. The authors concluded that "... more attention should be paid to the various possibilities for confounding .... detailed information on potential confounders should be sought and appropriate analyses performed."

Methodology:

A cross sectional survey of 1,216 persons (560 M, 656 F aged 16 to 86) attending a triennial health survey from 23 November to 3 December 1981 in Busselton (200 km south of Perth) in western Australia. The subjects representing 35 percent of those attending the survey, were chosen randomly and represented 17 percent of the residents of Busselton. The health survey was based on information obtained by a questionnaire and on semi-objective measures by the investigators.

Comment:

This is a useful survey of the interaction of many of the key variables in this area of research. There was, however, no discussion of the selection process involved in comparing those who volunteered for the survey compared to those other citizens of Busselton who did not.

Reference:

Holman, C.D.J., Armstrong, B.K., and Heenan, P.J. "Cutaneous malignant melanoma in women: Exogenous sex hormones and reproductive factors." Br. J. Cancer 50:673-680 (1984).

Investigator Results:

1. In a western Australia case-control study on women, there was no consistent evidence of a relationship between incidence rates of different melanoma histogenic types and age at menarche, duration of menstrual life, degree of obesity, number of pregnancies of more than 20 weeks duration, or use of oral contraceptives (OC).

2. No consistent trend was observed when OC was examined by age periods (10-19, 20-29, and 30+ years) and time intervals before diagnosis (10+, 5-9, less than 5 years).

3. Borderline evidence was shown of an association between superficial spreading melanoma and duration of estrogen use.

4. On the basis of seven studies on the relationship of OC use and melanoma, the authors estimated that the total melanoma incidence rate of an OC ever-user was unlikely to be increased by over one-third the rate in never-users. Only one of the seven studies produced a statistically significant relation and the combined estimate from the studies was 1.12 (95% C.I. 0.94-1.33).

5. The authors noted that data from Australia may not generalize to populations with a low incidence of melanoma. "With this proviso, the results of this study give no support for a role of endogenous sex hormones or related phenomena in the aetiology of melanoma in women."

Methodology:

A case-control analysis (see introduction to this section) of 276 female melanoma patients under 80 years old (out of 373 total) identified in the West Australia Lions Melanoma Research Project from 1980 to 1981. The mean age was 44.9 years (range 10-79 years). All but 7 tumors were histologically classified by six pathologists into one of four categories; HMFM, SSM, UCM, or NM. Sixty-two percent of the lesions were classified as SSM. 276 Age- and electoral subdivision-matched controls were selected from the Australian Commonwealth Electoral Roll and a few from a public school student roll. Information on cases and controls, obtained by interviewer questionnaire, included constitutional and hereditary factors, sun exposure, diet, exposures to known or suspected carcinogens, menstrual and obstetric histories, weight and height, and history of OC use or other estrogenic preparations. Conditional maximum likelihood estimation was used to calculate odds ratios (ORs).

Experimental Design and Analysis Issues:

An analysis of 278 female melanoma cases and age- and residence-matched controls.

For Result 3:

When only SSM cases and controls were analyzed by OC use, while controlling for skin reaction to sunlight, hair color, number of raised nevi on arms, age at arrival of migrants, level of residential sun exposure, weekend recreational sun exposure (from 10-24 years old), and frequency of summer outdoor activities, odds ratios were 0.78 in under 2-year OC users, 2.24 for 2-4 year users, and 1.62 for 5+ year users.

There was borderline evidence of an association between SSM and total duration of estrogen use (OR=2.26 for 13+ months use, p=0.082). When controlling for the same potentially confounding factors (above), the ORs were 2.51 in under 12-month users and 2.15 in 12+ month users.

Reference:

Holman, C.D.J. and Armstrong, B.K. "Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma." JNCI 72:257-266 (1984).

Investigator Results:

1. In a case-control study of 511 patients and 511 age-, sex-, and residence-matched controls in western Australia, the strongest risk factor was the number of palpable benign nevi on a subject's arms. The crude relative risks (RRs) of melanoma compared to persons having no nevi were 2.0 for 1-4 nevi, 4.0 for 5-9 nevi, and 11.3 for 10 or more nevi ($p=<0.0001$). The authors noted the probable importance of nevi either as an early stage in the pathogenesis of non-HMFM or as indicators of increased risk.

2. Inability to tan was the most important pigmentary trait associated with risk of melanoma. Susceptibility to sunburn and hair color were also significantly associated with risk of melanoma independent of tanning ability. After controlling for these traits, skin color and eye color had no additional effects. The authors concluded that the results suggested "that the ability to tan quickly in response to sunlight is of prime importance in reducing risk of skin cancers and is more important than the base-line skin color... That acute reaction to sunlight and hair color had significant effects" after taking chronic reaction into account "does not necessarily mean that they operate through different mechanisms."

3. Persons with two or more Southern European grandparents had a reduced risk of melanoma (odds ratio (OR) = 0.39, $p=0.025$). Persons of Celtic origin did not have a significantly increased risk of melanoma (OR=1.18).

4. Persons with one or more affected blood relatives were at higher risk (OR=2.69, $p=<0.0001$).

5. The effects of pigmentary traits, benign nevi, ethnic origin, and family history as risk factors were largely independent of one another based on a stepwise logistic regression.

Methodology:

A case-control study of 511 melanoma patients and 511 age-, sex-, and residence-matched controls in western Australia (see introduction to this section).

Experimental Design and Analysis Issues:

A case-control study of 511 cases diagnosed from 1980-1981 and 511 age-, sex-, and residence-matched controls in western Australia.

For Result 1:

Both the number of nevi on the arms and history of mole excision were strong risk factors for melanoma . The OR for two or more excised benign nevi was 5.09 (95% C.I. 0.26-11.46) and was 2.35 (95% C.I. 1.29-4.32) for one or more excised benign moles for the 267 SSM case-control pairs only. The association with nevi (one or more raised) was strongest from SSM (OR=3.00, 95% C.I. 1.98-4.57) and weakest for HMFM (OR=1.54, 95% C.I. 0.73-3.27).

For Result 2:

No consistent relationship was seen between risk of melanoma and skin color of the dorsum of the hand or of the shoulder tip although there was a tendency toward an increased risk in the fairest skin color group: for dorsum lightest skin group (reflectance >52%) OR=1.81 (95% C.I. 1.04-3.14) and for shoulder lightest skin group (reflectance >56%) OR=1.46 (95% C.I. 0.88-2.40). A stronger, significant association was observed for skin color of upper inner arm with a threefold greater risk for the fairest skin group (reflectance >65%, OR=3.07, 95% C.I. 1.47-6.39) compared to the darkest skin group (reflectance <47%). Persons with red hair were at higher risk (OR=2.33, 95% C.I. 1.26-4.30) as were those with blue eyes (OR=1.61, 95% C.I. 1.16-2.24).

Melanoma risk was strongly and significantly associated with acute and chronic skin reactions to sunlight with the highest risks among those whose acute reaction was to blister (OR=3.39, 95% C.I. 1.90-6.03) and whose chronic reaction was to freckle rather than tan (OR=3.53, 95% C.I. 1.82-6.84). In a stepwise logistic regression, chronic reaction to sunlight was the most important risk factor (OR for no tan = 2.44, p=0.000002 for contribution of step), followed by acute reaction to sunlight (OR for blistering = 2.08, p=0.008) and then hair color (OR for red hair = 1.89, p=0.039). After taking these three factors into account, skin color of upper inner arm and eye color were associated with much lower ORs compared to the crude ORs presented previously. The effects of skin color were apparently explained almost entirely by acute and chronic reaction to sunlight. An increasing severity of burn as an acute reaction was not associated with an increased risk.

Risks of all histogenic types increased with decreasing ability to tan (a chronic reaction). The association was much stronger for HMFM (OR for no tanning ability = 10.01, 95% C.I. 0.97-103.1, p=0.0002 for linear trend) than for SSM, UCM, or NM. Each histogenic type was also associated with acute reaction to sunlight, and hair, skin (upper inner arm), and eye color, except that HMFM and UCM were not associated with eye color.

For Result 3:

Possession of two or more Southern European grandparents was significantly associated with reduced risk in a logistic regression designed to separate the independent effects of having two or more grandparents from various ethnic groups and to control for confounding by age at arrival in Australia (OR=0.39, 95% C.I. 0.17-0.89, $p<0.05$). Low risks were also seen for African or Asian and Northern European grandparents. The strength of the protective effect of Southern European grandparents was reduced when confounding by pigmentary traits was controlled.

For Result 4:

A history of melanoma in a blood relative was a significant risk factor (OR for two or more affected relatives=5.00, 95% C.I. 1.45-17.27), especially for HMFM (OR for one or more=5.50, 95% C.I. 1.44-20.97.)

Reference:

Holman, C.D.J. and Armstrong, B.K. "Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: An analysis separating histogenic types." JNCI 73:75-82 (1984).

Investigator Results:

1. In a case-control study of 511 melanoma patients diagnosed from 1980-1981 and 511 age-, sex-, and residence-matched controls in western Australia, duration of residence in Australia of migrants was positively associated with melanoma risk.

2. Mean annual hours of bright sunlight averaged over a lifetime was positively associated with risk of melanoma .

3. Risk of melanoma increased with worsening skin condition (e.g., actinic damage).

4. Persons with a history of nonmelanotic skin cancer were at higher risk of developing melanoma.

5. The authors concluded that the hypothesis that melanoma is related to sun exposure was supported by the observed associations with actinic skin damage, history of nonmelanotic skin cancer, duration of residence in Australia of migrants, and mean annual hours of sunshine at subject's area of residence.

6. The findings regarding HMFM in this and the previous Holman and Armstrong (1984) study "are all consistent with the assertion that the causal relationship of sunlight with HMFM is more direct than with the other histogenic types.... HMFM ... may be related to the total accumulated dose of sunlight received on exposed body sites." The authors suggested that the results generally supported the hypothesis that "an individual's maximum potential to develop SSM would be fixed by the number of initiated nevus cells induced by UV radiation and other agents in childhood and young adulthood ... Evidence associating UCM with sun exposure was much weaker than for other histogenic types... A role of sunlight in the causation of NM is supported by these results." The risk factors for NM were a mixture of those associated with HMFM and SSM which was consistent with the authors suggestion that "NM represents a common end stage of the other histogenic types."

Methodology:

A case-control study of 511 melanoma patients and 511 age-, sex-, and residence-matched controls in western Australia (see introduction to this section).

Experimental Design and Analysis Issues:

For Result 1:

For migrants moving to Australia (23% of all subjects), duration of residence was based on year of arrival. For native-born Australians, duration was taken as age at interview. The odds ratios (ORs) for all melanomas and each histogenic type increased with increasing duration of residence. This trend was strongest for HMFM (OR for 60 or more years resident = 6.35, 95% C.I. 1.11-36.45) and NM (OR for 60 or more years residence = 14.72, 95% C.I. 1.16-186.16).

For all melanomas combined, age at arrival was a better predictor of melanoma risk (OR for arrival at 30 years or later = 0.30, 95% C.I. 0.08-1.13) than was duration of residence. The same result was observed when SSM and UCM) were analyzed separately. It was impossible to separate the effects of age at arrival and duration of residence for HMFM and NM. For SSM subjects, the incidence of SMM among migrants arriving before 9 years was near to or greater than that among persons born in Australia (OR for SSM arriving at 5-9 years = 1.65, 95% C.I. 0.34-7.97), whereas for migrants arriving after 10-15 years of age, the risks were lower than for native born Australians (ORs <0.38 for ages 15-19, 20-24, 25-29, >30). The authors suggested that "it is possible that exposure to sunlight in childhood is a factor in the production of benign nevi, which have their strongest relationship with SSM, probably as precursor lesions." They cited results showing a trend toward higher proportions of nevi in those arriving in Australia before 10 years of age compared with those arriving later in age (p=0.009).

For Result 2:

Among native-born Australians, ORs significantly increased with increasing mean annual hours of bright sunlight for all melanomas combined (p=0.003) and SSM (p=0.02). The OR gradient was steepest for HMFM. An analysis of the effects of more than 2,800 hours of sunlight exposure annually at different ages showed elevated ORs in all age periods for HMFM (ORs = 1.33 and 3.55 for exposure at >40 years and 0-9 years, respectively). High exposure at ages 10-24 years was a strong risk factor for SSM (OR=11.31, 95% C.I. 1.40-91.11). Exposure at 25-39 years was also associated with an increased risk of SSM whereas exposure at 0-9 years and >40 years had no effect. An elevated risk was also observed for those with SSM who had high sun exposure 10-19 years prior to diagnosis.

For Result 3:

The ORs increased progressively with worsening skin condition (graded by CMT) for all melanomas combined ($p=0.003$), HMFM ($p=0.048$), and SSM ($p=0.021$). HMFM had the strongest association with CMT (ORs for grades 5 and 6 were 4.05 and 4.37, respectively). No case had a CMT graded less than 4.

For Result 4:

Persons treated for at least one nonmelanotic skin cancer had more than a threefold increase in melanoma incidence. The OR for all melanomas combined was 3.71 ($p=0.000001$). For HMFM and SSM, the ORs were 5.25 ($p=0.001$) and 3.33 ($p=0.011$), respectively, After controlling for the effects of chronic and acute skin reactions to sunlight, hair color, and number of European, African, and Asian grandparents, the OR for all melanomas combined dropped to 2.87 ($p=0.0002$) suggesting that the association with nonmelanotic skin cancer was explained only partly by constitutional factors.

Reference:

Holman, C.D.J., Armstrong, B.K., and Heenan, P.J. "Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits." JNCI 76:403-414 (1986).

Investigator Results:

1. An increased incidence rate of SSM was associated with low total outdoor exposure in early adulthood and frequent participation in boating and fishing. SSM of the trunk was related to frequency of sunbathing at 15-24 years of age and to exposure of the trunk while working outdoors.

2. In females, the rate ratio for all types of melanoma occurring on the trunk was 12.97 (95% C.I. 2.0-83.9) in those who wore a bikini or bathed nude at 15-24 years of age compared to those who wore a more conservative one-piece bathing suit. There was little evidence that sunbathing or wearing a bikini within 10 years of case diagnosis were risk factors for melanoma of the trunk.

3. After control of confounding due to constitutional factors, only HMFM showed a relationship to severe sunburn. For NM, sunburn appeared to be protective.

4. Although many of the results supported the hypothesis that melanomas other than HMFM are related to occasional bursts of recreational sun exposure during early adult life, little support for the hypothesis was obtained when recreational sun exposure was expressed as a proportion of total outdoor exposure (a proportion which had been considered a priori to be an index of intermittent sunlight exposure). The authors noted, however, that "some but not all of our results" supported the hypothesis that intermittent exposure to sunlight plays an important role in etiology of SSM.

5. The authors concluded that their results suggested that "nevi and occasional or recreational sun exposure interact to produce an effect on rate of SSM greater than the addition of the two independent effects, but ... less than expected [based on] multiplication of effects."

Methodology:

A case-control study of 507 melanoma patients and 507 age-, sex-, and residence-matched controls in western Australia (see introduction to this section). Thirteen case-control pairs were excluded from the analysis of recreational and occupational outdoor exposure because they were rated by the interviewers as providing poor information.

Experimental Design and Analysis Issues:

For Result 1:

With the exception of HMFM, all histologic types of melanoma were inversely associated with mean total outdoor exposure (i.e., occupational and recreational) in summer (after controlling for constitutional factors). The strongest inverse association was for SSM with odds ratios (ORs) of 0.82, 0.72, and 0.57 for mean total outdoor exposures of 11-15, 16-22, and >23 hours/week, respectively (p=0.092 for trend). In an analysis of the relationships of histologic types to high levels of total outdoor exposure (>23 hours/week) at different ages, the inverse associations were strongest at 10-24 years of age for SSM (OR=0.45, 95% C.I. 0.21-0.98) and for NM (OR=0.08, 95% C.I. 0.01-1.33).

SSM was associated with frequent participation (once or more per week) in boating and fishing (OR for boating = 2.43, 95% C.I. 1.10-5.39; OR for fishing = 2.72, 95% C.I. 1.15-6.43). There was little evidence of a relationship between SSM and either swimming or sunbathing (either at 15-24 years of age or 0-9 years prediagnosis). The evidence was stronger when SSM on the trunk was considered separately. For sunbathing at 15-24 years of age, ORs (with never sunbathing as reference) were 1.20 (95% C.I. 0.51-2.81) and 2.55 (95% C.I. 1.05-6.19) for sunbathing less than once per week and once or more per week, respectively (p=0.044 for trend). For sunbathing within 10 years of diagnosis, the equivalent ORs were 1.50 (95% C.I. 0.53-4.20) and 1.56 (95% C.I. 0.62-3.93) (p=0.354 for trend). For other histogenic types, the results did not indicate an association with water sports and sunbathing except that regular swimmers had a reduced rate of HMFM (ORs = 0.98 and 0.26 for participation less than once per week and once or more per week, respectively; p=0.005 for trend).

In an analysis of habits of dress regarding the primary site of the case and the same site on the control during outdoor work in summer, the ORs (except for SSM) were higher in persons if the body site was sometimes exposed rather than usually exposed or usually covered. For SSM there was a linear trend of increasing risk from usually covered to sometimes exposed to usually exposed. The ORs for SSM of the trunk were 2.93 and 5.96 for sometimes exposed and usually exposed, respectively (p=0.032 for trend).

For Result 2:

The type of bathing suit worn by females while at the beach in summer was a strong risk factor for melanoma. In females who wore a bikini or bathed nude at 15-24 years of age (compared to those who wore a one-piece bathing suit with high back) the OR was 12.97 (95% C.I. 1.95-83.94). Similar results were seen for those who wore a bikini 0-9 years prediagnosis (OR=8.94, 95% C.I. 1.45-55.07). An additional analysis suggested that exposure at 15-24 years was more relevant than exposure 0-9 years prediagnosis. No relationships were observed between type of bathing suit and melanomas occurring at sites other than the trunk. The association between SSM of the trunk and exposure 0-9 years prediagnosis or at 15-24 years of age was weaker than for the other histologic types combined.

For Result 3:

In an analysis of the relationship of histologic types to the highest severity of past sunburn (no sunburn > peeling sunburn > painful sunburn > blistering sunburn), HMFM was related to the occurrence of severe sunburn even when confounding effects (eg., hair color, skin reaction to sunlight, ethnic origin, age at arrival in Australia) were taken into account. The ORs for HMFM were 0.64, 2.45, and 2.78 for peeling sunburn, painful sunburn, and blistering sunburn, respectively ($p=0.059$ for trend). For NM there was a protective effect of severe sunburn and for SSM and UCM there was no association.

After controlling for confounders, no relationship was observed between childhood sunburn or sunburn in early adulthood and any histologic type of melanoma. After controlling for confounders, reported use of sunscreen appeared to provide no protection against any histologic type of melanoma.

For Result 4:

In an analysis of intermittent recreational exposure, exposure was expressed as a percentage of total outdoor time in summer and the variable was called ROEP. For example, ROEP would equal 29% for 2 days recreational exposure and 5 days occupational outdoor exposure per week (2 out of 7 days). ROEPs of 30-100% are indicative of increasing concentration of outdoor time during leisure days. The effects of ROEP were examined for each histologic type, for four age groups (never, 10-24, 25-39, and >40 years), and for four intervals before diagnosis (0-4, 5-9, 10-19, and >20 year prediagnosis). The results provided little evidence of an association between melanoma and ROEP. Reanalysis using two different measurement approaches for recreational exposure to sun also provided no stronger evidence of an association.

ELWOOD AND COLLEAGUES -- WESTERN CANADA MELANOMA STUDY

This major case-control study of melanoma was conducted in western Canada consisting of the provinces of British Columbia, Alberta, Saskatchewan, and Manitoba.

Cases of newly diagnosed, histologically confirmed primary cutaneous malignant melanomas were obtained through the cancer registries of each province during the two year period from 1 April 1979 to 31 March 1981. There were 801 patients who were age eligible (20-29 years) out of the 904 diagnosed. Forty patients could not be located, 21 were dead, for 21 the physician felt that an interview would not be in the patients' best interests, and 54 persons declined participation in the study. The remaining 665 (83 percent) were interviewed along with matched controls.

Each patient was matched by gender and age within two years with a control subject selected at random from medical insurance plan lists of subscribers, which cover virtually the entire adult population of each province.

Fourteen cases had acral lentiginous melanoma and 56 had lentigo maligna so most analyses refer to the 595 cases with other diagnoses, i.e., 415 SSM, 128 NM, 23 UCM, and 29 borderline melanomas. Of the 595 cases, 361 were females and 234 males.

A standardized abstract of the medical record was made for each patient including data on symptoms, treatment, and recurrences. Pathological slides were reviewed in a standardized manner by one of two pathologists; for 20 percent of the patients, slides were unavailable resulting in use of the original pathology report.

Patients and controls were interviewed (1.5 to 2.0 hours) in their homes by trained interviewers using a standardized questionnaire. Information was obtained on pigmentation, skin freckling in childhood, sensitivity to sunlight, tanning, and sunbathing both as an adult and as a child, residence, occupational history, recreational activities with specific reference to sunlight exposure, medical history, chronic drug use, family history, diet, smoking and alcohol consumption, and for women reproductive history and use of oral contraceptives and menopausal estrogens.

Skin and hair color were determined by direct comparison with prosthesis and wigmaker samples made specifically for the project. Eye color was recorded based on direct observation. Natural hair color in childhood was asked for those whose hair had greyed with age.

Reference:

Elwood, J.M. and Gallagher, R.P. "Site distribution of malignant melanoma." Can. Med. Assoc. J. 128:1400-1404 (1983).

Investigator Results:

1. The anatomic site for a series of 300 CMM cases was studied. Sites usually covered by clothing had lower rates than those usually exposed. Rates of melanoma were higher for the face and upper arms in both sexes; rates were low for the abdomen and buttocks and for the forearm and hands in both sexes. Rates for the back, especially below the scapula, were higher in males than females; rates for the leg were greater than expected for women and lower than expected for men.

2. The mean age at diagnosis was 44.9 years. For tumors of the face the mean age was 52 years, and for tumors of the trunk and limb it was 43-44 years.

3. No seasonal variation of incidence was found.

4. The authors commented that "If melanoma occurrence were related directly to the total amount of solar exposure, as is the case for squamous cell carcinoma of the skin, the site-specific increase in melanoma could be explained by the argument that the exposure of those sites (the lower limbs in women and the back in men) has increased in recent years owing to changes in recreational and clothing habits, whereas the solar exposure of sites such as the face has presumably not changed." Prior studies have not validly compared tumor distribution with the body surface area.

Methodology:

A case series of 300 melanomas diagnosed from 1 January 1976 to 31 December 1979 in Vancouver, British Columbia, Canada were examined. Of these, 281 cases of superficial spreading or nodular melanoma were available for analysis. The site of the primary lesions was recorded on standardized forms for each case. The distribution was compared to the surface area of well-defined body surface divisions.

Reference:

Elwood, J.M., Williamson, C. and Stapleton, P.J. "Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources." Br. J. Cancer 53:64-74 (1986).

Investigator Results:

1. In a case-control study of 83 melanoma patients and 83 age-, sex-, and residence-matched controls from England, the presence of three or more moles on the upper arm was significantly associated with an increased risk of melanoma (relative risk (RR)=13.3).

2. The presence of many freckles on adults was significantly associated with an increased risk of melanoma (RR=6.0).

3. Risk factors which were not statistically significant included reaction to sun (burn easily/tan rarely), adult hair color (red, blond), and history of severe sunburn.

4. Exposure to undiffused or diffused fluorescent lighting did not produce consistent results. The authors concluded that "The current results on fluorescent lighting are equivocal. ... The current results are consistent with a real situation of no association or a weak positive association leading to an apparent stronger positive association because of bias."

Methodology:

A small case-control study of 83 out of 112 National Health Service patients in Nottingham, England who had a first primary cutaneous melanoma between 1 July 1981 and 31 March 1984. Controls were matched "precisely" for age, sex, and residence (in same area) and were selected from all persons who had an in- or outpatient attendance at a Nottingham hospital during the same time period. Seven controls were replaced by a second choice. Home interviews were conducted to obtain information on full occupational history, including in particular the lighting in the workplace. A count of palpable moles on the upper arm was also taken.

Experimental Design and Analysis Issues:

For Result 1:

Forty-two percent of melanoma patients and five percent of controls had three or more raised moles on the upper arm. Three or more moles gave a relative risk of 17.0 when compared to no moles (95% C.I. 6.6-43.8). In a multiple logistic model, moles on the upper arm had an RR of 13.3.

For Result 2:

Fifty-five percent of melanoma cases compared to 16 percent of controls had many freckles on the face and arms, giving an RR of 7.0 (95% C.I. 3.3-14.5) compared to those with no freckles. Freckles in childhood were associated with a similar but less strong relationship. In the multiple logistic model, the RR for many adult freckles was 6.0.

For Result 3:

The RR associated with red or blond hair was 2.5 (95% C.I. 1.2-5.3) for adulthood and 2.2 (95% C.I. 1.1-4.8) for childhood. Blue/grey eyes were not significant but the RR was 1.3 (95% C.I. 0.6-2.9). The tendency to burn easily/tan rarely gave an RR of 4.6 (95% C.I. 1.9-11.1) compared to the tendency to tan/no burn. A history of sunburn causing pain for two days or more gave an RR of 3.2 (95% C.I. 1.7-5.9). No significant risk was associated with social class. In the multiple logistic model, risk factors that were not statistically significant included reaction to sun (burn easily/tan rarely), adult hair color (red, blond), and history of severe sunburn. Ten cases and six controls spent a year or more living in a tropical or subtropical climate (RR=1.8, 95% C.I. 0.6-5.1), 14 due to military service overseas.

For Result 4:

No consistent effects were found with undiffused or diffused fluorescent lighting. Control for other variables did not change the results. Some of the occupational exposures to light sources were interesting, e.g., welding, cinema projection (carbon arc lamp), printing/dyeline copying, and UV lights, but the numbers of cases are too small for a definitive study.

Reference:

Elwood, J.M., Gallagher, R.P., Hill, G.B., Spinelli, J.J., Pearson, J.C.G. and Threlfall, W. "Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study." Br. Med. J. 288:99-102 (1984).

Investigator Results:

1. Pigmentation. Individuals with light hair color, light color of unexposed upper inner arms, and light eye color were at greater risk of developing CMM. After adjusting for these factors and freckles in adolescence, sun reaction, childhood sunburn, and ethnic origin, risks increases with increasingly light hair color ($p<0.001$) and skin color ($p<0.05$). Eye color was no longer a significant risk factor.

2. After controlling for the factors noted above, persons with many freckles between ages 5-15 years had higher risks of developing CMM than those with no freckles (RR =2.1, 95% C.I. 1.4-3.1, $p<0.001$ for trend). Freckling in adolescence was considered to be an independent risk factor because the crude RR (2.6) changed little when adjusted for other pigmentation factors. The authors concluded that their results "are consistent with the hypothesis that SSM and NM develop from nevi and suggest that SSM and NM have similar relations to characteristics of pigmentation."

3. Individuals who would burn and rarely tan after a few days' sunlight exposure had higher risks than those who would usually tan without burning with a crude RR=2.3 and an adjusted RR=1.7 (95% C.I. 1.0-2.6). History of severe or frequent sunburns in childhood showed a higher risk (crude RQ = 1.9) but this became smaller (RR=1.3) and non-significant after adjustment for pigmentation factors. "This suggests that rather than the occurrence of sunburn itself increasing the risk of melanoma, the risk is due to the characteristics of pigmentation associated with poor sun tolerance."

4. Persons of east or south European origin had low risks compared to those of English origin (crude RR=0.5). After adjusting for other factors, the differences remained significant (RR=0.6, 95% C.I. 0.4-1.0, $p<0.05$ for trend). Inclusion of ethnic origin did not substantially change associations seen with pigmentation factors or freckling.

5. In an analysis of SSM and NM cases the differences between the risks for the two tumor types were not statistically significant although associations with hair and skin color appeared to be weaker for NM than for SSM. Analysis by primary site showed no statistically significant differences in any of the risk factors although head and neck tumors showed a stronger association with sun reaction and a weaker association with hair color than the other sites.

6. After also adjusting for UV exposure during occupational or recreational activities, the risk factors identified above were not substantially changed.

7. The authors concluded that the strong associations observed for the host factors examined "are not substantially changed by including measures of sun exposure or ethnic origin in the analysis."

Methodology:

A case-control study of 595 CMM patients diagnosed in western provinces of Canada and 595 age-, sex-, and province-matched controls (see introductory discussion).

Experimental Design and Analysis Issues:

For Result 1:

The unadjusted relative risks (RRs) were 9.7 for blond vs. black hair, 3.4 for light vs. dark upper inner arm skin, and 1.6 for blue vs. brown eyes. After adjusting for hair, skin and eye color, freckles in adolescence, sun reaction, childhood sunburn, and ethnic origin, risks were significantly higher for blond vs. black hair color (RR=7.1, 95% C.I. 2.6-19.2) with a significant trend of increasing risk with increasingly light hair color ($p<0.001$). Light inner arm skin color was significantly associated with higher risks (RR=2.4), compared to dark skin color and the trend from dark to medium to light was significant ($p<0.05$).

References:

Elwood, J.M., Gallagher, R.P., Hill, G.B. and Pearson, J.C.G. "Cutaneous melanoma in relation to intermittent and constant sun exposure -- the Western Canada Melanoma Study." Int. J. Cancer 35:427-433 (1985).

Investigator Results:

1. Individuals with mild occupational sun exposure (about 8 hours/week) compared to those with no appreciable occupational sun exposure were at higher risk of developing CMM (crude RR=1.6, RR=1.8 with 95% C.I. 1.2-2.5 after adjusting for the host factors hair and skin color, freckles in adolescence, and ethnic origin. At higher exposures, however, the risks were similar to that of the lowest exposure group.

2. For recreational activities where a bathing suit or very light clothing is worn, risks for those exposed 1-4 hours/week over summer months were higher than for those not exposed (adjusted RR=17, 95% C.I. 1.2-2.5). Risks at higher levels of exposure showed no additional increases. For recreational activities where light clothing is worn (e.g., gardening), a similar but less marked trend was observed.

3. Among individuals who wore bathing suits or light clothing while vacationing, CMM risks were higher among those exposed 4-8 hours/week and 8 or more hours/week compared to those with no exposure (adjusted RRs=1.9 95% [C.I. 1.3-3.0] and [1.5 95% C.I. 1.0-2.3], respectively, $p<0.01$ for trend).

4. CMM risks significantly increased with increasing number of sunny vacations per decade, with adjusted RRs of 1.1 for §1 sunny vacation per decade, 1.3 for 1-3, and 1.7 for 4 or more. The trend of increasing risk was statistically significant ($p<0.001$).

5. The authors noted that the results indicated that "the effects of host factors, ethnic origin, and the measures of sun exposure used were independent of one another.

6. Sex-specific results were not significantly different from the combined results.

7. The authors concluded that their results "suggest that intermittent and continuous exposures have different effects," and "are consistent with the hypothesis that intermittent sun exposure raises the risk of melanoma, while long-term constant exposure may have no effect or may reduce risk." The authors noted that "increases in risk are sun in association with exposure to sun through vacation and recreational activities involving short-term, usually intense sun exposure, but longer term sun exposure achieved through regular outdoor work does not confer any further increase in risk."

Methodology:

A case-control study of 595 CMM patients diagnosed in western provinces of Canada and 595 age-, sex-, and province-matched controls (see introductory discussion).

Experimental Design and Analysis Issues:

For Result 2:

The adjusted relative risks for those involved in recreational activities where a bathing suit or very light clothing is worn were 1.1 for <1 hour/week (95% C.I. 0.7-1.6), 1.7 for 1-4 hrs/week (95% C.I. 1.2-2.5), 1.8 for 4-8 hrs/week (95% C.I. 1.2-2.7), and 1.7 for 8 or more hrs/week (95% C.I. 1.1-2.7). The factors which were taken into account were hair color, skin color and history of freckles (host factors) and ethnic origin.

For Result 3:

For individuals wearing bathing suits or light clothing during summer vacations, the adjusted relative risks were 0.9 for <1 day/season, and 1-4 days/season, 1.9 for 4-8 days/season (95% C.I. 1.3-3.0), and 1.5 for 8 or more days/season (95% C.I. 1.0-2.3).

For Result 5:

The association with each of the sun exposure, variables analyzed (occupational, vacation, and recreational exposure) and CMM risk were not substantially changed, nor was their statistical significance greatly reduced, by controlling for host factors (skin color, hair color, history of freckles) and ethnic origin. The associations between host factors and ethnic origin were similarly not substantially changed by inclusion of the sun-exposure variables.

For Result 6:

The highest risk in each sex group for occupational exposure was for moderate exposure (1-8 hours/week). At higher exposures no consistent trend was seen for females. For males, however, the relative risks fell with increasing exposure. Nevertheless, the sex-specific results were not significantly different than the combined results. For recreational and vacation exposures, the trends were similar as above, but stronger among females. The authors note that interpreting these results is difficult, particularly if males and females respond differently to the same questions.

Reference:

Elwood, J.M., Gallagher, R.P., Darrison, J. and Hill, G.B. "Sunburn, suntan and the risk of cutaneous malignant melanoma-The Western Canada Melanoma Study." Br. J. Cancer 51:543-549 (1985).

Investigator Results:

1. Risks of CMM were significantly elevated among those experiencing moderate to very severe sunburns on vacations, with relative risks (RRs) rising from 1.0 among those with no or mild sunburn to 1.8 among those with frequent, widespread sunburn ($p<0.01$ for trend). Risks were also significantly elevated for those experiencing sunburn in childhood and a history of sunburn severe enough to cause blistering or pain for over two days.

2. CMM risks increased regularly as degree of suntan (in winter and summer) decreased, with an RR of 2.0 among those with a wild winter and summer tan compared to those with a deep or moderate winter and summer tan ($p<0.01$ for trend).

3. When examined together, "usual degree of suntan" and "vacation sunburn" were observed to act independently, each remaining statistically significant when adjusted for the other.

4. Individuals with a tendency to sunburn had significantly higher risks than those with a tendency to tan (RR=2.4, $p<0.001$ for trend).

5. When history of sunburn was assessed jointly with usual reaction to sun, the association with usual reaction to sun was not greatly affected by controlling for sunburn (RRs and significance of trend were very similar). In contrast, the association with vacation sunburn became weather and non-significant after controlling for usual reaction to sun.

6. When usual degree of suntan was assessed jointly with usual reaction to sub, the association with usual reaction to sub remained essentially the same whereas the associations with usual degree of suntan became weaker and non-significant.

7. In a multivariate analysis of vacation sunburn, usual degree of suntan and usual reaction to sun, the associations with vacation sunburn and usual degree of suntan were weaker than when evaluated without usual reaction to sun and were non-significant.

   After also controlling for host factors (hair color, skin color, and freckles in adolescence), associations with usual degree of suntan were further weakened. The usual reaction to sun and the host factor score variables remained statistically significant in the presence of sunburn and suntan factors. Among those who burn only compared with those who tan and don't burn, the RR was 9.0 ($p<0.01$ for trend).

Among those with light hair and skin color and many freckles in adolescence, the RR was 37.5 compared to those with dark hair and skin color and no or few freckles in adolescence ($p<0.001$ for trend). "The results show that the tendency to burn easily and tan poorly is more strongly associated with melanoma risk than is the history of sunburn or of suntan."

8. The authors concluded that their results indicate that "the factor contributing to the risk of melanoma is the individual's tendency to burn rather than the history of having had burns..." and "that sunburn history is indicating a characteristic of the individual skin reaction, related presumably to variations in melanocyte function, distribution or prevalence..."

Methodology:

A cast-control study of 595 CMM patients diagnosed in western provinces of Canada and 595 age-, sex-, and province-matched controls (see introductory discussion).

Experimental Design and Analysis Issues:

For Result 1:

For vacation sunburn experiences of mild, moderate, severe, and very severe, the RRs were 1.0, 1.2, 1.3, and 1.8, respectively.

For Result 2:

For degree of suntan four groups were evaluated: moderate or deep tan in summer and winter, mild winter and deep summer tans, mild winter and moderate summer tans, and mild winter and summer tans. The RRs were 1.0, 1.5, 1.7, and 2.0, respectively.

For Result 4:

The usual reaction to sun variable was divided into four categories: tan with no burn, tan with no burn only by using protective lotions, some burn then tan, and only burn and rarely tan. The RRs for this variable were 1.0, 2.0, 2.0, and 2.4, respectively.

For Result 5:

For the four usual reaction to sun categories described above (Result 4), the RRS after adjustment for history vacation sunburns were 1.0, 1.9, 1.8, and 2.4 respectively ($p<0.001$ for trend). The RRS for vacation sunburn after adjustment for reaction to sun were 1.0, 1.0, 1.1, and 1.4 for mild, moderate, severe, and very severe vacation sunburns, respectively.

For Result 6:

When jointly evaluating usual reaction to sun and usual degree of suntan, the unadjusted RRs for usual reaction to sun (tan no burn, tan if protected, burn then tan, and burn only) were 1.0, 1.9, 1.9, and 2.4, respectively ($p<0.001$ for trend). After adjustment, the RRs were 1.0, 1.8, 1.8, and 2.3, respectively ($p<0.001$ for trend).

For Result 7:

When vacation sunburn, usual degree of suntan, usual reaction to sun, and host factors were jointly evaluated, the RRs for usual reaction to sun were 1.0, 1.6, 1.5, and 1.6, respectively ($p<0.01$ for trend).

DUBIN AND COLLEAGUES -- NYU MEDICAL CENTER MELANOMA STUDY

This large case-control study is based on patients seen at New York University Medical Center between 1972 and 1982 although the study was begun in 1979.

A case series of patients entering one of three New York City hospitals with a newly diagnosed primary malignant melanoma was constructed based on an interview and physical examination. Two-thirds of the cases were diagnosed in 1976 to 1980 because of changes in the number of cases presented at these hospitals, and from 1980 onward the speed with which patients were treated at and released from Day Surgery precluded interview for the study.

Potential controls were randomly chosen from patients 20 years of age and older with a first visit to the New York University Skin and Cancer Unit general skin clinic or a reregistration after two years absence. A total of 748 controls were interviewed between October 1979 and January 1982, about twice as many as concurrent cases. An additional 426 skin clinic patients refused to participate as controls. Based on a random sample of 100, those who refused participation differed only negligibly with respect to age, sex, marital status, race, year of visit, or dermatologic diagnosis.

Of the 1,132 potential cases, 29 were excluded for age less than 20 or unknown age (10 cases), non-white race (6), or previous melanoma (13). Of the 748 potential controls, 163 were excluded for non-white race (79 controls), age (1), previous melanoma (8), other prior skin cancer (35), other prior malignancy (18), or current diagnosis of cancer (22). For the study, this left 1,103 valid cases and 585 valid controls.

Supplementary questions were added to the original interview in 1979. Thus distribution of moles was asked of 289 cases and all 585 controls, skin color for 472 cases and 585 controls, and freckling diagram for 208 cases and 457 controls. In addition, moles and freckles were counted during physical examination for the patients.

There were 566 female and 537 male cases and 320 female and 265 male controls. Histology of the cases was as follows: SSM (813 cases), NM (102), LMM (52), acral lentiginous melanoma (35), unclassified radial growth phase (50), other (34), and unknown (17).

Reference:

Dubin, N., Moseson, M., and Pasternack, B.S. "Epidemiology of malignant melanoma: Pigmentary traits, ultraviolet radiation, and the identification of high-risk populations." Recent Results in Cancer Research 102:56-75 (1986). A partial report was also included in a Lancet letter to the editor (26 March 1974, 1:704) re: Fluorescent Lights.

Investigator Results:

1. In a multiple logistic regression of data on 1,103 melanoma cases and 585 (non-matched) controls, RRs were 2.39 for no ability to tan relative to average and 3.90 for no tendency to burn relative to tendency for painful burn. (Note that the latter RR is opposite of the usual finding.)

2. The RR for a history of freckling relative to no freckling was 3.61. The RR for more than 100 moles compared to 0-25 moles was 3.67

3. Red hair color and blue eyes were associated with higher risks of melanoma.

4. Mostly outdoor work was associated with an RR of 2.43 relative to mostly outdoor work.

5. Subjects reporting that free time was spent mostly outdoors had 1.65 times the risk of those spending free time mostly indoors. In the multiple logistic regression the RR dropped to 1.03.

6. A previous medical history of solar keratosis had an RR of 4.69, and included ten percent of the cases and 1.6 percent of the controls.

7. The interview data produced a relative risk of 2 or 3 for 7-8 or 9+ hours of fluorescent light exposure per day. The reliability questionnaire data showed relative risks of 0.95 and 0.61 for the same exposure parameters, respectively (i.e., a protective effect). The authors commented that the "results for fluorescent light exposure are disturbing. The reliability study data clearly do not support either the interview data that formed the basis of our preliminary report or the findings of Beral et al. (1982). Despite all our efforts to the contrary, interviewer bias may have affected our fluorescent light data."

8. An increased risk was found for persons 72 inches (183 cm) or more in diameter, for those with the largest body surface area, and for those who were unmarried (never married, separated, and divorced).

Methodology:

A case-control study of 1,132 cases with newly diagnosed primary malignant melanoma given an interview and a physical examination from three hospitals in New York between November 1972 and January 1982. From 1980 about one-third were lost because of one-day care and lack of interviews (note potential bias in ascertainment). There were 1,103 valid cases remaining after exclusions.

The controls were randomly chosen from patients age 20 and over at one of the hospitals for a first visit or reregistration after 2 years absence. Different interviewers were used. Of the 748 controls interviewed during the period October 1979 to January 1982, 585 remained after exclusions. An additonal 426 potential controls refused to participate.

A reliability questionnaire was mailed to all cases and controls in 1983. The questionnaire asked for information on sun exposure, fluorescent lighting exposure, and skin color (a repeat of some information from the interview). The physical exam included a count of moles and freckles.

Comment:

Since cases and controls were not concurrent, interpretations are made more difficult.

Reference:

Acquavella, J.F., Wilkinson, G.S., Tietjen, G.L., Key, C.R., Stebbings, J.H., and Voelz, G.L. "A Melanoma Case-Control Study at the Los Alamos National Laboratory." Health Physics 45:587-592 (1983).

Investigator Results:

1. The case-control study focusing on Los Alamos National Laboratory (LANL) employees did not uncover an association between melanoma and plutonium (Pu) body burden, or cumulative external radiation exposure.

2. Melanoma cases were more educated than controls, with melanoma risks of 2.11 among college-educated and 3.17 among those with graduate degrees, indicating importance of personal characteristics, especially higher education, as risk factors for melanoma. No significant association was apparent for chemists or physicists of both sexes.

Methodology:

A case-control analysis of 20 malignant melanoma (MM) cases (15M, 5F) employed at LANL for at least one year and diagnosed after original employment date reported in New Mexico Tumor Registry (1969-1982), in Los Alamos Medical Center (1951-1982), and in state records (1950-1976).

Four LANL controls randomly selected for each case were matched for sex, ethnicity (Anglo, Hispanic), birth date ($\pm$2.5 yr.), and date of first LANL employment. Data on each subject consisted of primary job title, education, dates of initial employment and termination, and radiation exposure history (Pu body burden, external radiation exposure 2 years prior to case's date of diagnosis and corrected for background radiation exposure).

Statistical analyses were based on 1-sample, 2-tailed t-test, contingency tables for matched and unmatched case-control studies, and 95% confidence intervals for odds ratios. Mantel-extension trend test was used to test for dose-response relationships.

Experimental Design and Analysis Issues:

A well-designed case-control study of LANL employees, but limited by the small number of cases.

For Result 1:

No differences between male cases and controls were observed for any type of radiation exposure (B, neutron) and Pu body burden. There was no indication of an association between melanoma and any particular form of radiation exposure. Note that the number of cases in each

exposure category ranged from 0 (neutron, Pu) to 6 (total external radiation).

For Result 2:

Contingency analysis suggested that male cases achieved a college education or graduate degree more often than controls, and were more likely to be employed in a professional capacity. For both sexes, no significant association was apparent for chemists or physicists. Standardized rate ratios (SRR) increased with increasing educational attainment (2.11 for college graduates, 3.17 for graduate level) and the Mantel-extension test for trend indicated a significant association with increased education ($p = 0.04$).

Reference:

Allyn, B., Kopf, A.W., Kahn, M. and Witten, V.H.. "Incidence of Pigmented Nevi." JAMA 186:890-893 (1963)

Investigator Results:

1. Incidence of nevi was evaluated among 1,000 randomly selected subjects; greater than or equal to 1 plantar nevi (9%), 1 palmar nevi (5.8%), 1 conjunctival nevi (0.8%), 1 nailbed nevi in whites (0%). Greatest concentration of plantar nevi was in arch region. Highest nevi incidence was in dark-skinned ethnic groups and male subjects. Incidence of nevi increased in first three decades of life and declined thereafter.

2. Routine excision of pigmented nevi on palms and soles was concluded to be infeasible and unwarranted because of their frequency.

Methodology:

A descriptive analysis of the incidence of pigmented nevi on 1,000 randomly selected individuals from inpatient and outpatient services of New York University Schools of Medicine Dermatology Departments and departmental personnel. Nevi were classified by site (palms, soles, conjunctival, nailbeds), size, surface characteristics and duration. Individuals were classified by ethnic background or color (Caucasian, Latin-American, Negro, Oriental), age, sex, and skin complexion.

Experimental Design and Analysis Issues:

Straightforward descriptive analysis of the data set.

For Result 1:

Incidence of pigmented nevi was provided by site, with 14.3% of overall nevi incidence on palms and soles. The data generally indicated increasing nevi incidence with increasing skin color groups and increasing incidence in the 1st and 2nd decades, a peak in the 3rd decade and a progressive decline thereafter. Plantar pigmented nevi were predominantly on the arch.

For Result 2:

Given a potential 10%-25% incidence of pigmented nevi on palms and soles, which on average indicated a possible 1 in 6 persons having greater than or equal to 1 nevi on a palm or sole, approximately 30 million pigmented nevi would have to be removed to catch the rare ones.

Reference:

Anaise, D., Steinitz, R. and Ben Hur, N.. "Solar Radiation: A Possible Etiological Factor in Malignant Melonoma in Israel: A Retrospective Study (1960-1972)." Cancer 42:299-304 (1978).

Investigator Results:

1. Incidence of malignant melanoma (MM) was higher among European-born Jews ($34/10^6$) than among African-born Jews ($2.7/10^6$) or Asian-born Jews ($4.4/10^6$).

2. Among European-born Jews of the same age and ethnic background, MM incidence was higher among earlier migrants ($58/10^6$, 20-30 years prior to diagnosis) than more recent migrants ($17/10^6$, 2-5 years).

3. Higher incidence was found among Kibbutz agricultural workers ($54/10^6$) compared to city residents ($17/10^6$) and among coastal residents ($35/10^6$) compared to mountain residents ($20/10^6$).

4. The predominant melanoma sites were lower extremity in females (50%) and trunk in males (30%). Lower extremity melanomas among females were higher in 50-79 year-olds (55%) than in 0-19 year olds (41%) and higher in less recent migrants (61%) than recent migrants (49%).

Methodology:

A descriptive analysis of all 966 new MM cases reported in the cancer registry of Israel from 1960-1972. All cases were histologically confirmed. Cases were classified by sex, age, ethnicity (African, Asian, European), and tumor site.

Experimental Design and Analysis Issues:

A straightforward descriptive analysis of age-adjusted MM incidence rates in Israel from 1960-1972.

Reference:

Austin, D.F., Reynolds, P.J., Snyder, M.A., Biggs, M.W., and Stubbs, H.A. "Malignant Melanoma Among Employees of Lawrence Livermore National Laboratory." Lancet 2:712-716 (1981).

Investigator Results:

1. The number of malignant melanoma (MM) cases observed from 1972-1977 among 5,100 Lawrence Livermore National Laboratory (LLNL) employees was significantly higher (p less than $2x10^{-6}$) than the expected number of cases in a comparable age/sex/race/geographical segment of the San Francisco Bay Area population, sugesting a role of an occupational factor.

2. Case-control comparisons indicated that MM risk was not associated with length of employment at LLNL nor with type of monitored radiation exposure.

3. The data did not show an association between MM incidence and all scientific job classifications combined, but an excess relative risk was observed among chemists.

Methodology:

Observed MM incidence was calculated from 5,100 full- or part-time white LLNL employees who lived in Alameda and Contra Costa counties from 1972-1977. Members were grouped by 5-year age group, sex, year of study, and concurrent census tract of residence. The 19 MM cases, identified from the California Tumor Regisity (CTR) for the San Francisco-Oakland Standard Metropolitan Statistical Area, were included only if diagnosis was made while employed at LLNL. Expected MM incidence for the LLNL study group was estimated based upon age, race, sex, and census-tract-specific incidence rates among all new MM cases reported to the CTR for the same counties and time period. The Mantel-Haenszel procedure was used to test for differences between observed and expected cases.

Each of the 19 LLNL cases were matched with 4 control LLNL employees by age group (5-year), race, sex, and area of residence. Information on cases and controls consisted of duration of employment (referenced to diagnosis date for each case), cumulative radiation exposure above background (gamma, neutron, tritium), beta radiation of the skin and hand, and job classification. Differences between cases and controls were tested by the 1-sample, 2-tailed t-test. Approximate relative risks for different job classifications (scientists vs. non-scientists, chemists vs. non-chemists) were assessed using a method described by Miettinen.

Experimental Design and Analysis Issues:

A comparison of observed-to-expected incident MM cases among LLNL employees followed by a case-control study.

For Result 1:

From 1972-1977, 19 MM cases (17M, 2F) were identified. For two types of melanoma (all or invasive only), the observed number of cases among males (17 all melanoma, 14 invasive only) was approximately three times higher than expected (5.6 all melanoma, 4.7 invasive only) (p less than 6×10^{-8} all melanoma, 2×10^{-6} invasive only). Similar results were observed among the entire study group but not among females (only 2 cases). The MM incidence rate for 20-64 year-old white males in the study group ($48.8/10^5$) was higher than that for a similar, non LLNL group of Alameda County residents ($11.7/10^5$).

For Result 2:

Case-control comparison did not indicate an association between MM incidence and length of LLNL employment (p=0.804). The mean duration of employment was 148.8 months for cases, 152.9 months for controls. Case-control data did not indicate a relation between MM incidence and any type of radiation (p=0.31 for gamma).

For Result 3:

Case-control data did not show a relation between scientist job classification and MM incidence (relative risk = 1.64, p=0.348). MM incidence may be higher than expected among chemists (4/19 cases were chemists vs. 3/76 controls, relative risk = 6.97, p=0.011).

Reference:

Bako, G., Hill, G.B., and Hendin, M. "Correlation of Incidence Rates for Selected Cancers in 29 Census Sub-Divisions of Alberta, Canada, 1961-1981." Ecol. Dis. 2:129-131 (1983).

Investigator Results:

In an analysis of correlations between age-adjusted male and female cancer incidence rates for 36 cancer sites, two of the 17 highest correlations were between melanoma and cancer of bone and connective tissue (r=0.62) and oesophagus cancer (r=0.61) in females.

Methodology:

A correlation analysis of age-adjusted male and female cancer incidence rates for 1961-1981 for 36 sites and 29 census sub-divisions of Alberta calculated from the Alberta Cancer Registry. Only correlations with r greater than or equal to 0.55 were considered.

Experimental Design and Analysis Issues:

A straightforward pairwise correlation analysis of cancer incidence rates in Alberta from 1961-1981.

Reference:

Baker-Blocker, A. "Ultraviolet Radiation and Melanoma Mortality in the United States." Env. Res. 23:24-28 (1980).

Investigator Results:

Melanoma mortality rates among white males and females in 18 U.S. counties for 1950-1969 were correlated with latitude and received ultraviolet (UV) radiation ($p<0.01$). No significant correlation was found between melanoma mortality in white males or females separately and UV radiation, suggesting that factors other than UV radiation may play a role in melanoma mortality.

Methodology:

Ultraviolet radiation measurements were obtained for 18 U.S. counties--8 counties from the federal network used Robertson-Berger meters (counts/day), the other counties used Eppley instruments (received UV radiation). Robertson-Berger counts/day were converted to UV radiation units, with the knowledge that the two instruments' measurements had a correlation coefficient of 0.88.

Melanoma mortality data was determined for the 18 counties (thus non-randomly). A comparison of melanoma mortality rates for each county to those for all U.S. counties revealed that the range of mortality rates among the 18 counties was slightly narrower than for all U.S. counties (e.g., for white males, 0.2-3.8 per 10^5 for all U.S. counties vs. 0.5-2.5 per 10^5 for 18 counties). Source of melanoma mortality data was not indicated.

Experimental Design and Analysis Issues:

A cross-sectional analysis of melanoma mortality rates, and latitude and received UV radiation for 1950-1969 in 18 U.S. counties.

Graphical analysis of received UV radiation and melanoma mortality rate showed no readily apparent correlation for either sex. Correlation coefficient for white male melanoma mortality and UV was -0.13, and for white females was 0.27. A similar analysis of male/female melanoma mortality ratio vs. latitude for the 18 counties yielded a correlation coefficient of 0.44 (significant at 10% level), indicating that the ratio decreases with decreasing latitude. For other skin cancers, the ratio increased significantly with decreasing latitude (coefficient = -0.49), significant at 5% level. The author stated that this difference in the sex ratio strengthened the hypothesis that UV radiation, while important in basal and squamous skin cancers, was not an important factor in melanoma. Increasing white female mortality was correlated with decreasing latitude (coefficient = ___, significant at 2% level), but a similar relationship was not observed for white males. There was a strong correlation between received UV and latitude (coefficient = 0.69, significant at 1% level).

Reference:

Balch, C.M., Karakousis, C., Mettlin, C., Natarajan, N., Donegan, W.L., Smart, C.R., and Murphy, G.P. "Management of Cutaneous Melanoma in the United States." Surg., Gyn. and Obst. 158:311-318 (1984).

Investigator Results:

1. Among 4,545 cases of invasive melanoma, a change in mole was the most common presenting symptom of melanoma.

2. The typical melanoma was relatively thin (less than 1.5 mm), not ulcerated (except in 9%) and did not reach Stage IV or V.

3. Melanomas occurred equally in both sexes, however the predominant sites were the trunk for males (53%) and upper and lower extremities for females (50%).

Methodology:

A descriptive analysis of 4,545 histologically confirmed invasive melanoma cases reported from 614 hospitals from throughout the U.S. in 1980. Patients with melanoma from an unkown site, melanomas of the eye or mucous membrane, or melanoma diagnosed at autopsy were excluded.

Experimental Design and Analysis Issues:

A descriptive analysis of 4,545 invasive melanoma cases reported in 1980. Simple comparisons among cases which were described included symptoms of melanoma (change in mole most common), clinical features of melanoma (87% of cases with Stages I and II), sex (occurrence was equal in both sexes), site (male trunk predominance, female upper and lower extremity predominance), age, and race (98% of cases were white). Pathologic features which were examined included level of invasion (35% Level IV, about 25% Level II), tumor thickness (over 33% "thin" lesion--less than 0.76 mm), ulceration (occurred in 9% of cases, usually in thicker lesions), and growth pattern (56% superficial spreading, 30% nodular, 14% lentigo maligna). Surgical and nonsurgical treatments were summarized. Noninvasive melanomas in 225 patients occurred in a slightly older population and more commonly on the head and neck than invasive melanomas.

Reference:

Balch, C.M., Soong, S., Milton, G.W., Shaw, H.M., McGovern, V.J., McCarthy, W.H., Murad, T.M., and Maddox, W.A. "Changing Trends in Cutaneous Melanoma Over a Quarter Century in Alabama, USA, and New South Wales, Australia." Cancer 52:1748-1753 (1983).

Investigator Results:

1. From 1955-1980, there was a steady increase in proportion of patients presenting with clinical Stage I (localized) melanoma among 1,110 patients from the University of Sydney.

2. Melanomas of the trunk in males significantly increased while those of the head and neck decreased as a proportion of the total. No significant change in site distribution was observed for females from 1955-1980.

3. Melanomas became thinner, less invasive, and less ulcerative, and exhibited more of a radial growth phase. Clinical and pathological parameters among Alabama and New South Wales patients differed minimally even when accounting for year of diagnosis.

4. Stage I melanomas became more curable from 1955-1980 with long-term survival rates increasing slightly for the study population.

5. The authors concluded that the changes that occurred were probably due to earlier diagnosis and changes in the biological nature of melanoma.

Methodology:

A descriptive analysis of 1,647 clinical Stage I patients treated at the University of Alabama in Birmingham and the University of Sydney (Australia) between 1955 and 1980. The University of Alabama melanoma Registry provided information on 537 patients, prospectively or retrospectively followed-up since 1975, who were treated since 1955. The Melanoma Clinic at the Sydney Hospital provided information on 1,110 patients prospectively followed-up since 1955. Clinical evaluation, surgical treatment, and pathologic interpretation were carried out or supervised by the authors. All melanomas were histologically confirmed by one of the two pathology authors. Survival curves were calculated based on the Kaplan-Meier method, the log-rank test was used to evaluate differences, and the median and chi-square tests were also used.

Experimental Design and Analysis Issues:

A descriptive analysis of clinical and pathological parameters for 1,647 clinical Stage I melanoma patients.

For Result 1:

Overall incidence of patients presenting with localized (Stage I) melanoma increased in Australia from 73% of all patients before 1960 to 81% for 1976-1980. The upward trend was not as consistent in Alabama (83% in 1955, 91% in 1975, 86% in 1980).

For Result 2:

An examination of melanoma cases by site and gender indicated a significant increase in trunk melanomas among males (40% to 56%, p=0.0004) and a significant decrease in male head and neck melanomas (36% to 17%, p=0.001). No significant changes in site distribution were observed for male extremities or any site on females.

For Result 3:

Median tumor thickness decreased from predominantly thick lesions (3+ mm) prior to 1960 to an average 1.3 mm thickness after 1975 (p less than 0.0001). The proportion of thin melanomas increased from 11% before 1960 to 26% during 1976-1980 period. Level of invasion also changed, with increasing level II melanomas (13% to 25%) and decreasing level IV melanomas (54% to 42%, p less than 0.0001). Incidence of ulceration significantly decreased (p less than 0.0001) in Alabama (54% to 35%) and New South Wales (47% to 19%). The incidence of nodular melanomas decreased while incidence of superficial spreading melanomas increased significantly (p less than 0.0001).

For Result 4:

The 8-year survival rate for Stage I patients increased by 5% over 2 decades for both Alabama and New South Wales.

Reference:

Balch, C.M., Soong, S., Milton, G.W., Shaw, H.M., McGovern, V.J., Murad, T.M., McCarthy, W.H., and Maddox, W.A. "A Comparison of Prognostic Factors and Surgical Results in 1,786 Patients with Localized (Stage I) Melanoma Treated in Alabama, USA, and New South Wales, Australia." Annals Surg. 6:677-684 (1982)

Investigator Results:

1. Similarities among two series of Stage I melanoma patients (from the Universities of Alabama and Sydney) were observed with respect to actuarial survival rates, tumor thickness, level of invasion, surgical results, and age and sex distributions. The greatest differences between the two series were observed for anatomic distribution, growth pattern, and incidence of ulceration. The trunk was the most common site, occurring more frequently among Australian patients (37% vs. 28%). The biologic behavor of melanoma in Sidney, Australia and Birmingham, Alabama was "virtually the same, with only minor differences that did not significantly influence survival rates."

2. In a multifactoral analysis, the dominant prognostic factors (p less than 0.001) were ulceration, tumor thickness, initial surgical management, anatomic location, pathologic stage, and level of invasion.

Methodology:

A descriptive and multifactorial analysis of two series of Stage I melanoma patients treated since 1955 at the University of Alabama (676) and the University of Sydney (1,110). The median follow-up period of observation was 7 years. Clinical and pathological information on the patients were provided and all cases were histologically confirmed.

Experimental Design and Analysis Issues:

For Result 1:

A simple comparison of the clinical features of the two patient series revealed similarities with respect to age- and sex-distributions and hair and eye color, and differences with respect to anatomic distribution (lower extremity and trunk melanomas higher in New South Wales, head and neck melanomas higher in Alabama).

A comparison of prognostic features indicated similarities with respect to tumor thickness, level of invasion, degree of lymphocyte invasion, and pigmentation. The two major prognostic differences were incidence of ulceration (37% in Alabama vs. 22% in New South Wales) and growth patterns (nodular growth patterns predominated in Alabama and superfical lateral spreading predominated in New South Wales). Correlations were observed between tumor thickness and level of invasion, and between ulceration and gender.

Overall survival rates were "virtually the same over a 25-year period of time (p=0.14)." Comparison of survival rates for wide local excision (WLE) vs. WLE plus elective regional lymph node dissection (RLND) showed improved survival in patients having WLE and RLND for melanomas of intermediate thickness (0.76-3.99 mm).

No major differences among melanoma patients in Alabama and New South Wales were found in terms of survival rates and major prognostic parameters. The dominant prognostic factors, tumor thickness and ulceration, were virtually the same for the two patient series and were the most predictive factors for metastatic disease.

For Result 2:

A multiple regression analysis of eleven clinical and prognostic factors indicated that tumor thickness, ulceration, level of invasion, initial surgical treatment, and lesion location were significant ($p < 0.001$ determinants of melanoma incidence among Australian patients (n=776). Pathological state (I vs. II) was probably not significant due to the small sample with clinical Stage I, pathologic Stage II melanoma (n=24). In the 293 Alabama patients, tumor thickness, ulceration, initial treatment, and pathological stage were significant factors (p less than 0.01). A final multiple regression model for the combined data in which all the factors were significant (p less than or equal to 0.001) was $\log g(t)/g_o(t) = 0.3216$ (tumor thickness) + 0.6455 (lesion location) - 0.9408 (surgical treatment) + 0.9013 (ulceration) + 0.4399 (level of invasion) + 1.137 (pathologic/stage), where $g(t)/g_o(t)$ was relative risk.

Reference:

Barger, B.D., Acton, R.T., Soong, S., Roseman, J., and Balch, C. "Increase of HLA-DR4 in Melanoma Patients from Alabama." Cancer Res. 42:4276-4279 (1982).

Investigator Results:

1. There was a significant increase in frequency of HLA-DR4 phenotypes (p=0.0003) among 91 melanoma patients (38.5%) compared to 106 controls (16.0%) producing a relative risk of 3.3. The difference remained significant after correcting for number of antigens (p=0.0018), suggesting that DR4 may be associated with melanoma development.

2. Clinically assessed "high risk" patients had significantly lower DR3 (p=0.02) than "low risk" patients suggesting that DR3 may represent a marker for long-term survival

Methodology:

A case-control study of 91 Caucasian melanoma patients treated at the University of Alabama Melanoma Clinic whose diagnoses were histologically confirmed. "Low risk" patients (decreased risk for metastases) were characterized by Stage I melanoma, tumor thickness less than or equal to 4.0 mm, and no ulceration. Patients at "high risk" for metastases were those with Stage I tumor thickness greater than 4.0 mm or ulceration, or those with Stage II or III (regional or distant metastases). All patients were long-term Alabama residents, 93% of whom were born in southeastern U.S.

The 106 Caucasian controls were (apparently non-randomly) selected from hospital personnel, paternities, and acquaintances from the Birmingham metropolitan area. Over 76% of controls were born in southeastern U.S. There was no restriction on place of residence for cases or controls. No attempt was made to match controls for age, sex, or ethnic background.

All cases and controls were HLA typed (DR1-5,7) with microdroplet lymphocytotoxicity test using B-lympocytes. Antigen frequencies were estimated by maximum likelihood, and odds ratio (relative risk) was estimated by Woolf method. The likelihood ratio asymptotic chi-square was used to test for HLA antigen associations.

Experimental Design and Analysis Issues:

An unmatched case-control analysis (91 cases, 106 controls) of HLA-DR determinants among Caucasians in Alabama, followed by a comparison among high- and low-risk patients.

For Result 1:

The only HLA-DR determinant that differed significantly between cases and controls (from DR1-5,7) was HLA-DR4 (38.5% of cases vs. 16.0% of

controls, p=0.0003) with a relative risk of 3.3. The attributable risk was 69.4% indicating that the genetic component was an important factor. The difference was still significant after correction for number of DR antigens (p=0.0018).

For Result 2:

THe DR4 antigen was higher in low-risk patients (n=67) than in controls (p=0.0009) with a relative risk of 4.0. There was no significant DR4 difference between high- and low-risk patients. When patients were grouped according to time interval between presentation and HLA typing (1-4+ years), DR4 remained significantly elevated in each group and there were no significant DR4 differences among the groups. The DR3 antigen was significantly lower in high-risk patients (n=24) than in controls (p=0.01) and in low-risk patients (p=0.02), but when corrected for number of DR antigens the differences were no longer significant.

Reference:

Bellet, R.E., Vaisman, I., Mastrangelo, M.J., and Lustbader, E. "Multiple Primary Malignancies in Patients with Cutaneous Melanoma." Cancer 40:1974-1981 (1977).

Investigator Results:

1. The observed number of non-melanocytic, non-cutaneous malignancies among 295 melanoma patients (23/281) did not differ significantly from expected based on patient-years at risk.

2. Patients with primary non-melanocytic, non-cutaneous tumors were significantly older at time of diagnosis than patients with melanoma alone. Patients with multiple primary tumors were at risk for a significantly longer period of time. With the exception of breast cancer, the association of cutaneous melanoma with additional non-melanocytic, non-cutaneous malignancies appeared to be random.

3. The observed number of additional primary melanomas among melanoma patients (9/267) was significantly greater than expected. Patients with multiple primary melanomas were not at risk significantly longer than patients with one melanoma. The authors concluded that development of additional primary melanomas in patients with an initial melanoma was not a random event, but probably represents greater susceptibility to malignant transformation of melanocytes.

Methodology:

A descriptive analysis of 295 histologically confirmed Caucasian melanoma patients (126F, 169M) evaluated at the Fox Chase Cancer Center Melanoma Unit (no dates provided). Where possible, the primary melanoma was classified according to Clark's system. The study population was divided into four groups: single primary cutaneous malignant melanoma (MM) (Group 1, n=259); non-melanocytic, non-cutaneous malignancies and single primary MM (Group 2, n=22); multiple primary cutaneous MM (Group 3, n=8); and primary cutaneous non-melanocytic malignancy and single primary cutaneous MM (Group 4, n=6) (Group 4 not analyzed). Patients underwent extensive initial evaluation including detailed history, physical exam, and routine lab studies. Statistical analyses included use of Fisher's Exact Test, 2-sample t-test, Wilcoxon Signed Rank test, or the Mantel-Haenszel chi-square test. The expected number of additional primary cancers was based upon the number of years at risk for developing cancer for which input age-specific incidence rates for 1970 were extracted from the Third National Cancer Survey for all cancers (excluding skin cancer) as well as for melanoma and breast cancer in Caucasians.

Experimental Design and Analysis Issues:

For Result 1:

Observed number of patients in Group 2 (23/281, prevalence 8.2%) was not significantly different from the expected number for each sex (14.71 expected vs. 12 in males, 12.72 vs. 11 in females).

For Result 2:

A comparison of Groups 1 and 2 by sex, age at diagnosis, years at risk for developing additional malignancy, or histologic type, revealed no significant difference in male/female ratio. Group 1 patients were significantly older at time of diagnosis than Group 2 patients (p less than 0.005 males, p less than 0.1 females), and were at risk a significantly greater period of time (p less than 0.005 males, p less than 0.02 females).

For Result 3:

The observed number of cases in Group 3 (9/267, prevalence 3.4%) was significantly greater than expected (0.31 expected in males vs. 5, 0.22 vs. 3 in females, p less than 0.001 for both sexes). A comparison of Groups 1 and 3 indicated no significant differences with respect to sex composition, age at diagnosis, or years at risk of developing an additional primary melanoma.

Reference:

Letters to Lancet re: Beral et al. (7 August 1982)

Investigator Results:

T.S. Davies (23 October 1982, p. 935) -- polychlorinated biphenyls (PCBs) are found in office atmospheres and could explain the finding reported, i.e., it is not the fluorescent light but the PCBs emitted by fluorescent lighting fixtures in offices.

R.S. Stern (27 November 1982, p. 1227) -- findings could be explained by biases in control selection such as higher socioeconomic status.

V. Beral and S. Evans (27 November 1982, p. 1227) -- a reply presenting additional data showed that biases in selection of controls did not occur or did not effect the reported finding.

B.S. Pasternak, N. Dubin, and M. Moseson (26 March 1983, p. 704) -In an ongoing study of melanoma with 136 cases and 282 skin clinic controls in New York, fluorescent light exposure was recorded as average hours per day at home or at work during three time periods: up to five years, five to ten years, and ten to twenty years previously. Exposure during the last five years, after adjusting for other risk factors, was insignificant.

D.S. Rigel, R.J. Friedman, M. Levenstein, D.I. Greenwald (26 March 1983, p. 704) -- UV-A exposure from fluorescent lights was 1/3000th that of autumn sun in New York. In a preliminary study of 114 patients and 228 age-matched controls, no increased risk for melanoma for persons with fluorescent light exposure was found. "These results suggest that the factor that puts these indoor office workers at risk is not their fluorescent light exposure, but their weekend and holidays at the beach which give them intense sun exposure to normally covered body sites."

K.J. Maxwell and J.M. Elwood (3 September 1983, p. 579) -- spectral power irradiance calculations show that at a wavelength of 290 nm the dose received from fluorescent lights may considerably exceed that from sunlight.

Reference:

Beral, V., Evans, S., Shaw, E., and Milton, G. "Cutaneous factors related to the risk of malignant melanoma." Brit. J. Dermatology 109:165-172 (1983).

Investigator Results:

Red hair at age five had a relative risk (RR) of 3.0 (95% C.I. I.95-4.73). The RR was 4.4 for both red hair and fair skin and 3.2 for red hair and dark skin. Eighteen percent (51 women) of cases and 8% (47 women) of controls had red hair. Graying of the hair was found to be protective (RR = 0.60, 95% C.I. 0.46-0,83). After adjusting for hair color, fair skin had an RR of 1.9 (95% C.I. 1.38-2.50). Fifty-nine percent of cases and 40% of controls were faired skinned. Eye color had no independent effect on risk. Forty-five percent of cases and 37 percent of controls had blue eyes. An above average number of nevi increased the risk (RR = 3.5).

Methodology:

A case-control analysis of 287 white females who attended the Melanoma Clinic at Sydney Hospital aged 15-84 years and 574 age-matched controls. Controls from the general population for 213 "old cases" (diagnosed between 1974-1978) were also matched by area of residence. Controls for "new cases" (diagnosed between 1978-1980) were selected from hospital inpatients (excluding those with vascular disease, gyn. disorder, diabetes, gallbladder or breast disease, or chronic disease of 2+ years duration).

Reference:

Beral, V., Evans, S., Shaw, H. and Milton, G. "Malignant melanoma and exposure to fluorescent lighting at work." Lancet 2:290-293 (7 August 1982).

Investigator Results:

1. In a case-control study of 274 females with melanoma and 549 controls, exposure to fluorescent light at work was associated with a relative risk of 2.1 (95% C.I. 1.32-3.32) compared to the 25 women who were never exposed to fluorescent lights. Relative risks tended to increase with increasing years of exposure. Melanomas occurred on the trunk among 24% of the ever exposed compared to the 9% of others with melanoma. Although other factors were shown to increase the risk, stratification on these factors did not change the relationship to fluorescent lights. Fluorescent lights in the home were not associated with melanoma (RR = 0.9, 95% C.I. 0.6-1.6). Previously collected information on 27 males with melanoma and 35 controls yielded an RR of 4.4 (95% C.I. 1.1.-17.5).

2. Among cases, a significant excess of lesions ($p<.05$) was observed among those exposed to fluorescent lights (24%) compared to those never exposed (99%).

3. The authors commented that "It is curious, however, that fluorescent lights appear to be so important, especially since they emit much smaller amounts of 'erythemal' ultraviolet (UV-B wavelength 280-315 nm) than solar radiation."

Methodology:

A case-control study of 274 female melanoma patients obtained from the melanoma clinic in Sydney Hospital. There were 213 "old" cases (diagnosed after June 1978 in a study of the relation of oral contraceptives and melanoma) out of 300 potential cases and 74 "new cases" who were 18-54 year old females diagnosed between June 1978 and December 1980.

Two controls were chosen for each case and were matched by 5-year age groups. Old cases were also matched by area of residence. Controls for new cases were Sydney Hospital inpatients who did not have a long term disease.

Trained interviewers asked the subjects about demographic factors, occupation, exposure to sunlight and other factors from a standard questionnaire. Occupational information was not available for 13 cases and 25 controls leaving 274 cases and 549 controls. The age range in both groups was 18-54 years.

Experimental Design and Analysis Issues:

The association with fluorescent lights had not been reported before and although it is possible, it must be viewed cautiously pending the results of additional studies.

Reference:

Beral, V., Evans, S., Shaw, H. and Milton, G. "Oral Contraceptive Use and Malignant Melanoma in Australia." Br. J. Cancer 50:681-685 (1984).

Investigator Results:

1. Women with melanoma were more likely to have taken oral contraceptives for long periods of time, the relative risk (RR) associated with 5+ years use begun 10+ years before melanoma diagnosis was 1.5 (95% confidence interval 1.03-2.14). This elevated risk persisted after controlling for reported hair and skin color, frequency of moles on body, place of birth, and measures of sunlight and fluorescent light exposure. Results suggested that prolonged contraceptive use after lag of 10 or more years may increase risk of MM.

2. Cases were more likely than controls (but not significantly) to have used hormones to regulate periods (RR=1.9), used hormonal replacement therapy (RR=1.4), and been given hormone injections to suppress lactation (RR=1.4).

Methodology:

A case-control analysis of 287 white females who attended the Melanoma Clinic at Sydney Hospital aged 15-84 years and 574 age-matched controls. Controls from the general population for 213 "old cases" (diagnosed between 1974-1978) were also matched by area of residence. Controls for "new cases" (diagnosed between 1978-1980) were selected from hospital inpatients (excluding those with vascular disease, gyn. disorder, diabetes, gallbladder or breast disease, or chronic disease of 2+ years duration). Information obtained from interviewer questionnaire included pregnancy history and use of oral contraceptives and other hormones.

Experimental Design and Analysis Issues:

A case-control analysis of the effect of oral contraceptive and hormone use, as well as pregnancy history on risk of melanoma among 287 female cases and 574 age-matched controls.

For Result 1:

A nonsignificant difference was observed between cases who had taken oral contraceptives for 5+ years (29.3%) and controls (24.3%). A significantly greater percentage of cases than controls had begun taking the pill at least 10 years earlier (46.6% vs. 38.5%, p=0.05). A consistently increased risk of melanoma was only observed in those who had begun pill use 10+ years before and whose use had continued for 5+ years (RR=1.5, 95% confidence interval 1.03-2.14).

After adjusting for marital status, hair, eye and skin color, country of birth, number of moles on body, educational status, exposure to

fluorescent light, history of cholasma, extent of outdoor activity at 10, 20, 30, and 40 years, and sunburn history, the RR varied between 1.43-1.58. There was no significant difference in site of lesion, tumor thickness, or tumor type between those who had and had not used the pill.

For Result 2:

The RRs and 95% confidence intervals for use of hormones to regulate periods was 1.9 (0.85-4.12), for hormone replacement therapy 1.4 (0.78-2.61), and for hormones to suppress lactation 1.3 (0.92-1.82).

Reference:

Beral, V., Ramcharan, S. and Faris, R. "Malignant melanoma and oral contraceptive use among women in California. "Br. J. Cancer 36:804-809 (1977).

Investigator Results:

1. In the Group A case-control comparison, rates of melanoma were higher in oral contraceptive (OC) users than nonusers but the difference was not statistically significant. Only eye color (light-colored versus brown) was a significant risk factor for melanoma. A history of skin cancer was more common in OC users than never-users.

2. In the Group B case-control comparison, ever versus never use of oral contraceptives was 1.8 times as high in the cases as controls. No relation with type of OC or oestrogen/progesterone content was found.

3. Both groups combined showed an excess of lesions in OC/oestrogen users of lower limb melanoma.

Methodology:

A case-control study conducted for two groups of cases. Group A was based on a prospective study of 17,942 females aged 17-59 years for whom OC use was recorded between December 1968 and February 1972. The cases were predominantly white middle class (see Ramcharan 1974). OC users included those who reported estrogen use. Skin cancer among Group A cases was determined from Kaiser-Permanente records. Case data were recorded by questionnaire. Follow-up was about 5 years per woman. Group B cases were 37 females who were not in Group A and were diagnosed for melanoma between 1 January 1968 and 30 June 1976. Age was 20-59 years at diagnosis. Two controls were matched to each case with respect to date of birth (within one year) and were chosen from Kaiser Health Plan files. Outpatient records were searched for information on OC and estrogen use during comparable periods for cases and controls.

Reference:

Beral, V., and Robinson, N. "The Relationship of Malignant Melanoma, Basal and Squamons Skin Cancers to Indoor and Outdoor Work." Br. J. Cancer 44:886-891 (1981).

Investigator Results:

In England and Wales from 1970-1975, office work was associated with excess trunk and limb melanomas, whereas outdoor work in which prolonged occupational exposure to sunlight would occur was associated with excess head, face, and neck melanomas, as well as basal- and squamous-cell skin carcinomas. The high rate of trunk and limb lesions in office workers may have reflected sunbathing or other recreational habits but contrasted with observed low nonmelanoma skin cancer rates among indoor workers.

Methodology:

A descriptive analysis of melanoma incidence and mortality data in England and Wales from 1970-1975 obtained from the Office of Population Censuses and Surveys, which included information on occupation, type of cancer, and anatomical site. On the basis of occupation, cases were assigned to one of three groups: outdoor workers, indoor office workers, and other indoor workers (mainly factory). Standardized cancer registration ratios (SRR) based on age-specific rates in all occupational groups combined, and standardized mortality ratios (SMR) based on 1971 population by occupational group were calculated by indirect standardization.

Experimental Design and Analysis Issues:

A descriptive analysis of incidence of basal- and squamous-cell skin cancers and melanoma including calculation of SRRs and SMRs.

Based on SRRs for males 15-64 years, outdoor work was associated with a 10% excess of squamous- and basal-cell carcinoma, a 9% excess of head, face, and neck melanomas, and a 22% deficit of melanomas at other sites compared to the national 1971 averages. Office work was associated with a 31% melanoma excess of "other" sites. Other indoor workers had a deficit of all tumor types. When reanalyzed only for social class III the findings were similar except for moderate increases of squamous- and basal-cell carcinomas and head, face and neck melanomas among office workers.

Reference:

Blair, A. and Hayes, H.M., Jr. "Mortality Patterns Among U.S. Veterinarians, 1947-1977: An Expanded Study." Int. J. Epi. 11:391-397 (1982).

Investigator Results:

Proportions of death among 5,016 white male veterinarians were significantly elevated for cancers of the skin as compared to a distribution based on the general U.S. population. Although economic and methodological factors may have been involved, the pattern suggested that sunlight exposure was responsible for the excess among vets whose practices were not exclusively limited to small animals.

Methodology:

A descriptive analysis of mortality data for 5,016 white male veterinarians who died between 1947-1977 obtained from the Journal of the American Veterinary Medical Association. Each case was grouped according to reported professional specialty into one of two large categories: practitioners (2,846) and non-practitioners (2,170), and into one of five subcategories: small-animal practitioners (331), other practitioners (2,515), meat inspectors (178), lab specialists (110), and regulatory vets (713). Expected numbers of deaths were calculated based on 5-year age and calendar period groups for white U.S. males; proportionate mortality ratios (PMRs) were calculated and tested by a chi-square test.

Experimental Design and Analysis Issues:

A descriptive analysis of vet mortality data by professional specialty.

The observed number of deaths due to skin cancers was 24 compared to 14.9 expected deaths ($p<0.025$). Among the 24 skin cancers, 18 were malignant melanomas. Most of the skin cancers occurred in the other than small animal practitioner group for which the number of observed cases was not significantly different than expected (12 vs. 7.5). The seven observed skin cancers among more recent vets (began practice between 1908-1957 and ended between 1965-1974) who died at or before 64 years of age was significantly higher than the 2.1 expected $p<0.005$).

Reference:

Boyle, P., Day, N.E., and Magnus, K. "Mathematical Modelling of Malignant Melonoma Trends in Norway, 1953-1978." Am. J. Epi. 118:887-896 (1983).

Investigator Results:

Malignant melanoma (MM) time trends in Norwegian Cancer Registry data from 1953-1978 (by subsite and sex) could be explained by a common age effect and a separate birth cohort effect for each subsite in both sexes, or by a common cohort effect but different age effects for each subsite and sex. In neither case was the time period of registration an important factor.

Methodology:

A descriptive analysis of the fit of various melanoma risk models to data on 5,741 MM cases reported in the Norwegian Cancer Registry between 1953-1978 and classified by sex, year of birth, year of diagnosis and subsite. The time period of registration was divided into six periods: 1953-1954, 1955-1959, 1960-1964, 1965-1969, 1970-1974, and 1975-1978. Nine 10-year birth cohorts (1870-1879 to 1950-1959) and 7, 9-year age categories (10-19 to 70-79) were considered. Ninety-nine percent of cases in the registry had histological verification. Cases of lentigo maligna melanoma were excluded. The model used estimated melanoma risk as a function of sex, age, years of birth and diagnosis, and subsite, factors included as single and interaction terms in the models.

Experimental Design and Analysis Issues:

A descriptive analysis of the fit of various age, birth cohort, and time period dependent melanoma risk models to Norwegian melanoma data from 1953-1978.

Among four additive models (age, age with cohort, age with time trend, and age with both), the fit to the data by sex and subsite did not vary by much except for male trunk tumors for which a cohort effect gave superior fit. Two additional models including interaction terms for age with cohort and age with time indicated an improved fit for the age-time model over the additive age and time model.

Among a series of models variously including terms for age, sex, subsite, time trend, and cohort (but not cohort and time trend simultaneously), two models provided alternative but equally good pictures of the data: 1) a model with a single cohort effect for all subsites and both sexes, but varying by an age-sex-subsite interaction factor; and 2) a model with an age effect for each sex-subsite-cohort group.

All subsites in both sexes showed rapidly increasing risk by year of birth cohort, especially for the trunk and lower limbs. Incidence of tumors in both sexes of head, neck or other sites rose approximately linearly on the log-log scale with age, i.e., an exponential rate.

For trunk and lower limb melanomas, incidence increases fell off in older age groups, especially for lower limbs in females for whom incidence remained constant after 40 years.

Reference:

Boyle, J., MacKie, R.M., Briggs, J.D., Junor, B.J.R., and Aitchison, T.C. "Cancer, Warts, and Sunshine in Renal Transplant Patients." Lancet, 1:702-705 (1984).

Investigator Results:

Melanoma was not addressed in this study. Among 94 renal transplant patients and 94 age, sex, and sun exposure matched control, 17 patients with high exposure to sunshine had 2 squamous cell carcinomas, 3 basal cell carcinomas, and 7 actinic keratoses, lesions which did not appear in the other patients or the controls. The immunosuppressive effect of UV radiation (290-320 nm) may be related to increased incidence of cutaneous malignancy, actinic keratoses, and warts among renal transplant patients (already immunosuppressed by drugs).

Methodology:

A case-control study of 94 renal transplant patients (62M, 32F) from the Western Infirmary, Glasgow and 94 sex-, age-, and sun exposure-matched controls treated at the infirmary's emergency department. Cases and controls were questioned and grouped according to history of sun exposure before reference transplantation date (more than 3 months in tropical or sub-tropical climate or worked outdoors for 5+ years were considered high exposure). Details of previous herpes simplex and zoster infections and presence of warts, fungal infections, and malignant and premalignant cutaneous lesions were also noted. Data were analyzed by McNemar and chi-square tests.

Experimental Design and Analysis Issues:

Seventeen patients and matched controls had history of high sun exposure, and among these 7 patients had actinic keratosis, 3 had basal cell carcinoma, and 2 had squamous cell carcinoma; no controls had these lesions.

Reference:

Brown, J., Kopf, A.W., Rigel, D.S., and Friedman, R.J. "Malignant Melanoma in World War II Veterans." Int. J. Dermatol. 23(10):661-663 (1984).

Investigator Results:

1. In a case-control study of 89 World War II (WWII) veterans with melanoma and 65 age-matched controls, 83% of the melanoma group compared to 76% of the control group had served in armed forces during WWII; moreover, a significantly greater percentage (p=0.0002) of the cases (34%) served in tropics than did controls (6%).

2. A greater percentage of melanoma patients among those who had served in the tropics had malignant melanomas (MM) originating in nevocytic nevi compared to melanoma patients who had served in nontropical areas.

3. The authors suggested that Caucasians heavily exposed to sunlight in the tropics for several years during early life might be at higher risk of developing MM. They also suggested a two-step phenomenon: first step solar induction of nevocytic nevi, second malignant transformation within them.

Methodology:

A case-control analysis of 89 (out of 120) patients entered into the Melanoma Cooperative Group at New York University School of Medicine during 1972-1980 who were 18-31 years-old during WWII (out of 1,067 consecutive patients total) and 65 age-matched controls who visited NYU Department of Dermatology for cutaneous ailments other than MM. Questionnaire information determined whether cases and controls had served in WWII and if so, in which theater(s) of operation.

Experimental Design and Analysis Issues:

A case-control analysis of 89 male melanoma patients and 65 age-matched controls.

For Result 1:

A greater percentage of cases (83%) had served in Armed Forces during WWII than controls (76%) and a significantly greater percentage had served in tropics (34% cases vs. 6% controls, p=0.0002).

For Result 2:

Among the 89 melanoma patients, those who had served in the tropics had their tumors arise more often in nevocytic nevi (53%) than those who had served in U.S./Europe (24%). There were no significant differences between these two groups in thickness, level of penetration, histologic type, or anatomic site.

Reference:

Crombie, I.K. "Distribution of malignant melanoma on the body surface." Br. J. Cancer 43:842-849 (1981).

Investigator Results:

1. From a review of 37 cancer registries which published detailed site-incidence data on malignant melanoma among whites, a higher incidence on the female lower limb and the male trunk was found. For all 37 registries, the proportion of melanoma by site in the order head, upper limb, lower limb, and the remainder (mostly trunk) for males was 24.4, 14.4, 18.4, and 42.8% and the for females was 16.1, 15.4, 42.4, and 26.1%. The melanocyte density was quoted as being 13, 31, 19, and 37% in the same order.

2. Females had a significantly higher incidence of melanoma than males. Differences in the rates by sex were statistically significant for all sites combined for all 37 registries combined, for the 15 North American registries, but not for the 20 European registries. By body site all differences in incidence rates were significant except for the upper limb in the 15 North American registries.

3. The median incidence per 100,000 and the male to female sex ratio by site were as follows: head 0.526 and 0.425 giving 1.24; upper limb 0.261 and 0.528 giving 0.494; lower limb 0.378 and 1.079 giving 0.350; and remainder (mostly trunk) 0.927 and 0.674 giving 1.37.

Methodology:

The distribution of melanoma on the body surface was examined based on data from Cancer Incidence in Five Continents using a four digit ICD classification.

Reference:

Crombie, I.K. "Variation of melanoma incidence with latitude in North America and Europe." Br. J. Cancer 40:774-781 (1979).

Investigator Results:

In North America and in England, melanoma incidence increased with decreasing latitude; in Europe the relationship was in the opposite direction.

A regression of cancer incidence rates for 16 North American registries and for 14 regions in England (1967-1973) on latitude showed a statistically significant relationship for melanoma but not for all sites, for both male and females. In 27 European registries, the relationship was reversed with a significant increase in melanoma as the latitude was increased for males and females and a significant increase in all sites for females but not males.

Methodology:

The relationship between melanoma incidence rates and latitude was studied for 43 population-based cancer registries in North America and Europe. From Cancer Incidence in Five Continents, data on rates between 1967 and 1973 from 43 registries in Europe and North America which record cancer incidence among white populations were studied. Also 14 hospital regions in England were studied.

Comments:

The effect of the very high incidence in Norway and Sweden on this regression needs to be investigated. It is not known if the regression would still be significant if Norway and Sweden were omitted.

Reference:

Fears, T.R., Scotto, J., and Schneiderman, M.A. "Skin Cancer, Melanoma, and Sunlight." AJPH 66:461-464 (1976).

Investigator Results:

The authors applied a modeling approach which estimated increases in nonmelanoma and melanoma incidence and mortality with increases in ultraviolet (UV) radiation. The results indicated that total UV dose increased with decreasing latitude, latitude decreased with incidence increases, and latitude decreased with increasing mortality. The model predicted an additional $49.7/10^5$ cases of nonmelanoma cancer, $0.69/10^5$ cases of melanoma, and 0.13 additional deaths from melanoma associated with a 10% increase in radiation dose.

Methodology:

A cross-sectional analysis of the fit of melanoma and nonmelanoma incidence and mortality rate data to a single-variable (latitude) linear regression model.

Incidence rate data, obtained from the Third National Cancer Survey (TNCS) for the 1969-1971 period included nonmelanoma skin cancer data for four U.S. regions and melanoma data for nine U.S. regions. Regions were classified by latitude. Age-adjusted melanoma mortality rates were obtained from Mason and McKay. The data were fit to a single-variable (latitude) linear regression model: log R= x+BL where R=age-adjusted rate and L=latitude.

Experimental Design and Analysis Issues:

A cross-sectional linear regression analysis investigating the relationship of latitude to melanoma incidence and mortality rate data and nonmelanoma incidence data.

The regression coefficient (slope) for melanoma incidence (9 data points) was significant (B=-0.03 males, p less than 0.01) whereas for nonmelanoma incidence (4 data points) the negative slope was steeper but not significant. For melanoma mortality data, the less steep slope (B=-0.017 males) was not significantly different from that for melanoma incidence. Risk of developing melanoma doubled with every 9.8 (males) and 10.7 (females) decrease in degrees latitude.

For 33 northern hemisphere locations, latitude was converted into Biologic Effective Units (BEU) for 12 months representing the sum of UV radiation from 295 nm-325 nm weighted by erythema effectiveness. Correlation between degrees north latitude and BEU was 0.97 (p less than 0.005).

The effects of 10%-30% increases in radiation dose on incidence and mortality, based on 650, 850, and 1,050 BEUS (for North Dakota, Iowa,

and Oklahoma latitudes, respectively), indicated increases for a 10% BEU increase of $49.7/10^5$ cases of nonmelanoma, $0.69/10^5$ cases of melanmona, and $0.13/10^5$ deaths from melanoma. The increases were larger for nonmelanoma than melanoma, men than women, and incidence than mortality.

Reference:

Hinds, M.W. "Anatomic Distribution of Malignant Melanoma of the Skin Among Non-Caucasians in Hawaii." Br. J. Cancer 40:497-499 (1979).

Investigator Results:

Among 64 non-Caucasian malignant melanoma cases in the Hawaii Tumor Registry during 1960-1977, predominant lesion sites were the feet in males (n=41, 41.5%) and in females (n=18 27.8%).

Methodology:

A descriptive analysis of all 64 non-Caucasian invasive malignant melanoma (MM) cases reported in the Hawaii Tumor Registry during 1960-1977. Over 94% of all cancer cases in the registry had been histologically confirmed.

Experimental Design and Analysis Issues:

In addition to the information cited above, site distributions were summarized for several ethnic subgroups. Among the 20 Japanese cases, 30% occurred on the feet. Among the 9 Filipinos, 78% on feet and among the 5 Chinese, 40% on feet. Among the 16 Hawaiians and part-Hawaiians (4 part-Caucasians), 25% of lesions were on feet. Among the 14 mixed racial background cases (2 part-Caucasian), 21% on feet. Of the 22 foot lesions, 12 were on plantar surface and 7 on toe.

Reference:

Houghton, A.N., Flannery, J., and Viola, M.V. "Malignant Melanoma of the Skin Occurring During Pregnancy." Am. J. Cancer 25:95-103 (1980).

Investigator Results:

1. In a non-matched case-control study of 12 patients with melanoma during pregnancy (cases) and 175 nonpregnant melanoma patients (controls), 3- and 5-year survival rates were significantly lower for cases (65% and 55%, respectively) than controls (86% and 83%, respectively, p less than 0.05). When controls were matched to cases by age, anatomic site, and stage at diagnosis, 3- and 5-year survival rates were not significantly different.

2. Melanoma occurred more often on the trunk and at more advanced stages in cases than in controls.

3. MM incidence did not substantially increase during pregnancy when compared to the expected number of melanoma cases among pregnant women.

4. Melanoma occurring during pregnancy usually carried poor prognosis but once diagnosed, disease course was not worse considering stage of disease and primary site.

Methodology:

A case-control study based on review of female MM patients between 15-40 years of age reported in the Connecticut Tumor Registry from 1950-1954, 1960-1964, and 1970-1974. Patients diagnosed with MM during pregnancy were selected as cases (n = 12) and 175 female patients diagnosed during the same calendar periods not during pregnancy were selected as controls. Each case was matched with 2 controls by age, anatomic site, and stage of disease at diagnosis. Number of expected live births per year for female melanoma patients was calculated from Connecticut live birth rates. Survival rates were compared by 2-sided Fisher's exact and logrank tests.

Experimental Design and Analysis Issues:

A case-control study of survival rates among female MM patients pregnant during diagnosis (cases) vs. nonpregnant (controls).

For Result 1:

Among cases, 50% died of melanoma compared to 14.8% among controls. Three- and five-year survival rates were higher among all 175 controls (86% and 83%, respectively) compared to the 12 cases (65% and 55%, respectively, p less than 0.05). However, 3- and 5-year survival rates did not differ significantly when compared for 12 cases and 24 matched controls.

For Result 2:

A comparison of the 12 pregnant cases and 175 nonpregnant controls indicated occurrence of melanomas among cases more often on trunk (50% vs. 32% controls), and less often on lower extremities (33% vs. 43% controls). Regional and distant metastases were more common among cases than controls (16.7% vs. 9.7% for regional and 16.7% vs. 2.3% for distancts).

For Result 3:

The expected number of pregnant women among the 187 MM patients reviewed, estimated from Connecticut live birth rates, was 13.3, compared to the observed 12 pregnancies, suggesting MM incidence did not substantially increase during pregnancy.

Reference:

Houghton, A.N., Munster, E.W., and Viola, M.V. "Increased Incidence of Malignant Melanoma After Peaks of Sunspot Activity." Lancet April:759-760 (1978).

Investigator Results:

1. Age-adjusted malignant melanoma (MM) incidence rates in Connecticut (CT) rose from $1.1/10^5$ in 1935 to $6.2/10^5$ in 1975. Superimposed on linear incidence increases were 3-5 year periods of cyclic incidence rises occurring every 8-11 years.

2. Significant partial correlations (p less than 0.01) were observed, after adjustment for time, between CT melanoma incidence and sunspot numbers from 1 to 3 years following sunspots (closest association for 2 years with r = 0.695 (males and females) and r = 0.717 (males)).

Methodology:

A descriptive and cross-sectional anaysis of 2,983 histologically confirmed incident melanoma cases registered in the CT Tumor Registry from 1935-1974. Relative sunspot numbers were obtained from Waldmeir and Eddy.

Experimental Design and Analysis Issues:

A descriptive analysis of melanoma incidence rates in CT and a cross-sectional analysis of the association between melanoma incidence and sunspot activity.

For Result 1:

Age-adjusted incidence rate was $1.1/10^5$ (1935) and $6.2/10^5$ (1975). Superimposed on the 40-year steady incidence increases were 3-5 year periods of more acute incidence. Between 1935 and 1975 this cycle occurred 4 times in 8-11 year intervals.

For Result 2:

The correlation using a linear regression equation between melanoma incidence and time over three sunspot cycles (33 years) was significant (r = 0.9327, p less than 0.01). Examinations of deviations from a time-adjusted regression model indicated cyclic correlations between sunspot cycles and MM incidence rates. Partial correlations between annual sunspot numbers and melanoma incidence, controlling for time effect, found statistically significant correlations in each of the subsequent 3 years, the closest association being 2 years later. Correlation coefficients with p less than 0.01 were observed for males and females 1 and 2 years following sunspots and for males 1, 2, and 3 years following sunspots.

Data for New York, Norway, and Finland cancer registries for 1950-1971, similarly analyzed, indicated significant partial correlations ($p < 0.01$) 1-2 years following sunspot activity for New York. Nonsignificant correlations were observed for Norway 0-4 years subsequent to sunspots. In Finland, a significant partial correlation ($p < 0.05$) was observed for the year of sunspot activity.

Reference:

Houghton, A.N., and Viola, M.V. "Solar Radiation and Malignant Melanoma of the Skin." J. Am. Acad. Dermatol. 5:477-483 (1981).

Investigator Results:

A review of clinical and epidemiologic evidence supporting the role of solar (UV) radiation in pathogenesis of malignant melanoma (MM). Discussion includes apparent correlation between sunspot cycles, UV maxima, and increased MM incidence, and apparent promoter effect of UV radiation in melanoma pathogenesis.

Methodology:

A general review of epidemiological and clinical findings supporting role of solar (UV) radiation in pathogenesis of MM.

Experimental Design and Analysis Issues:

The evidence for a role of sun exposure in MM comes from epidemiological and clinical observations indicating that MM incidence among whites is inversely proportional to latitude, and ultraviolet radiation is more intense at lower latitudes; MM tends to occur on more heavily exposed sites during recreation such as trunk in men and lower legs in women; and MM is more likely to develop in lightly pigmented persons. Other less compelling observations include: susceptible persons living in sunny climate for their lifetimes have higher MM incidence than recent migrants from less sunny areas; MM rates are relatively low for those with outdoor occupations and higher for higher income groups, suggesting recreational but not chronic sun exposure is one pathogenic factor.

The correlation between sunspot cycles and MM incidence increases (in Connecticut, Denmark, Finland, and New York) further relates solar radiation to MM. Similar fluctuations were not observed for non-melanoma malignancies. Sunspot numbers are clearest indicator of solar activity and amount of UV radiation reaching the Earth's surface. Rises in MM incidence occur 0-3 years after sunspot peaks suggesting importance of heavier exposures.

For most non-melanoma skin cancers (e.g., basal- and squamous-cell skin carcinomas), solar radiation behaves as dose-dependent (initiator) carcinogen usually on most chronically exposed body parts. Excluding lentigo maligna melanoma, solar radiation does not act as a dose-dependent carcinogen in most melanoma cases, but appears to act proximally in melanoma pathogenesis usually on intermittently and intensively exposed body parts (e.g., during recreation). Evidence suggests that UV radiation may act as promoter in melanoma pathogenesis.

Other potentially important factors in melanoma pathogenesis may include genetic susceptibility, recreational behavior, cultural and socioeconomic factors, altitude, cloud cover, and time of day during exposure.

Reference:

Kripke, M.L. "Speculations on the role of ultraviolet radiation in the development of malignant melanoma." (guest editorial) JNCI 63:541-548 (1979).

Investigator Results:

1. In this guest editorial, the author stated that the incidence of and mortality from melanoma were doubling every 10-17 years.

2. The author discussed animal models for melanoma. A possible mechanism of melanoma is one in which UV lights "affect tumor growth but not tumor production." Another possibility was that UV produced "a systemic alteration that was conducive to tumor growth. ...This systemic alteration could be immunologic, like the one we have described for nonmelonoma skin tumors in mice; alternatively, it could be a biochemical alteration in which skin photoproducts provide a nutritive advantage for proliferating tumor cells."

3. The authors stated that it was "not unreasonable to suppose that at least some human melanomas might also arise for reasons that do not include UV light. Human melanomas might have in common only the cell affected in the neoplastic process and need not share an etiology in every case."

Reference:

Lew, R.A., Sober, A.J., Cook, N., Marvell, R., and Fitzpatrick, T.B. "Sun exposure habits in patients with cutaneous melanoma: a case-control study." J. Dermatol. Surg. Oncol. 9:981-986 (1983).

Investigator Results:

1. Telephone interviews to 111 patients and 107 controls revealed that painful or blistering sunburns during either childhood or adolescence were associated with increased risk of developing cutaneous melanoma.

   Risk factors were blistering sunburns during adolescence (odds ratio (OR) = 2.05, 95%, C.I. 1.18-3.56), poor vs. good tanning ability (OR = 1.93, 95% C.I. 1.13-3.3), and 30 days of vacation in sunny warm places during childhood vs. fewer days (OR = 2.5, 95% C.I. 1.18-5.8). The same set of risk factors was found for those less than 50 years old and those 50 and over. Among those with no painful sunburn, cases were more frequently encouraged to be outdoors (OR = 3.32, 95% C.I. 1.2-5.7).

2. No differences were found between cases and controls regarding use of hormones and oral contraceptives.

3. The authors commented that "Sunlight appears to play a role in the etiology of melanoma....the present study suggests that traumatic dosage may outweigh lifetime cumulative dosage as a factor."

Methodology:

A case-control study of 111 patients (cases) in the Melanoma Clinical Cooperative Group of the Massachusetts General Hospital in Boston. Controls were friends of the patients (age within 5 years) and of the same sex. Matching was not used because 46 patients provided no controls, 30 provided 1, 28 provided 2, and 7 provided 3. Telephone interviews were conducted to determine the history of sun exposure and related behavior for childhood into the adult years.

Reference:

MacKie, R.M. and Aitchinson, T. "Severe Sunburn and Subsequent Risk of Primary Cutaneous Malignant Melanoma in Scotland." Br. J. Cancer 46:955-960 (1982)

Investigator Results:

1. Melanoma patients had increased incidence of severe sunburn, significantly less recreational sun exposure, and were of higher social class than non-melanoma controls. Among males alone, social class, occupational sun exposure and severe sunburn were significantly different from controls, while recreational sun exposure was not significantly different. Among females, only severe sunburn differed significantly between patients and controls. Skin type was not a significant factor.

2. Individuals with histories of multiplicative severe sunburns were 2.8 times more likely to have melanoma (95% relative risk confidence interval 1.1-7.4) than individuals without histories of severe sunburns.

3. The authors commented that "Questions about severe sunburn were confined to the 5-year period before the development of the primary tumor, as it was felt that distant memory might well be inaccurate. It is likely, however, that patients with a tendency to severely sunburn will have had more than one such episode in their lifetime and this was in many cases confirmed by the patients." At the end of the interview, only 24 percent of cases reported that they thought sunlight exposure and/or sunburn might be related to their disease thus in the minds of the authors eliminating concern with bias in response.

4. The authors concluded that "This study thus provides evidence to suggest that short intense episodes of UV exposure resulting in burning may be one of the aetiological factors involved in subsequent development of melanoma."

Methodology:

A case-control study of 113 patients with superficial spreading melanoma (SSM) and nodular melanoma (NM) in the west of Scotland between 1978 and 1980 and 113 age- and sex-matched control patients. Patients with lentigo malignant melanoma were excluded. Interviewer questionnaire included information on skin, eye, and hair color, skin responses to sunlight exposure, total hours of occupational and recreational sun exposure in winter and summer, weeks in warm climate and history of severe and prolonged sunburn (in 5-year period before development of primary tumor), and social class. Thirty-three percent of the cases and 27 percent of the controls had never left the UK.

Experimental Design and Analysis Issues:

The matched case-control data was analyzed using conditional multiple logistic regression, which yielded estimates of relative risk.

For Result 1:

In the male group, three factors were significant at the 5% level in predicting increased melanoma risk--social class (negative association), occupational sun exposure (negative asociation), and severe sunburn (positive association). Among females, only one factor, severe sunburn, was significant at the 5% level. For the combined data set, social class (negative association), recreational sun exposure (negative association), and severe sunburn (positive asociation) were significant predictors of excess melanoma risk. Skin type was not a significant factor in the group as a whole or in males and females separately. The number of holidays and days spent in summer climates were similar between cases and controls. Overall, 56% of the melanoma patients had histories of severe burning (vs. 22% of controls). A history of severe burning was given by 26 (50 percent) of male cases and 12 (23 percent) of controls; and by 37 (61 percent) of female cases and 12 (20 percent) of controls.

For Results 2:

The relative risk of melanoma for an individual with a history of severe sunburn (in the 5-year period before develoment of primary tumor) was 2.8 with a 95% confidence interval of 1.1-7.4 ($\text{Exp}(B_i)=2.8$). "This may be associated with enhanced photosensitivity which is not correlated to skin type."

Reference:

Morton, W., and Starr, G.F. "Epidemiologic Clues to the Cause of Melanoma." West. J. Med. 131:263-269 (1979).

Investigator Results:

1. Risk of melanoma was highest in a moist, flat residential area in Oregon's Lane County urban portion and in its agricultural area. Overall melanoma risk was higher in urban areas. The incidence pattern strongly suggested local cycles of etiologic agents in subcounty units.

2. An apparent widespread rural epidemic was identified beginning in 1965 and lasting several years.

Methodology:

A descriptive analysis of 146 new melanoma cases from 1958-1972 obtained from pathology files representing all six Lane County hospitals, coastal portions of Lane County, the Veterans Administration Hospital tumor registry in Portland and the University of Oregon Medical School tumor registry in Portland. Ocular melanomas were added to the data. Mortality from cutaneous or ocular melanoma from 1958-1972 was also reviewed for Lane County residents.

Census tracts, to which each case was assigned, were grouped into geographic regions or socioeconomic strata. Incidence rates were directly age-standardized to the 1970 U.S. population.

Experimental Design and Analysis Issues:

A descriptive analysis of melanoma incidence and mortality data.

For Result 1:

Lane County incidence rate ($5.5/10^5$/year) and mortality rate ($1.4/10^5$/year) increased from 1958-1972 (except for male mortality from 1968-1972). Male mortality was consistently greater than female due mostly to high death rates among male 75-84 years-olds. Total incidence for 1968-1972 exceeded Third National Cancer Survey incidence for 1961-1971 by 67.4% (males) and 54.5%(females). Age-distributions for incidence show maximum incidence rates for 75-84 year-olds (males) and 65-74 (females) with secondary peaks from 35-44.

Geographic analysis by census tract of incidence and mortality rates indicated that place of residence influenced melanoma risk. "Very high" incidence rates ($10.5/10^5$ +) occurred in urban areas of north and northwest Eugene, whereas "high" rates ($7.0/10^5$ to $10.4/10^5$) occurred in flat, moist bottom land adjacent to "very high" risk areas in urban tracts (with history of vigorous insect control measures) and in the rural agricultural area. Effect of socioeconomic status

on melanoma distribution was weaker and more inconsistent than geographic pattern.

For Result 2:

An analysis of rates for four groups (1958-1961, 1962-1964, 1965-1968, and 1969-1972) by region (rural with 5 subdivisions and urban with 7 subdivisions) indicated the onset of a rural epidemic in 1965, two similar incidence peaks (decade apart) in rural north, and a consistently greater incidence in north Eugene than in county as a whole. Otherwise, incidence data displayed significant local deviations from respective county-wide rates. Investigation of potential seasonal patterns of occurrence (by diagnosis date) showed some grouping of cases during summer months from 1958-1963 but a general year-round pattern in subsequent years. There were differences in occurrence by sex but no seasonal pattern for either.

Reference:

Moss, A.L.H. "Malignant Melanoma in Maoris and Polynesians in New Zealand." Br. J. Plast. Surg. 37:73-75 (1984)

Investigator Results:

1. The lower limb was the predominant site for primary malignant melanoma (MM) tumors (13 out of 24 Maori and Polynesian MM patients), with almost half of these occurring in the sole. Half of the six head and neck MM primary tumors occurred in the oral mucosa.

2. Based on the medical history of 24 patients, MM in Maoris and Polynesians appeared to have poor prognoses.

Methodology:

Collection over a 19-year period from the National Cancer Registry of the National Health Statistics Centre, the New Zealand Health Statistics, and New Zealand Hospital Boards of information on 21 Maoris and Polynesians with 24 primary MMs. Histologic material, where available, was reviewed and autopsy reports were used to confirm the diagnoses on the other patients. Patient information included race, anatomical distribution, stage at presentation, depth of tumor invasion, and follow-up mortality.

Experimental Design and Analysis Issues:

A simple descriptive summary of a small, probably non-randomly selected populaton of 24 Maoris and Polynesians presenting with MM.

For Result 1:

The predominant primary tumor site was the lower limb (13 of 24 patients) for which the sole was most common (6 of 13). Three of the 6 head and neck tumors were of the oral cavity. There were 11 nodular and 5 superficial spreading MMs, and 8 unclassified lesions.

For Result 2:

Only 2 patients survived longer than five years. One patient was lost to follow-up at 6 years. Of the patients known to have died, 13 died of their malignancy within 52 months. It was concluded that Maoris and Polynesians, perhaps because of their general reluctance to seek medical advice, have poor prognoses for MM.

Reference:

Malec, E., and Eklund, G. "The Changing Incidence of Malignant Melanoma of the Skin in Sweden, 1959-1968." Scand. J. Plast. Reconstr. Surg. 12:19-27 (1978).

Investigator Results:

1. The age- and sex-adjusted incidence of malignant melanoma (MM) of the skin increased from 1959 to 1968 by 7% per year, with most pronounced increases for the trunk and legs in both sexes.

2. The ages for which incidence increases were greatest were 30-39 for females and 40-64 for males.

3. The incidence in females on the legs was higher during the summer months.

4. Negligible changes in MM mortality were observed from 1959 to 1968.

Methodology:

A descriptive analysis of 3,289 MM patients (1,534 M, 1,755 F) registered in the Swedish Cancer Registry between 1959 and 1968. Notification of all cancer cases to the Registry is required under a special decree. All cases were histologically confirmed. The clinical reports provided information on primary tumor site, metastases, and sex. Additional information on 1,409 patients (808 M, 601 F) whose deaths were from melanoma was obtained from the Swedish Bureau of Statistics.

Experimental Design and Analysis Issues:

A straightforward, descriptive analysis of MM incidence rates between 1959 and 1968.

For Result 1:

The annual MM age- and sex-adjusted incidence rate (per 100,000) rose by 7.0% for both males and females between 1959 and 1968. The rise in incidence rate was highly significant ($r = 0.94$ for males, $r = 0.90$ for females). The rate was higher for women. The trunk was the most frequent site in males and the leg in females. The correlation between incidence rate and year was highly significant for the trunk and head and neck in males and the trunk in females (p less than 0.001) and moderately significant for the legs in females (p less than 0.01).

For Result 2:

The increase in incidence with age was significant in many age groups: it was highly significant in males between 50 and 54, 55 and 59,

and 60 and 64 and highly significant in females between 30 and 34 and 50 and 54. The most pronounced increases were for 40-64 year-old males and 30-39 year-old females.

For Result 3:

Based on month of tumor diagnosis information, a highly significant increase in MM incidence on the lower extremity and totally for females was observed when summer months (June-August) were compared to winter months (December-February). For leg melanoma, the seasonal difference was highly significant (p less than 0.001). No seasonal increase was observed in males.

For Result 4:

Age-standardized mortality rates for MM were fairly constant for both sexes and were substantially lower than corresponding incidence rates.

Reference:

Magnus, K. "Incidence of Malignant Melanoma of the Skin in the Five Nordic Countries: Significance of Solar Radiation." Int. J. Cancer 20:477-485 (1977).

Investigator Results:

1. A descriptive comparison of malignant melanoma (MM) incidence in five Nordic countries showed similar incidence rates in Denmark, Norway and Sweden, and lower incidence rates in Finland and Iceland.

2. Increasing incidence rates were clearly observed for successive birth cohorts, with a doubling of the rate occurring in a period of 10-17 years.

3. The anatomic distribution of MM tumors differed between males and females: the predominant tumor site was the neck/trunk for males and the lower limb for females. Increasing MM incidence was observed for the neck/trunk among males and the lower limbs among females. Only a slight increase was seen in MM of the face. Authors concluded that there had been a real increase in MM incidence in all Nordic countries which was in accordance with the hypothesized association between solar radiation and risk of MM.

Methodology:

Analysis of time trends in MM incidence data based on 13,101 cases recorded in cancer registries of Denmark, Finland, and Norway (1957-197_), Iceland (1955-1974), and Sweden (1959-1971). Lentigo maligna was excluded except in Sweden's data. Tumors were classified by anatomical site. Indirect age-standardized incidence rates (based on age-specific rates pooled for all countries) were calculated.

Experimental Design and Analysis Issues:

A descriptive analysis of MM incidence rates in five Nordic countries.

For Result 1:

Annual age-adjusted MM incidence rates (both sexes) were similar in Denmark, Norway, and Sweden (4.5-5.0 per 10^5) from late 1950's to early 1970's. The rate in Finland was $3.4/10^5$ and in Iceland about $2/10^5$. Only in Denmark and Iceland was there a marked sex difference (female incidence exceeded male incidence).

For Result 2:

The time trend of incidence in Iceland was not statistically significant. For the four other countries, annual percentage increases ranged from 4.1% to 7.0%, corresponding to a doubling of the MM incidence rate in 17 and 10 years, respectively. There was no significant difference in

rates by sex. Incidence rates generally increased steeply in adolescence, levelled off in middle age, and rose again in later years. This pattern was most evident in high incidence countries and for females.

For Result 3:

When grouped by tumor site, differences were observed between sexes. Excess incidence was observed for the neck/trunk in males, and the lower and upper limbs in females. There was no systematic difference for facial tumors. The distribution of cases by sex and site is similar for the five countries, with neck/trunk and extremities accounting for about 75% of all cases, and the face 15-20%. A slight or unnoticable increase in facial MM was observed in all countries except Sweden where incidence increased (possibly due to classification of neck tumors as face tumors in the data set for Sweden). For neck/trunk tumors there was a consistent increase, more prominent for males. A doubling of incidence rates was observed over a 7-9 year period for male neck/trunk tumors and female lower limb tumors (Denmark, Norway, and Sweden).

Reference:

Magnus, K. "Habits of Sun Exposure and Risk of Malignant Melanoma: An Analysis of Incidence Rates in Norway 1955-1977 by Cohort, Sex, Age, and Primary Tumor Site." Cancer 48:2329-2335 (1981).

Investigator Results:

1. Malignant melanoma (MM) incidence increased in Norway from 1955-1977 by approximately 7% per year for both sexes. Incidence increases and birth cohort variations were greater for trunk and lower limb melanomas than for face and neck melanomas.

2. The shape of the age-specific incidence rate curves for cohorts also differed for these sites, indicating that carcinogenic exposure through life differed for the face-neck and the trunk-lower limb. For generations born 1930-1949, MM incidence per unit skin area was greater for trunk-lower limb than for face-neck. The authors suggested that both cumulative dose and solar radiation intensity may be significant factors in MM.

Methodology:

A descriptive analysis of 5,108 new MM cases (99.5% histologically confirmed) reported in the Cancer Registry of Norway from 1955-1977 by primary site, sex, age, and birth cohort.

Experimental Design and Analysis Issues:

A clear descriptive analysis of MM incidence data from Norway by age, site, sex, and birth cohort.

For Result 1:

The distribution of cases by sex and primary site showed male excess of trunk melanomas and female excess of lower limb melanomas. Age-adjusted incidence rates increased at a fairly constant, similar rate for both sexes (approximately 7% per year), more than quadrupling from 1955-1977. Increasing age-adjusted incidence rates by site indicated a doubling of face-neck melanoma, and a five-fold increase for trunk and lower limb melanomas. Incidence increases were not as linear by melanoma site subgroups due to smaller sample sizes and systematic deviations from linearity. For trunk and lower limb melanomas, the annual increases in incidence rates by sex were more similar from 1970-1977 than from 1955-1970.

For Result 2:

Age-specific incidence curves showed increasing incidence in adolescence, a leveling off in middle-age and further increases in older ages. A comparison of incidence rates for birth cohorts born before 1900, from 1900-1930, and after 1930, showed increasing risk of MM

in later cohorts with greatest increases occurring from 1900-1930. Cohort variations were minimal for face-neck melanomas, but were clearly evident for trunk and lower limb melanomas. Incidence rates for trunk melanomas among those born 1920-1929 were over six times greater than among those born 1900-1929.

The ratio of age-specific trunk-lower limb to face-neck incidence rates by birth cohort indicated that the ratio of carcinogenic exposure to the two site areas varied by year of birth. A comparison of incidence per area of primary site for face-neck melanomas and trunk melanomas (males) or lower limb melanomas (females) indicated a common cancer pattern for face-neck (gradual increase to age 50, steep rise thereafter) but a unique pattern for the 1930-1949 trunk and lower limb cohorts (steep increases to age 40, gradual increases thereafter). Face-neck melanomas were higher among the 1890-1909 cohort than the 1930-1949 cohort.

Reference:

Moss, A.L.H. "Malignant Melanoma in Maoris and Polynesians in New Zealand." Br. J. Plast. Surg. 37:73-75 (1984)

Investigator Results:

1. The lower limb was the predominant site for primary malignant melanoma (MM) tumors (13 out of 24 Maori and Polynesian MM patients), with almost half of these occurring in the sole. Half of the six head and neck MM primary tumors occurred in the oral mucosa.

2. Based on the medical history of 24 patients, MM in Maoris and Polynesians appeared to have poor prognoses.

Methodology:

Collection over a 19-year period from the National Cancer Registry of the National Health Statistics Centre, the New Zealand Health Statistics, and New Zealand Hospital Boards of information on 21 Maoris and Polynesians with 24 primary MMs. Histologic material, where available, was reviewed and autopsy reports were used to confirm the diagnoses on the other patients. Patient information included race, anatomical distribution, stage at presentation, depth of tumor invasion, and follow-up mortality.

Experimental Design and Analysis Issues:

A simple descriptive summary of a small, probably non-randomly selected populaton of 24 Maoris and Polynesians presenting with MM.

For Result 1:

The predominant primary tumor site was the lower limb (13 of 24 patients) for which the sole was most common (6 of 13). Three of the 6 head and neck tumors were of the oral cavity. There were 11 nodular and 5 superficial spreading MMs, and 8 unclassified lesions.

For Result 2:

Only 2 patients survived longer than five years. One patient was lost to follow-up at 6 years. Of the patients known to have died, 13 died of their malignancy within 52 months. It was concluded that Maoris and Polynesians, perhaps because of their general reluctance to seek medical advice, have poor prognoses for MM.

Reference:

Nicholls, E.M. "Development and Elimination of Pigmented Moles, and the Anatomical Distribution of Primary Malignant Melanoma." Cancer 32:191-195 (1973).

Investigator Results:

The number of pigmented moles per person increased to age 15 (males) and age 20-29 (females), with peak values reached soonest on most exposed parts of body. The number then decreased to almost no moles in 80 year-olds. Depigmented spots and nevi with definite/faint halos were more common soon after peak nevi values had been reached.

Methodology:

A study population of 1,518 individuals (570F, 948M) was selected and the number of moles, site of moles, age and sex were recorded. The source of the study population and the selection method were not identified.

Experimental Design and Analysis Issues:

A simple descriptive analysis of data. The analysis summarized the age at which the number of moles was greatest and the body sites where moles were most prevalent.

Reference:

Paffenbarger, R.S., Wing, A.L., and Hyde, R.T. "Characteristics in Youth Predictive of Adult-Onset Malignant Lymphomas, Melanomas, and Leukemias: Brief Communication." JNCI 60:89-92 (1978)

Investigator Results:

Outdoor environmental exposure was associated with increased relative risks of malignant melanoma (MM) based on a comparison of data from 45 Harvard University and University of Pennsylvania male alumni who died from MM and four times as many surviving classmates.

Methodology:

A cohort of 50,000 male alumni of Harvard University (entering classes 1916-1950) and the University of Pennsylvania (entering classes 1931-1940) was retrospectively followed-up with less than one percent lost to follow-up. Forty-five alumni were identified who had died from MM. Using this data, relative risks were estimated in a case-control study using the 45 MM deaths as cases and the 180 surviving classmates born in the same year as controls.

Potential predictive factors obtained from university records included history of contagious disease, familial tendencies, physical attributes, personal traits, and social influences. Causes of death were identified and classified from official death certificates.

Experimental Design and Analysis:

From the cohort, 45 men who had died from malignant melanoma were identified (incidence rate $2.6/10^5$ person-years). The potential predictive characteristics examined for the cases and controls were history of eight contagious diseases (e.g., measles, mumps), parent dead, only-child, two or more siblings, tonsillectomy, ponderal index, cigarette smoker, coffee drinker, exercise, outside work, and New England origin. Of these, only outdoor employment before college was significantly associated with malignant melanoma, indicating a relative risk 3.9 times greater than that of men not reporting outdoor work.

Reference:

Schreiber, M.M., Bozzo, P., and Moon, T. "Malignant Melanoma in Southern Arizona." Arch. Dermatol. 117:6-11 (1981)

Investigator Results:

1. The crude incidence rate of malignant melanoma (MM) in southern Arizona increased from $6.5/10^5$ in 1969 to $28.6/10^5$ in 1978, representing an average annual increase of about 18% (note: the authors state an annual increase of 35%, but 18% is the actual annual rate of increase).

2. The highest tumor incidence was in 50-59 and 60-69 year-olds. The most common site was the back, especially in males. The occurrence of tumors on legs (13% of total) was eight times higher in females.

3. The high melanoma incidence in southern Arizona was "probably due to meteorologic and geographic factors" allowing penetration of UV radiation to earth's surface.

Methodology:

The study included information for 533 MMs in whites from all 8 Tucson hospitals, all 17 practicing Tuscon dermatologists, the 3 private Tucson pathology laboratories and 8 small southern Arizona hospitals from January 1969 to December 1978. Patient information consisted of date of tumor removal or biopsy, age, sex, race, occurrence of metastases and type of treatment used. Tumor information consisted of location, size, color, Clark level of invasion, tumor type, and histologic depth (where available) as well as histopathological confirmation (60% reviewed by authors). Incidence rates were calculated using 1969-1978 annual population figures for six southern Arizona counties from the Arizona Statistical Review.

Experimental Design and Analysis:

A simple descriptive analysis of MM tumor incidence rates in southern Arizona.

For Result 1:

From 1969-1978, 533 MMs were removed from 533 patients (277 M, 256 F). The number of MMs increased from 20 (1969) to 120 (1978), an increasing crude incidence rate of 6.49 to 78.57 (27.20 standardized) per 10^5, respectively.

For Result 2:

The highest percentage of melanomas for the study period occurred in 50-59 (24%) and 60-69 (18%) year-olds. The most common location was the back (31%) with twice as many in males as in females. Other

sites with similar sex distribution were the face (16%) and arms (8%). Leg tumors (13%) were eight times as common in females as in males. "Not specified" melanomas were most common (44%) followed by superficial spreading melanomas (35%), which were common on backs of males and females (13%).

For Result 3:

The annual average increases in southern Arizona melanoma incidence rates (34-37%) were significantly higher than comparable U.S. rates (5%, p less than 0.05) based on Third National Cancer Survey data for 1973-1976. The melanoma distribution by age or sex in southern Arizona did not substantially change from 1969-1978, nor was it substantially different from the total U.S. distribution. "There are certain meteorologic and geographic factors in southern Arizona that allow a greater quantity of UV radiation to reach the earth's surface, thus increasing the incidence of malignant melanoma..." The authors noted that Tucson has more sunlight, more clear days, and less daytime cloudiness than any populated site in North America, and also has low average humidity, high average temperature, relatively high altitude, low latitude and low atmospheric ozone.

Reference:

Pathak, D.R., Samet, J.M., Howard, C.A., and Key, C.R. "Malignant Melanoma of the Skin in New Mexico 1969-1977." Cancer 50:1440-1446 (1982)

Investigator Results:

1. Malignant melanoma (MM) incidence rates varied with ethnicity. Rates for non-Hispanic whites (Anglos) exceeded comparison U.S. rates, and were approximately six times higher than for other ethnic groups. Annual incidence rates for Hispanics, American Indians, and blacks (both sexes) ranged from $0.0\text{-}1.8/10^5$.

2. Lower extremities were the most common MM sites in Anglo women, while the trunk was most common in Anglo men. For Hispanic men and women, the trunk was the most common site.

3. Statistically significant increasing incidence was observed only for Anglo women.

4. MM mortality rates varied widely during the study period and did not correlate with incidence rates.

Methodology:

A descriptive analysis of incidence and mortality rate data was conducted for 495 New Mexico MM cases reported in the New Mexico Tumor Registry (NMTR) from 1969-1977. Factors analyzed included ethnicity, sex, age, and site distribution. Ethnicity of MM cases was determined from reporting facilities or hospital charts (American Indians), NMTR records or surnames (Hispanics), and medical records (Anglos). The 1970 Census and 1975 University of New Mexico Bureau of Business and Economic Research population estimates were used to estimate age-standardized (to 1970 U.S. population) MM incidence rates.

Mortality data was obtained from the New Mexico Bureau of Vital Statistics, which included information on ethnicity. Mortality rates were calculated in the same manner as incidence rates. The ratios of New Mexico MM incidence rates to white rates from the Third National Cancer Survey and from the SEER program were tested by a method based on the Poisson distribution. Gart's exact test was used to assess incidence ratios adjusted for age, sex, and ethnicity. Time trends in incidence and mortality were assessed with a log-transformed linear regression model. An exact test described by Zelen was also used.

Experimental Design and Analysis Issues:

A descriptive analysis of incidence and mortality rate data for New Mexico MM cases.

For Result 1:

Anglo incidence rates (mean $8.7/10^5$ male; $9/10^5$ female) were much higher than for other ethnic groups (e.g., mean Hispanic $1.2/10^5$ male; $1.8/10^5$ female). The overall Anglo-to-Hispanic incidence ratio (Gart's exact method), age- and sex-adjusted, was 6.0 (p less than 0.01). The differences in incidence were consistent with a protective effect of skin pigmentation. Except for American Indians, female incidence rates exceeded male rates in each group. Age distributions of MM diagnosis were similar for Anglos and Hispanics. Anglo rates exceeded comparison U.S. rates (for 1969-1971 and 1973-1976) whereas Hispanic rates were below comparable rates.

For Result 2:

For Anglos and Hispanics, site distribution varied by ethnicity and sex. Site-specific, sex-adjusted ratios of Anglo-to-Hispanic incidence (calculated with Gart's exact method) indicated significantly higher (p less than 0.01) Anglo incidence at each site. Incidence ratios were 10.0 (head and neck), 6.2 (trunk), 5.6 (upper extremities), and 24.9 (lower extremities). Male-to-female, ethnicity-adjusted incidence ratios showed similar risk for head and neck MM, higher male risk for trunk MM (ratio = 1.6, p less than 0.01), higher female risk for upper extremities (ratio = 0.61, p less than 0.05) and lower extremities (ratio = 0.23, p less than 0.01). The overall male-to-female ratio, age- and ethnicity-adjusted, was not significantly different from one.

For Result 3:

Age-specific incidence rates, calculated for Anglos only, increased with age for all sites combined. Age-specific rates for head and neck MM increased slowly to age 50 and rose steeply thereafter in males and females. Incidence rates for male trunk rose until 50-59 and then declined. In women, rates for lower extremities increased up to 60-69 years. In both sexes, the age-rate ralationship for head and neck MM was significantly different than for trunk MM.

A logarithmic regression model showed a statistically significant incidence rate increase from 1969-1977 for Anglo women (5.5%/year, p less than 0.05) but not for men (6.8%/year, p = 0.10). Zelen's exact method did show a statistically significant (p less than 0.05) incidence rate increase for Anglo men.

For Result 4:

Annual age-adjusted MM mortality rates did not exhibit trends from 1969-1979 and were not consistent with age-adjusted incidence rates for Anglos and Hispanics.

Reference:

Pondes, S., Hunter, J.A.A., White, H., McIntyre, M.A., and Prescott, R.J. "Cutaneous Malignant Melanoma in South-East Scotland." Quart. J. Med. Winter 103-121 (1981)

Investigator Results:

1. In a retrospective clinical follow-up of 477 cutaneous malignant melanoma (MM) patients in south-east Scotland, mean annual incidence during 1971-1976 was 4.6/100,000 with female incidence almost twice as high as males.

2. Median age at presentation was in 6th decade (both sexes), with 88% having clinical Stage I disease. One-third of all primary lesions were on female lower leg. Superficial spreading melanoma (SSM) was the most common growth pattern.

3. Overall 5-year survival rate for males (48%) was significantly less than for females (67%). Other factors with effects on prognosis were thickness of primary lesion (best index of prognosis), age, tumor site, and mitotic rate. Improved survival may be achieved better by earlier diagnosis and treatment than by change in management.

Methodology:

A descriptive analysis of a retrospective clinical follow-up of 477 patients (315 F, 162 M) presenting with MM from 1961-1976 in south-east Scotland. Cases were identified primarily from 3 pathology departments, the regional cancer registry and the Lothian Health Board's list of hospital admissions. Incidence rates were calculated for 1971-1976 patients. Case information included sex, age, address, site of primary lesion, clinical stage of disease, operative treatment, date and site of first recurrence. Follow-up information was from general practitioners, case records, regional cancer records, and death certificates. When available, specimens were histologically reviewed and used to determine histogenic type, primary tumor depth, level of penetration, and mitotic activity.

Experimental Design and Analysis Issues:

For Result 1:

Mean annual incidence for males and females from 1971-1976 was $4.6/10^5$, $3.2/10^5$ for males and $5.8/10^5$ for females. Fluctuations in incidence rates were due to the small number of cases.

For Result 2:

Clinical stage of disease at presentation (in 385 of 404 case records) was Stage IA and II local disease (88%), Stage II regional node disease (10%), and Stage III disease (2%). The age/sex specific incidence rates showed little incidence change between 30-70 years ($3.1-6.0/10^5$

males, 7.7-9.3/10^5 females) and higher incidence over 70 years (11.4-16.1/10^5 males and females). Nearly a third of all tumors were on the female leg. Trunk melanomas represented 27% of male tumors, 14% of female tumors. Head and neck melanomas occurred significantly later than tumors at other sites and this was the only site where mean age of sexes differed (p less than 0.05).

Distribution of tumor size was similar for males and females, but larger tumors were more frequent in older patients. SSM was most common (51%), followed by nodular melanoma (35%), and lentigo maligna melanoma (9%). The distribution of histogenic type was similar in each sex. There was no significant association between sex and lesion thickness and no apparent relationship between size and depth (less than 3.5 mm) of tumors. Deep tumors were most common on the trunk, thin tumors were most common on head, neck, and upper limbs. Deeper tumors and nodular melanomas had higher mitotic indexes.

For Result 3:

Five-year survival rates in men (48%) and women (67%) were significantly different (p less than 0.001). The survival prognosis worsened in women after 70 years, and in men after 50 years. Survival varied significantly (p less than 0.01) by site, with decreased survival for trunk melanoma patients (in females, 39% trunk vs. 76% head and neck).

Depth of primary tumor was most important prognostic factor, with 97% 5-year survival rate for tumors less than 0.5 mm deep vs. 38% for tumors greater than 3.5 mm deep.

High mitotic index was also associated with poor prognosis, even when depth was taken into account (p less than 0.01). There were no significant differences in survival for three patient cohorts (1961-65, 1966-70, 1971-76).

Reference:

Reintgen, D.S., McCarty, K.S., Cox, E., and Seigler, H.F. "Malignant Melanoma in the American Black." Curr. Surg. 40:215-217 (1983)

Investigator Results:

1. The median survival (MS) time for 31 blacks with melanoma was 31.4 months, with a 5-year survival rate of 22%. Black men (MS = 26.3 months) and Stage II patients (MS = 10.5 months) had worse prognoses than black women (MS = 40.0 months) and Stage I patients (MS = 41.4 months).

2. Blacks had statistically significant lower actuarial survival rates than whites ($p = 0.000001$) which could not be accounted for by differences in age, sex, stage of disease at diagnosis, Clark's level or primary site. The most common site for blacks was the foot vs. the trunk for whites.

Methodology:

A descriptive analysis of survival rates among 31 black melanoma patients (15M, 16F) registered at the Duke University Comprehensive Cancer Center since 1972 and 100% followed-up for periods ranging from 6 months to 10 years. Information included age at diagnosis, primary site, sex, disease stage, and Clark's level. The number of Caucasians registered at the Cancer Center and used in the study were not identified, nor were their follow-up periods indicated.

Experimental Design and Analysis Issues:

Acturial survival curves were constructed for black and white populations and the Cox-Mantel rank test was used to test for statistical significance.

For Result 1:

No additional information provided.

For Result 2:

Black actuarial survival rates were lower than white survival rates ($p = 0.000001$) even when adjusted for age ($p = 0.0007$), sex ($p = 0.0002$), Clark's level ($p = 0.0003$), or primary site ($p = 0.001$). When controlled for Clark's level, the mean survival time for whites was 86.1 months compared to 26.8 months for blacks.

The most common site for blacks was the foot (60% plantar or subungual), whereas for Caucasions the predominant site was truncal. Blacks presented with more advanced disease stage (64% Stage I vs. 85.3% whites) and showed more invasive disease (88% Clark's level 4 or 5 vs. 60% for whites).

Reference:

Reynolds, P. and Austin, D.F. "Epidemiologic-Based Screening Strategies for Malignant Melanoma of the Skin." Advances in Cancer Control: Epidemiology and Research. Alan R. Liss, New York (1984). Pp. 245-254

Investigator Results:

Individuals with 12 or more large moles, previous diagnosis of basal or squamous cell skin cancer, parental history of skin cancer and propensity to burn with sun exposure were at high risk for melanoma. A screening program for individuals at high risk for developing melanoma was proposed.

Methodology:

Relative risk and odds ratios were calculated in a case-control study of 31 malignant melanoma (MM) employees of the Lawrence Livermore National Laboratory (LLNL) diagnosed between 1969 and mid-1980 (cases) and 110 LLNL controls matched by age, race, and sex. The data which was collected by mailed questionnaire and personal interview included presence of moles, previous diagnosis of basal or squamous cell cancer, parental history of skin cancer, propensity to sunburn/tan, eye, hair and skin color, and freckling or Celtic heritage.

Experimental Design and Analysis Issues:

Four familial risk factors were significantly associated with MM: presence of moles greater than 1/2 cm diameter (p less than 0.0005) previous diagnosis of basal or squamous cell skin cancer, parental history of skin cancer, and propensity to burn rather than tan with sun exposure (all p less than 0.05). With increasing number of moles, risk of having MM increased. Individuals with 12 or more moles were 41 times more likely to have MM (p less than 0.005).

Small subgroups with 12 or more moles and the identified familial risk factors may experience over a 200-fold risk. Comparison of cases with controls and another random sample of white Contra Costa County residents (CA) indicated that about 2% or less of general white population may be at high risk by having 12 or more large moles. The risk factors represented criteria which could easily be used for melanoma screening. The proposed screening program would consist of dermatological examination, health education, collection of questionnaire/interview data, and follow-up.

Reference:

Scotto, J., and Nam, J. "Skin Melanoma and Seasonal Patterns." Am. J. Epi. 111(3): 309-314 (1980)

Investigator Results:

A strong seasonal pattern of melanoma incidence with summertime peak was observed for females, particularly those under 55 years and those of all ages for melanomas of the upper and lower extremities. For males, a seasonal pattern with summertime peak was observed only for melanomas of the upper extremities.

The authors concluded that it was difficult to determine if seasonal melanoma patterns resulted from promoting effects of UV-B exposure or from enhanced recognition during summer months.

Methodology:

Data were obtained from the Third National Cancer Survey for nine U.S. locations during 1969-1971 of 2,168 skin melanomas in whites for which month of first diagnosis, age, sex, and anatomic site were reported. A sine curve first-order harmonics model was used to test for seasonal patterns. The model was:

$$y = \frac{1}{k} + b \sin\left(P + \frac{2]}{k} x\right)$$

where y = proportional distribution of skin melanomas for interval x (e.g., month), k = no. intervals in full cycle, b and P are amplitude and phase angle, respectively (estimated by maximum likelihood method). A chi-square goodness-of-fit test was used to verify the fit of the model to the data, and if not rejected was followed by Edwards' test of b.

Experimental Design and Analysis:

A statistical analysis of the fit of the first-order harmonics model to the data (using chi-square or Edwards' test) was conducted by sex and anatomic site.

Among females, over 20% of all cases were diagnosed during summer months (June and July) while less than 14% were diagnosed during winter months (December and January). The seasonal pattern among females was statistically significant ($p = 3 \times 10^{-5}$ Edwards' test). No sustained peak or trough was observed for males.

When monthly seasonal trends by anatomic site were examined, female seasonal patterns for upper and lower extremities were statistically significant (p less than 0.001) while for males the upper extremity pattern did not quite achieve statistical significance (p = 0.11). When analyzed for bi-monthly seasonal patterns, both male and female trends for upper extremities were statistically significant (p = 0.07 and p = 0.003, respectively).

Analysis of seasonal patterns by age (under 55 or 55 and over), indicated significant trends for females only ($p = 0.002$ for less than 55, $p = 0.004$ for 55 and over). Among females less than 55, significant peaks in summer were observed for lower extremities ($p = 0.001$) and upper and lower extremities pooled ($p = 0.0003$), but not for trunk or face and head.

By geographic region, female seasonal patterns were most significant in the south ($p = 0.008$), followed by the north ($p = 0.03$), but were not significant in mid-laditude region.

Reference:

Shaw, H.M., McGovern, V.J., Milton, G.W., Farago, G.A., and McCarthy, W.H. "Histologic Features of Tumors and the Female Superiority in Survival from Malignant Melanoma" Cancer 45:1604-1608 (1980)

Investigator Results:

1. In 780 Stage I malignant melanoma (MM) patients, a direct correlation between 5-year survival rate and tumor thickness was observed in males and females, but females had higher survival rate at each thickness level. Average tumor thickness was significantly less in females due to preponderance of thin lesions in females and thick lesions in males.

2. No significant sex differences in survival were apparent when evidence of regression, histogenic type, and mitotic activity were examined. Prognosis for regressing and nonregressing lesions was markedly different only for very thin lesions.

Methodology:

A descriptive analysis of the survival rates of 780 patients (372M, 408F) who presented with Stage I MM at the Sydney Hospital Melanoma Clinic between January 1950 and March 1978. Patient information consisted of tumor thickness (0.1-0.7 mm (196 patients), 0.8-1.5 mm(225), 1.6-3.0 mm (220), and 3.1+ mm (139)), evidence of regression, histogenic type and grade of mitotic activity. Cumulative survival rates were calculated (life table method) and differences were statistically analyzed (logrank method).

Experimental Design and Analysis Issues:

For Result 1:

The 5-year survival rate was significantly higher for females (82.7%) than for males (66.6%) (p less than 0.001). Five-year survival rates also differed for males and females at all tumor thickness levels. Average tumor thickness was less in females due to preponderance of thin lesions in females (62% vs. 37.2% in males, p less than 0.001) and thick lesions in males (56.8% vs, 43.2% in females, p less than 0.02). The largest difference in 5-year survival rates was for lesions 3.1+ mm thick (63.2% males, 42.9% females).

For Result 2:

Significantly more lesions in males than females had evidence of regression (42.9% vs. 28.9%, respectively, p less than 0.001), and this occurred for all thicknesses. Evidence of regression was slightly, but not significantly, associated with improved survival rates. There was no difference between males and females 5-year survival rates when histogenic type or grades of mitotic activity were examined.

Reference:

Shiu, M.H., Schottenfeld, D., Maclean, B., and Fortner, J.G. "Adverse Effect of Pregnancy on Melanoma." Cancer 37:181-187 (1976)

Investigator Results:

No significant difference in 5-year survival rate for Stage I melanoma patients was observed between nulliparous, parous nonpregnant, and pregnant females. For Stage II patients, a significantly lower 5-year survival rate (p less than 0.05) was observed for pregnant patients (29%) and parous patients who had lesion activation in a previous pregnancy (22%) as compared with that for nulliparous patients (55%) and other parous patients (51%).

Differences in survival rates and symptoms in Stage II patients (e.g., bleeding, ulceration, irritation, and elevation of lesion) "strongly suggest an adverse influence of pregnancy among females with Stage II melanoma."

Methodology:

A descriptive analysis of survival rates in 251 15-45 year-old female cutaneous melanoma patients (165 Stage I, 86 Stage II) who received treatment at Memorial Sloan-Kettering Cancer Center from 1950 to 1969 and for which accurate recorded data on pregnancy at time of admission was available. The effect of pregnancy on prognosis was examined through four study groups: nulliparous women, parous women with no activation of lesion during previous pregnancy, parous women with definite activation of lesion during previous pregnancy and women with melanoma admitted and treated during pregnancy. Statistically significant differences were evaluated using the chi-square test with Yates correction.

Experimental Design and Analysis Issues:

A descriptive analysis of 5-year survival rates among female melanoma patients.

The overall 5-year survival rate was 84% for Stage I patients with little difference between study groups. For Stage II patients, overall survival rate was 42%, and was higher for nulliparous women (55%) and parous women with no lesion activation in previous pregnancy (51%). Significantly lower 5-year rates (p less than 0.05) were observed for parous women with lesion activation in previous pregnancy (22%) and for pregnant women (29%) combined when compared with the two other study groups combined.

Age differences for the study groups did not contribute towards differences in 5-year survival rates. Lesions on the lower extremity accounted for 49% of all melanomas. Trunk lesions were more frequent for parous women with prevous lesion activation and pregnant women, especially for Stage II patients. Parous patients with previous lesion activation

and pregnant patients had more frequent symptoms of melanoma (bleeding, irritation, itching, scaling, ulceration, and/or elevation) but did not have statistically significantly poorer survival rates than asymptomatic patients.

Reference:

Stevens, R.G. and Moolgavkar, S.H. "Malignant Melanoma: Dependence of Site-Specific Risk on Age." Am. J. Epi. 119:890-895 (1984)

Investigator Results:

1. Analysis of melanoma incidence data from Connecticut and Denmark showed steadily increasing rates in successive birth cohorts, which accounted for secular trends in melanoma of the trunk and limbs and for differences seen among cross-sectional age curves of various sites.

2. Incidence data did not support hypothesis that melanoma of the face and melanoma of the trunk and limb involve distinct pathogenic mechanisms.

Methodology:

Melanoma incidence data specified by site from Connecticut (1935-1981) and Denmark (1943-1972) were fit to two models that estimated the expected number of melanoma cases at each site (Model I) and the expected number of cases at all sites (Model II) based on age, year of birth, and person-years at risk.

Experimental Design and Analysis Issues:

A study of the fit of incidence data to two age, birth cohort models.

For Result 1:

Age-adjusted incidence rates of melanoma of the trunk increased the most in males, and melanoma of the legs increased the most in females. Model I and Model II fit the data for each population by sex and by site well. The fit of the models were consistent with an age dependence that was similar for each site. The slope of estimated age effects was not close to zero for any individual site or all the subsites fitted simultaneously. The slope of the regression line of log(age effect) on log(age) was 4.3 for males and 3.5 for females in Connecticut and 4.5 for males and 4.2 for females in Denmark. In both Connecticut and Denmark, the male slope was greater than the female slope, indicating more rapid incidence increases with age in males than females.

For Result 2:

The results showed that increases in melanoma of trunk and limbs could be described by cohort effects. The relationship of age to incidence was the same in all sites, thus different pathogenic mechanisms did not necessarily explain site-specific melanoma incidence data.

Reference:

Swerdlow, A.J. "Incidence of Malignant Melanoma of the Skin in England and Wales and its Relationship to Sunshine." Br. Med. J. 2:1324-1327 (1979)

Investigator Results:

1. Mean skin malignant melanoma (MM) incidence in 14 English health regions and Wales correlated negatively with latitude and positively with hours of sunshine, suggesting that exposure to sunshine was an important causal factor.

2. Male and female MM incidence within a region tended to show similar yearly fluctuations implying a common factor affecting incidence in both sexes with a short latent period of action.

3. Incidence of MM in females correlated positively with hours of sunshine 2 years earlier, indicating that exposure to sunshine may cause melanoma after about a 2-year induction period.

Methodology:

For Oxford Region residents, age-standardized sex-specific annual MM incidence rates for 1952-1975 were calculated using 1961 Oxford Region population, incidence data from the Oxford Cancer Registry and age-specific 1955-1974 population data from published sources. For other regions of England and Wales, crude incidence rates for 1955-1969 in the Southwestern Region and for 1962-1970 in the remaining regions and in England and Wales overall were used. Mean incidence, the rate of increase in incidence, and the expected incidence in each year were calculated for each region. Mean daily hours of bright sunshine were estimated for each region from the meteorological office "District values station" nearest to main population centers. For England and Wales, overall sunshine hours were obtained from the Registrar General's Statistical Review of England and Wales.

For each region for males and females separately, mean incidence and rate of incidence increase were correlated with latitude of main regional population center and with hours of sunshine in the region 2 years earlier. Correlations for deviations of male and female rates from expected rates (based on linear regression) were also calculated. Correlations were also calculated between annual deviations from expected melanoma incidence and deviation from expected annual hours of sunshine 1, 2, 3, 4, and 5 years earlier.

Experimental Design and Analysis Issues:

A cross-sectional analysis of the relationship of incidence data and hours of sunshine and latitude in England and Wales.

For Result 1:

Age-standardized MM incidence rates rose for females in all but three regions and in all but four regions for males, the increases generally being greater in females. Both the mean incidence and rate of secular increase in incidence for males and females were negatively correlated with latitude and positively correlated with hours of sunshine in the 15 English regions and Wales combined (several of the correlations were statistically significant).

For Result 2:

The annual female MM incidence correlated positively with annual male incidence in 12 of 15 regions after discounting for long-term trends. The positive correlation was statistically significant in three regions ($p < 0.05$) and for all regions combined ($p < 0.01$).

For Result 3:

After discounting for long-term trends, correlations between female incidence and hours of sunshine 2 years earlier were positive in 11 of 15 regions ($p < 0.01$ in one region) and for all regions combined ($p < 0.05$). No other time interval, from 1 to 5 years, indicated a strong pattern of positive correlation for females, with the 1-year period showing negative correlations for all but three regions (two were significant with $p < 0.05$).

For males, no association between yearly MM incidence and prior sunshine was apparent for any lag interval. The 2-year period gave positive correlations in 6 of 15 regions and for all region-years combined.

Reference:

Teppo, L., Pakkanen, M., and Hakulinen, T. "Sunlight as a Risk Factor of Malignant Melanoma of the Skin." Cancer 41:2018-2027 (1978)

Investigator Results:

1. The age-adjusted incidence of malignant melanoma (MM) in Finland (1953-1973) was equal in males and females, and more than doubled during the study period. The most common locations were the trunk (48% in males, 28% in females) and lower limbs (17% in males, 36% in females).

2. The incidence of trunk melanomas in both sexes and lower limbs in females (Group I) increased markedly with time, with age-specific incidence rates for these sites increasing sharply in middle age and levelling off thereafter. Melanomas on head and neck in both sexes and lower limbs in males (Group II) did not increase with time, and risk was low in middle age but increased throughout life.

3. Age-adjusted incidence rates were higher in urban areas than in rural areas and higher in southern parts of the country. After adjusting for urban/rural differences, north/south differences almost disappeared, implying that the north/south gradient was attributable to degree of urbanization and not necessarily to the effect of latitude itself.

4. The increased MM incidence with time could be accounted for by a cohort effect. Recognition of sunlight as the only important MM risk factor may be an oversimplification.

Methodology:

The study analyzed all 2,501 (1,108 M, 1,393 F) cases of MM (malignant lentigo excluded) reported to the Finnish Cancer Registry in 1953-1973. Histological confirmation was provided for 98% of cases. Also obtained from the Registry were 1966-1970 data on basal cell carcinomas and "other" skin cancers, as well as death certificates for cutaneous melanomas used to calculate mortality rates. All rates were age-adjusted to "world standard population" and urban/rural-adjusted. The country was geographically divided into four regions.

Experimental Design and Analysis Issues:

A descriptive and birth cohort analysis of Finnish MM incidence and mortality data.

For Result 1:

The most common tumor sites were the trunk (48% in males, 28% in females) and lower limbs (17% in males, 36% in females), whereas only 14% of tumors were on the face. The annual age-adjusted incidence

rates more than doubled for both sexes from 1953-1973 and was about $3.5/10^5$ in early 1970's. The increase in time was most marked for trunk tumors in males (80% of increase) and females (28% of increase), and on upper and lower limbs (44% of increase) in females. The timing of the increase in melanoma was similar to that observed in many other countries and the same birth cohorts were involved. Since mortality from melanoma increased at the same time as the increase in incidence, changes in diagnosis do not explain the increases.

For Result 2:

The increase in risk mainly concerned age groups over 30, with melanomas on the trunk in both sexes and on lower limbs in females showing relatively high rates in the 30-49 age group and a levelling off in older age groups. For head and neck tumors, and lower limb tumors in males, middle- age rates were lower and increased continuously with age. The shape of the curves were similar for successive time periods (1953-59, 1961-70, 1971-73). Male MM excess on the trunk and female excess on lower limbs were apparent in almost all age groups.

For Result 3:

Age-adjusted MM incidence among males increased more in urban than rural areas. In both urban and rural areas, increasing incidence was observed for the male trunk and the female lower limbs. Age-adjusted incidence rates were also higher in the south than the north. When adjusted for urban/rural population ratios, the north/south gradient decreased for 1953-1959 and almost disappeared for 1961-1970. The authors suggested that "... people in urban areas in Finland probably experience more exposure to the sun (open air leisure, holidays) than those living in rural districts where skin has traditionally been more protected from direct sunlight. The association with urbanization is consistent with the findings from England and Wales that the risk of melanoma in males is highest in professional and managerial workers and administrators, particularly at younger ages.

For Result 4:

Each successive male birth cohort born before 1940 and each female cohort born before 1930 experienced a higher risk of melanoma than the previous cohort. The increase in melanoma incidence in Group I can be interpreted in terms of a cohort effect accounted for by changing clothing habits which increased sunlight exposure to Group I sites. In Group II, exposure didn't change with time and no changes in melanoma risk were observed. However, the anatomical distribution of melanomas does not correspond to degree of sunlight exposure, and incidence rates in the face of both sexes equaled that of lower limbs in males although there is a marked difference in sunlight exposure for these sites.

Reference:

Venzon, D.J., and Moolgavkar, S.H. "Cohort Analysis of Malignant Melanoma in Five Countries." Am. J. Epi. 119:62-70 (1984)

Investigator Results:

1. A cohort analysis of malignant melanoma (MM) mortality data, after adjusting for geographic and temporal trends, indicated a higher proportion of deaths in females than in males among younger age groups.

2. Increases in mortality rates by birth cohort were approximately equal in different regions and appeared to be slowing down in more recent years.

Methodology:

Mortality data for MM in England and Wales, Canada, New Zealand, and the U.S. were obtained from the WHO which included five five-year cross-sections from 1951-1975 except for New Zealand with four cross-sections from 1955-1974 and a fifth from 1975-1977. Australian data were provided for nine five-year cross-sections from 1931-1975. For all countries, 14 five-year age groups (covering 15-84 year-olds) were used.

The data were fit to several different models (tested with chi-square goodness-of-fit) which estimated expected MM deaths. Model 1 estimated the expected number of deaths based on age group, birth cohort, sex and country:

$$E_{ijcs} = N_{ijcs}\, a_{ics}\, b_{ijcs}$$

where E_{ijcs} = expected deaths in age group i, birth cohort j, country c, and sex s, N_{ijcs} = size of population (person-years), a_{ics} = effect of being in age group i, c, and s, and b_{ijcs} = effect of belonging to birth cohort j and i,c, and s. Model 2 was a simplified version of model I, but added a parameter r_{cs} to adjust for relative rates in each sex- and country-specific population. Model 1 represented complete dependence of age and cohort parameters on population, whereas Model 2 represented complete independence. Model 3 assumed that mortality was similar in all populations but that cohort effects differed by more than a multiplicative constant ($E_{ijcs} = N_{ijcs}\, a_i\, b_{jcs}$). Model 4 tested for age effects which differed by sex but were constant over countries ($E_{ijcs} = N_{ijcs}\, a_{is}\, b_{jcs}$).

Experimental Design and Analysis Issues:

A descriptive analysis of the fit of mortality data to a range of age, birth cohort, country and sex dependent models.

For Result 1:

Model 1 fit the data well (p less than 0.05) except for Australian males. Model 2 did not fit Australian males, U.S. white females, nor England and Wales females well. The total fit for Model 3 was poor, primarily due to the U.S. white female population. The data on U.S. females differed in that mortality increased less rapidly with age than for all other populations. Two age curves, one for males and one for females, were believed to suffice for all five countries. The curve for males increased faster with age than for females, implying that a larger proportion of female deaths occurred in younger age groups.

For Result 2:

The fit of the data to Model 4 indicated that relative increases in mortality by birth cohort have been approximately the same (2-4%/year) in different regions. This trend appeared to be slowing down or leveling off in more recent birth cohorts.

Reference:

Viola, M.V., and Houghton, A.N. "Solar Radiation and Cutaneous Melanoma." Hosp. Prac. 17:97-106 (1982).

Investigator Results:

1. Melanoma incidence rates in Connecticut (CT) and Denmark (DK) were similar over approximately 3 decades of study.

2. Rising incidence of melanoma has occurred in non-random patterns identifiable in terms of site, age, sex, and country.

3. Birth cohort effects in DK melanoma incidence were observed for the trunk-neck and upper and lower extremities.

4. Greater than expected number of facial melanomas (both sexes) and trunk-neck lesions (males) were obserbed in both CT and DK. Lower than expected rates were observed for upper extremities (both sexes) and lower extremities (males).

5. Differences observed in facial versus nonfacial melanoma suggested both an acute and a chronic effect of sun exposure.

6. Age-adjusted incidence rates in CT were significantly correlated with time over three sunspot cycles ($r = 0.9327$), and significant partial correlations were observed between annual sunspot numbers and annual melanoma incidence.

Methodology:

Over 7,500 melanoma cases registered in the CT Tumor Registry (2,966 cases from 1935-1974) and the Danish Cancer Registry (4,547 cases from 1943-1974) with information on age, sex, and tumor site were analyzed. Age-adjusted incidence rates were calculated using relevant U.S. and Eurpoean data.

Experimental Design and Analysis Issues:

A descriptive analysis of melanoma incidence in CT and DK by age, sex, and tumor site, and an analysis of correlations between incidence and sunspot cycles.

For Result 1:

Melanoma incidence was $1.1/10^5$ in CT (1935) and in DK (1943). By 1974, incidence had risen to $5.7/10^5$ in DK and $5.8/10^5$ in CT. Age-specific data indicated increasing rates after age 20, leveling off between 40 and 60, and increasing after age 60. When analyzed by sex, DK incidence data in females increased more rapidly, whereas the CT incidence in males increased by more.

For Result 2:

The mean age of facial melanoma development was higher than for other sites, with incidence rising rapidly after age 60. Incidence of facial melanoma changed little over study decades. Incidence of nonfacial melanoma rose steadily until middle age and then plateaued. Increasing male melanoma rates in CT were accounted for by 10-fold increases in trunk and neck lesions between 1970-1974 and 1935-1944. Increased female melanoma rates in DK were largely attributable to rapid increase in lower extremity lesions particularly among 30-39 year-olds.

For Result 3:

When the DK data were analyzed according to birth cohorts, little change in facial melanoma incidence was observed, but rates for the trunk-neck and upper and lower extremities tended to increase with younger cohorts (beginning with 1882 cohorts).

For Result 4:

The ratio of observed to expected annual melanoma incidence relative to melanocyte density indicated excessive rates of facial melanoma (both sexes) and trunk-neck lesions (males) but lower than expected rates of upper extremity melanoma (both sexes) and lower extremity melanomas (males) in CT and DK. Declining ratios of facial melanoma were observed during the study period with greatest decreases in middle ages.

For Result 5:

Differences observed in facial versus nonfacial melanoma suggested an acute and chronic effect of sun exposure. Of all sites, the face is most chronically exposed. Facial melanomas are strongly age-related (incidence rises sharply after age 60) and are more frequent than would be predicted from facial surface area and melanocyte density. Sites less exposed to sun, such as male trunk and female leg, show excessive melanoma incidence strongly associated with middle, not old, age. Effects of continued prolonged solar radiation appear to be implicated in facial melanoma, whereas short-term, noncumulative effects of intense solar radiation appear to be related to melanomas of the trunk or leg.

For Result 6:

The increase in age-adjusted incidence rates in CT from 1935-1975 was significantly correlated in a linear regression equation with time over three sunspot cycles that occurred in the 33-year study period ($r = 0.9327$). Deviations in incidence from the regression line were also cyclic. Statistically significant partial correlations were observed between annual sunspot numbers and annual melanoma incidence in each of the 3 years following sunspot maxima,

with closest correlations 2 years after maxima. In additional New York data, the timing of increased melanoma rates was also significantly correlated with annual sunspot numbers (with 1-2-year lag).

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