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***Health Effects from
Ultraviolet Radiation***

*Report of an Advisory Group
on Non-ionising Radiation*



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HEALTH EFFECTS FROM ULTRAVIOLET RADIATION

Report of an Advisory Group on Non-ionising Radiation

CHAIRMAN: SIR RICHARD DOLL

(PREPARED BY A SUBGROUP ON ULTRAVIOLET RADIATION)

This report from the Advisory Group on Non-ionising Radiation reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.

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Executive Summary

EFFECTS OF ULTRAVIOLET RADIATION ON HUMAN HEALTH

SCOPE

- 1 The National Radiological Protection Board has a statutory responsibility to provide advice and information on standards of protection for exposure to non-ionising radiation. This includes the health effects and hazards associated with exposure to ultraviolet radiation (UVR)*.
 - 2 The Board's Advisory Group on Non-ionising Radiation has a remit
'to review work on the biological effects of non-ionising radiation relevant to human health and to advise on research priorities'
 - 3 In this, its seventh report, the Advisory Group has updated its previous review of the health effects from UVR (NRPB, 1995). It has considered both natural and artificial sources of exposure, as well as experimental studies relevant to understanding the effects of UVR on cells and tissues. It has examined information on the clinical effects of UVR and the results of epidemiological studies with the aim of providing advice on the health effects of exposure. The Advisory Group has also made recommendations for further research aimed at improving the basis for assessing exposures to natural and artificial sources as well as furthering knowledge of the effects of UVR on health through experimental and epidemiological studies.
 - 4 This summary reviews the main conclusions of the Advisory Group. At the specific request of the Board it also gives advice on the means of protection of human health. This applies both to members of the public and to those who are occupationally exposed and is intended to provide a practical basis for reducing UVR exposure and increasing awareness of its effects.
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SOURCES

- 5 For most people, the main source of UVR exposure is the sun, but for some individuals substantial exposures occur from artificial sources including sunbeds used for cosmetic tanning, industrial lamps, arc welding, and medical UVR therapies.
-

EFFECTS

- 6 There is convincing evidence that UVR can cause damage to DNA and in animal experiments it has been shown to be a cause of cancer. The International Agency for Research in Cancer (IARC) has concluded that solar radiation, broad-spectrum UVR,

* UVR is radiation in the range of wavelengths 100–400 nm. It is divided by wavelength into UVA 315–400 nm, UVB 280–315 nm and UVC 100–280 nm. Blue light lies in the range of about 400–500 nm.

and UVA, UVB or UVC radiation are all carcinogenic to experimental animals (IARC, 1992). Exposure to UVR also increases the risk of skin cancer in man and produces other undesirable health effects. The main tissues of the human body affected are those of the skin and the eye. There are also effects on the immune system, the significance of which for human health is not yet clear. The principal known beneficial effect of UVR exposure is its role in the production of vitamin D in the skin.

Skin

- 7** The most serious adverse health effects for which exposure to UVR is a recognised risk factor are the cutaneous malignancies (skin cancers). UVB has been recognised for some time as carcinogenic in experimental animals, and there is increasing evidence that UVA, which penetrates more deeply into the skin, also contributes to the induction of cancer. UVC from the sun is absorbed by the Earth's atmosphere, and any arising from artificial sources does not readily penetrate to the sensitive basal layer of the skin.
- 8** Excessive short-term exposure of the skin causes sunburn, principally consisting of erythema (skin reddening resulting from vasodilation) and oedema (swelling), both of which may be very severe. In some people sun exposure is followed by increased production of melanin and is recognised as a suntan. Genetically determined skin pigmentation will provide some protection against sunburn. A suntan offers only limited protection against further exposure and is not an indication of good health (CRC, 1989; UK Skin Cancer Prevention Working Party, 1994).
- 9** Excess sun exposure can increase the risk of both non-melanoma and melanoma skin cancers, the latter being the main cause of skin cancer death. Skin cancers cause about 2000 deaths each year in Britain, which is about 1.4% of all cancer deaths. The non-melanoma skin cancers (NMSCs) are mainly basal cell carcinomas and squamous cell carcinomas. They are relatively common in white populations, although they are rarely fatal. The overall incidence is difficult to assess because of under-reporting. Reported NMSCs account for about 15% of registered malignancies in the UK, but only around 0.3% of cancer deaths. Incidence rates of these tumours have increased in white populations progressively for many years. They occur most frequently on sun-exposed areas of the body such as the face and hands and their incidence increases with age. Risks are greatest in people with fair complexions (light skin, red or blond hair, and blue eyes) and sun-sensitive skins. The findings from epidemiological studies indicate that the risk of both of these skin cancers can be related to cumulative UVR exposure, although the evidence is stronger for squamous cell than basal cell carcinomas. UVR induces NMSCs in experimental animals.
- 10** Malignant melanoma is the main cause of skin cancer death, particularly in young people, although its incidence is less than that of NMSC. It is responsible for about 80% of skin cancer deaths. The risk of developing malignant melanoma has increased substantially in white populations for several decades and the annual incidence in the UK now approaches about 10 new cases per 100 000 population; more than double the rate 20 years ago. Melanoma mortality has, however, levelled off or even fallen in recent birth cohorts. Melanomas commonly occur at relatively young ages; at ages 20–39 years they account for about 1 in 11 of all cancers and about 1 in 20 of all cancer

deaths. A raised incidence is found in association with large numbers of naevi (moles), with atypical naevi, with a fair skin and red or blond hair, and with a tendency to freckle and burn and not tan on exposure to the sun. There is evidence that short, intense exposures of the type arising from sunbathing are important in the causation of melanoma, but chronic cumulative exposures may also be relevant. Childhood exposures may be particularly important.

- 11** Sunscreens will protect against sunburn and there is evidence from trials that they can reduce the risk of squamous cell carcinoma. Overall, however, it is unclear how effective sunscreens are at protecting against skin cancers, especially melanoma.
- 12** Although it has not been established directly whether sunbeds cause skin cancer, they are an appreciable source of intense, intermittent UVR exposure and as such represent a potential health risk.
- 13** Chronic exposure to solar radiation causes photoageing of the skin, which is characterised by a leathery, wrinkled appearance and loss of elasticity. Corroborating evidence for a role of UVR in the aetiology of these changes has been produced from extensive biological studies.
- 14** Certain individuals have abnormal skin responses to UVR exposure ('photosensitivity') because of genetic, metabolic or other abnormalities, or show photosensitive responses because of intake or contact with certain drugs or other chemicals.
- 15** The main known benefit of UVR exposure is the generation of vitamin D, which can be synthesised in the skin and is essential for healthy bone growth and maintenance. Dietary intakes of vitamin D are often low in the UK population, but short periods outdoors, as normally occur in everyday life, will produce sufficient vitamin D, and additional or intensive exposures will not confer further benefit. Research is ongoing into the possibility that dietary factors may affect risks of UVR-associated skin cancer, but this is not yet established.

Eye

- 16** Pathological responses of the human eye to excessive UVR exposure include photokeratitis and photoconjunctivitis (inflammation of the cornea and the conjunctiva, respectively). Repeated exposure is considered to be a major factor in the causation of non-malignant clinical lesions of the cornea and conjunctiva such as climatic droplet degeneration (discrete areas of yellow protein deposits in the cornea and conjunctiva), pterygium (an overgrowth of the conjunctiva on to the cornea) and, probably, pinguecula (small yellow growths in the conjunctiva). Damage can result from exposure to UVA, UVB and UVC.
- 17** There is epidemiological evidence that chronic exposure of the eye to intense levels of UVR contributes to the development of cortical cataract. Evidence for a causal role of solar radiation in macular degeneration (a major cause of blindness) is conflicting. The extent to which UVR exposure is an important risk factor for cataracts in the general population is unclear, as is its relation to eye melanoma.
- 18** There is good evidence that prolonged gazing at very bright light sources, particularly those emitting shorter wavelength blue light, causes retinal damage resulting in transient or permanent loss of visual acuity. Staring at the sun can damage the retina permanently. Such an effect would normally be prevented by the natural aversion

response invoked by looking at a bright light, but this response can be intentionally suppressed. Similar damage has also been induced in the non-human primate retina following acute exposure, particularly to blue light. It is not clear to what extent UVA is involved as its transmission through the lens is low in adults but is higher in children.

Immune responses

19 There is experimental evidence in animal models and human subjects of suppressive effects of UVR on the immune system. Biological studies have shown that exposure to UVR can suppress the normal antigen-specific immune response to some skin tumours and to various pathogens. The significance for human health of UVR-induced immune suppression is not, however, clearly established at present.

20 A link has been demonstrated between sun exposure and the reappearance of the symptoms of herpes simplex virus (cold sores) in a proportion of latently infected individuals. In addition, there is a risk of converting benign papillomas caused by various human papillomavirus types, to squamous cell carcinomas in immuno-compromised subjects in areas of the skin that are normally exposed to the sun.

Non-Hodgkin's lymphoma (NHL)

21 Overall, the data are not consistent with a major role for solar UVR in the aetiology of non-Hodgkin's lymphoma (NHL), but they leave open the possibility of a minor role, or an aetiological relation for a particular subtype of the disease.

RECOMMENDATIONS

22 There is a need for public health advice on limiting exposure to UVR. Provision of information to the population as a whole about the risks of exposure is important. UVR can cause skin damage in people of all skin colours, although fair skins are more sensitive. Eye damage can occur in all populations. Particular care is desirable in children and young people, people with large numbers of naevi and those with fair complexions (light skin, red or blonde hair and blue eyes) and sun-sensitive skins.

Awareness of UVR risks

23 Educational programmes should continue to aim at increasing awareness of the health effects of UVR exposure. This is particularly important for parents, those working in nurseries, school teachers and others responsible for the day-to-day care of children. The objectives are to improve knowledge, influence attitudes and change behaviour in relation to UVR exposure. The programmes should aim to reduce the cumulative exposure to UVR and, particularly, exposure to high levels resulting in acute damage to the skin and/or eyes. In this context, national and international initiatives such as the development of the Global Solar UV Index (as an indication of exposure) and campaigns by the World Health Organization are important.

24 Information relating to early diagnosis of skin cancer should be readily available to the public.

25 There is a need to continue to measure the levels of solar UVR throughout the country and to publish these data regularly. The measurements by NRPB provide a basis for realistic exposure assessments.

Protection from solar and artificially produced UVR

- 26** The skin can be protected by wearing hats and clothing and by applying sunscreens. However, sunscreens should not be used to intentionally prolong exposure. Protection by sunscreens is less certain than that provided by reducing exposure. The continued development and use of suitable and scientifically valid protection criteria for clothing and other protective products is desirable, as is the development of internationally agreed standards.
- 27** The eyes can be protected by wearing a hat, eye shades and using sunglasses that exclude both direct and reflected UVR. It is important that these incorporate wrap-around protection. Sunglasses fitted with small lenses offer inadequate protection and may actually increase risk of eye damage as they can cause dilation of the pupils and allow the entry of more UVR into the eye from around the periphery of the sunglasses.
- 28** There is a need for advice limiting exposure to UVR at work, both indoors and outdoors. The Health and Safety Executive has issued advice to outdoor workers and their employers (HSE, 2001).
- 29** The Advisory Group recommends that the use of sunbeds and sunlamps for cosmetic tanning should be discouraged.
- 30** Some prescribed medicines, drugs, foods, cosmetics and various plant materials can cause sensitisation of the skin and eyes to UVR. Patients and the general public should be warned by health professionals and manufacturers of these interactions with UVR.
- 31** Approaches to be considered in educational and awareness programmes for protection from UVR are given in the table.

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| <p>1 Take sensible precautions to avoid sunburn, particularly in children.</p> <p>2 Remember that a suntan offers only modest protection against further exposure. It is not an indication of good health.</p> <p>3 Limit unprotected personal exposure to solar radiation, particularly during the four hours around midday, even in the UK.</p> <p>4 Seek shade, but remember sunburn can occur even when in partial shade or when cloudy.</p> <p>5 Remember that overexposure of skin and eyes can occur while swimming and is more likely when there is a high level of reflected UVR, such as from snow and sand.</p> <p>6 Wear suitable head wear, such as a wide-brimmed hat, to reduce exposure to the face, eyes, head and neck.</p> <p>7 Cover skin with clothing giving good protection – examples are long-sleeved shirts and loose clothing with a close weave.</p> <p>8 Sunglasses should exclude both direct and peripheral exposure of the eye to UVR, ie be of a wrap-around design.</p> <p>9 Apply sunblocks, or broad-band sunscreens with high sun protection factors (at least SPF15*), to exposed skin. Apply generously and reapply frequently, especially after activities that remove them, such as swimming or towelling.</p> <p>10 Remember that certain individuals have abnormal skin responses to UVR exposure and may need medical help. Certain prescribed drugs, medicines, foods, cosmetics and plant materials can also make people more sensitive to sunlight.</p> |
|--|

*Approaches to
minimising
UVR-induced skin
and eye damage*

*The sun protection factor (SPF) is the ratio of the UVR exposure to produce minimal reddening of the skin on a site protected by sunscreen to the UVR exposure to produce a comparable reddening on unprotected skin (FDA, 1978; CIE, 1991). An SPF of 10 would reduce exposure to 10% of that of unprotected skin.

Research

- 32** Areas in which research is needed include: the UVR outputs of artificial sources; the molecular basis of UVR cutaneous carcinogenesis in cellular systems and in animals; the immunological effects of UVR and their relevance to human health; the effects of UVR on risk of eye disease especially macular degeneration and choroidal malignancy; the relation of different types of UVR exposure to skin diseases including photodamage, photosensitivity disorders and skin cancers; the possible prevention of skin cancer by dietary factors; and the optimisation of UVR exposure in different situations for maintenance of adequate vitamin D status.
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1 Introduction

- 1 Ultraviolet radiation (UVR) arises from both natural and artificial sources. It is a component of the non-ionising part of the electromagnetic spectrum and lies within the range of wavelengths 100–400 nm. Conventionally, 100 nm is taken as the boundary between non-ionising radiations and the shorter wavelength ionising radiations. UVR is normally classified into three regions: UVA (315–400 nm), UVB (280–315 nm) and UVC (100–280 nm).
- 2 The sun is the principal source of exposure for most people. The broad spectrum and intensity of the UVR emitted from the sun are due to its high surface temperature. The levels of UVR reaching the Earth's surface depend on the time of year, the transmission properties in the atmosphere and the power output of the sun. Whilst both UVA and UVB penetrate the Earth's atmosphere, the shorter wavelength UVC does not as it is absorbed by the stratospheric ozone layer. In contrast, most artificial sources of UVR emit a spectral continuum containing characteristic peaks, troughs and lines. Sources include various lamps used in medicine, industry, commerce, research, the home, and welding. Such sources can give high local exposures if they are not correctly used.
- 3 Exposure to UVR can give rise to deleterious health effects, the extent depending upon individual sensitivity. These are mainly confined to the skin and the eyes, as penetration of UVR into body tissues is very limited. Excessive exposures can give rise to skin burns and blistering as well as causing systemic discomfort. The retina in the eye is normally protected from acute retinal damage, as can be caused by staring at the sun, by involuntary aversion responses. Acute exposure may, however, damage the cornea and conjunctiva, for example causing inflammation of the eye. Chronic exposure may also affect the skin by increasing ageing effects and the risk of cancer and it probably increases the risk of certain types of cataracts in the eyes. The rapid increase in the incidence of skin cancer in the UK has been attributed to the greater recreational exposure to UVR, including the trend over the last 30 years of taking holidays abroad. It is known that exposures to low levels of UVR can alter the skin's immune system causing immunosuppression. Apart from these deleterious effects, exposure to UVR at low levels generates vitamin D which is necessary for bone health.
- 4 The National Radiological Protection Board has the responsibility for advising UK government departments on standards of protection for exposure to ionising and non-ionising radiations. In November 1990, the Director of NRPB set up an Advisory-Group on Non-ionising Radiation which has as its terms of reference:

'to review work on the biological effects of non-ionising radiation relevant to human health and to advise on research priorities'
- 5 The Advisory Group was reconstituted in 1999 as an independent body and now reports directly to the Board of NRPB. The Advisory Group has issued a number of reports related to concerns about health effects of exposure to non-ionising radiations. It has provided advice on health effects of exposure to electric and magnetic fields

(NRPB, 1992, 1994a,b, 2001a,b) and in 1995 issued a report on the health effects from ultraviolet radiation (NRPB, 1995a). It has also issued statements on the solar eclipse and on the use of sunbeds (NRPB, 1999a,b). The statement on the eclipse stressed the need to take great care when viewing it, with indirect methods being those of choice.

- 6** The first report on UVR (NRPB, 1995a) aimed to provide a comprehensive overview of sources of exposure and evidence of health effects. It considered both natural and artificial sources. It reviewed experimental work on the biological effects of UVR carried out at the cellular and molecular level, in particular in relation to carcinogenic processes and the aetiology of skin tumours. It also reviewed animal experiments and information from human volunteer studies on the biological effects of UVR. Clinical effects of exposure to both acute and chronic UVR arising from both natural and artificial sources were examined, with emphasis on describing the different types of skin lesion that might arise as well as damage to the eyes. It reviewed the epidemiological evidence on the relationship between exposure to solar radiation and to artificial UVR and the risks of cutaneous melanoma and non-melanoma skin cancer (NMSC). Finally, the report examined dose–response relationships and the relative effectiveness of different wavelengths in relation to their effectiveness in causing skin cancer. The information provided the basis for estimating a risk of NMSC from a given exposure to UVR for populations, although not for individuals. Also considered were the small increases in risk that may result from the predicted decreases in ozone levels and the extent to which they could be offset by small changes in behaviour in the summer months. The report finally made recommendations for further research.
- 7** The report by the Advisory Group provided the scientific support for a statement by the Board of NRPB which underlined the present state of knowledge on health effects of UVR and highlighted approaches to be considered in educational and awareness programmes (NRPB, 1995b).
- 8** The Advisory Group has kept the issue of exposure to UVR under review and in 1999 issued a statement on the use of sunbeds and cosmetic tanning (NRPB, 1999b). This statement summarised the available information on health effects of UVR and gave advice about the use of sunbeds. Its principal recommendation was that the use of sunbeds and sunlamps for cosmetic tanning should be discouraged and that information about their potential adverse health effects should be made available to users and the general public. The statement applied to cosmetic tanning and not to the use of UVR as part of a medical treatment where the benefits and potential risks needs to be assessed in a clinical context.
- 9** Since publication of its first report on UVR (NRPB, 1995a), substantially more information has become available both nationally and worldwide related to an assessment of the health effects of exposure to UVR (WHO, 1994; NRPB/ICNIRP/WHO, 2000). In the UK this has in part arisen as a result of the programmes of research funded by the European Commission and by the Department of Health, as well as the increasing awareness of the health effects of exposure to UVR. It is timely therefore to undertake a further comprehensive review of the health effects of exposure to UVR. The aim of the present report has been to extend the information provided in the earlier review (NRPB, 1995a) to take account of more recent information. Unless it was specifically necessary, the information provided earlier is not repeated here and should, therefore, be referred to as appropriate.

- 10** There has been concern that depletion of ozone in the stratosphere could give rise to increasing levels of UVR. Although measurements of solar UVR have been made worldwide for many years, it is only in the last ten years or so that coordinated measurements with accurate calibrations have been carried out so that temporal changes can be followed. So far there is little evidence from the measurement data for long-term changes in UVR levels, although some (temporal) variations have been reported. The only exception is in Antarctica where high levels of UVB are observed during the recurrent springtime ozone depletion. Chapter 2 summarises the solar radiation measurement data presently available and the physical and biological methods that can be used for assessing exposure. It also reviews information on artificial sources of exposure to UVR, which may contribute significantly to total exposure in some circumstances. Appendix A gives more information on the use of physical and biological dosimeters for assessing personal UVR exposure.
- 11** In relation to health effects, exposures to UVA and UVB in solar radiation are the principal concern. There is strong experimental evidence that shorter UVB wavelengths are strongly absorbed by, and can damage, DNA. UVA interacts with tissues by generating an oxidative stress. Considerable new information has emerged on DNA repair as the relevant genes are cloned and recent studies have focused on the type of oxidative DNA damage induced by UVA radiation and the modulation of damage by endogenous antioxidants. There have also been considerable advances in knowledge of the modulation of gene expression by UVA and UVB radiation. Chapter 3 reviews information from *in vitro* and cellular studies on the effects of UVA and UVB on DNA damage and gene expression, the role of melanin and the possible implications for skin tumour induction.
- 12** Squamous cell carcinomas are readily induced in rodents by exposure to solar radiation or to UVR. IARC (1992) considered that the evidence was sufficient to conclude that solar radiation, broad-spectrum UVR, and UVA, UVB and UVC radiation were all carcinogenic to experimental animals. In its previous report the Advisory Group noted that skin tumours in experimental animals have occurred after single exposures to UVR but more often result from experiments involving protocols in which irradiation was given daily for weeks or months. Chapter 4 reviews recent information on photocarcinogenesis in experimental animals, in particular in relation to work on mice. It also considers the implications of a number of transgenic mouse melanoma models for providing improved information on the effect of UVR on the induction of skin tumours and examines the results of recent studies with previously described natural animal models of melanoma, namely the opossum and certain hybrid fish.
- 13** Photoimmunology is an area of considerable interest and research activity. The skin has a complex immune system with the involvement of many cell types, some resident in the dermis or epidermis and others highly mobile, frequently connecting the cutaneous environment with blood or lymphatic systems. Chapter 5 outlines the current state of knowledge regarding the effects of UVR on immune responses and work aimed at understanding the complex sequence of events that can occur following exposure. It encompasses studies carried out at the molecular and cellular level as well as in experimental animal and human subjects. It is notable that immunological changes have been observed at levels of exposure to UVR that could be readily encountered in natural sunlight. The immunoprotective properties of sunscreens are also considered.

- 14** There is evidence for both acute and chronic injury to the conjunctiva and cornea in animals and human subjects. Acute exposure to UVR can cause photokeratitis (inflammation of the cornea) and conjunctivitis (inflammation of the conjunctiva) in experimental animals. Acute exposure to UVB may also induce lens opacities and is probably a cause of cataracts. Chronic exposure to UVR is an important risk factor for pterygium, pingueculae and climatic droplet keratopathy, it is associated with a raised risk of human cataract and can give rise to cancer in the tissues of the eye. Chapter 6 considers clinical and epidemiological studies concerned with assessing the effects of exposure to UVR on the eye.
- 15** In the previous report the Advisory Group concluded that, although both malignant melanoma and NMSC are associated with UVR exposure, the relationship for NMSC is probably to cumulative exposure, whereas in the case of malignant melanoma the relationship is complex. For malignant melanoma sharp episodes of intense exposure of unacclimatised (lightly coloured) skin to the sun appear to be a major risk factor, although cumulative lifetime exposure may also play a part. NMSCs consist of both squamous cell carcinomas (SCC) and basal cell carcinomas (BCC). Chapter 7 summarises epidemiological evidence on the relationship between exposure to solar radiation and artificial UVR and the development of SCC, BCC and malignant melanoma as well as photoageing of the skin. Emphasis is placed on evidence published since the last report. It includes a consideration of the finding that, whereas the incidence of SCC appears to depend upon accumulative exposure for BCC and malignant melanoma, it is possibly a combination of intermittent and cumulative exposure that is important. Chapter 7 also includes a review of data on the wide range of health conditions associated with abnormal sensitivity to exposure to UVR.
- 16** Primary and acquired immunosuppression are risk factors for non-Hodgkin's lymphoma. The possibility has been considered that the immunosuppressive effects of UVR might be involved in causing these malignancies. Chapter 8 reviews the evidence.
- 17** A number of environmental factors may affect the consequences of exposure to UVR. Chapter 9 examines information on the effect of dietary factors that could influence the response of skin to UVR exposure. An early effect of UVR on the skin is the generation of excessive amounts of free radicals and reactive oxygen species (ROS), which can overwhelm the skin's antioxidant defences. A nutritional approach to protection has involved dietary supplementation with antioxidant agents and this has been examined both in cell culture and animal models as well as in healthy humans and patients with skin cancer or photosensitivity disorders. A number of other dietary modifications that have aimed to protect against the effects of UVR exposure are also considered.
- 18** The synthesis of vitamin D in the skin is recognised as a beneficial effect from exposure to UVR. Vitamin D is essential for calcium metabolism and a healthy skeleton. Irradiation with UVR can cure rickets in children or guard against the development of osteomalacia in adulthood and may have other beneficial effects. Chapter 10 considers the effect of UVR on the synthesis of vitamin D and levels of exposure needed to produce the vitamin in sufficient amounts.
- 19** In the previous report (NRPB, 1995a) information was given on dose-response relationships for the induction of skin cancer following exposure to natural and artificial sources of UVR. At that time, risk estimates could only be provided for basal and

squamous cell cancer. Knowledge about the action spectrum and the dose–response relationship for the induction of melanoma were inadequate to permit use for risk estimates. Since then, no information has been published that would require the judgements made in 1995 to be modified. The previous information is therefore summarised in Chapter 11 and reproduced in Appendix B.

- 20** As indicated previously, for most people the main source of exposures to UVR is the sun and advice was given in a Board Statement on protection measures that may be adopted to reduce exposure (NRPB, 1995b). Chapter 12 summarises information on protective measures. These cover the need to change people's behaviour in the sun, the use of protective clothing and eyewear as well as the application of topical sunscreens.
- 21** Chapter 13 summarises the main conclusions of the report. Chapter 14 gives the overall conclusions and Chapter 15 identifies priorities for further research. A glossary is also included.
- 22** Finally, the previous statements by the Advisory Group on the solar eclipse (NRPB, 1999a) and on the use of sunbeds for cosmetic tanning (NRPB, 1999b) are reproduced at the end of the report.

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2 Solar Radiation and Artificial UVR

INTRODUCTION

- 1 The main source of ultraviolet radiation (UVR) contributing to personal exposure is the sun. Levels of solar UVR are generally at their highest during clear days in summer at and around noon and unprotected exposure to the sun during such times contributes significantly to personal dose. The levels of solar UVR have been measured, albeit spasmodically, from two main standpoints. The first relates to obtaining baseline data on solar UVR at different geographical locations and the second relates to assessing the environmental impacts of stratospheric ozone depletion. Temporal variations in solar UVR levels, particularly in relation to stratospheric ozone depletion, have been analysed and changes have been reported, particularly in Antarctica (Madronich *et al.* 1998).
 - 2 For some individuals, UVR from artificial sources could also contribute significantly to their total exposure. Such sources of exposure include sunbeds used for cosmetic tanning and high intensity sources used in industry, including welding arcs, and those used in medical therapy. For occupational exposure, guidelines are published to limit exposures for non-therapeutic and non-elective activities. These guidelines represent conditions under which it is expected that nearly all individuals may be repeatedly exposed without adverse effect.
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SOLAR UVR

- 3 As stated above, the sun is the main source of ultraviolet radiation (UVR). The broad spectrum and intensity of the UVR emitted from the sun are due to its high surface temperature. The quantity and spectral distribution of solar radiation at the Earth's surface depend on the power output of the sun, the path of the radiation through the Earth's atmosphere, and the transmission properties of the atmosphere. Solar UVR undergoes absorption and scattering as it passes first through the outer layers of the atmosphere and then the stratosphere and the troposphere before reaching the Earth's surface. The most important of these processes are absorption by molecular oxygen and absorption by ozone (O₃). The boundary between the troposphere and the stratosphere is at approximately 10 km from the surface. The stratospheric ozone layer, formed between 10 and 40 km above the Earth's surface, prevents almost all UVR of wavelengths less than 290 nm and a substantial proportion (70%–90%) of UVB radiation from reaching the Earth. Therefore, the ground-level component of the solar UVR spectrum consists of wavelengths in the range from about 290 to 400 nm. Ground-level UVR consists of two major components, namely radiation received directly from the sun and radiation that has been scattered by the atmosphere. The ratio of the scattered to direct radiation varies with wavelength and with solar elevation. It increases as both wavelength and solar elevation decrease.
- 4 Stratospheric ozone depletion and the predicted associated increase in solar UVR reaching the Earth's surface have become major environmental issues. Although it is of value to investigate, monitor and model stratospheric ozone depletion and atmospheric

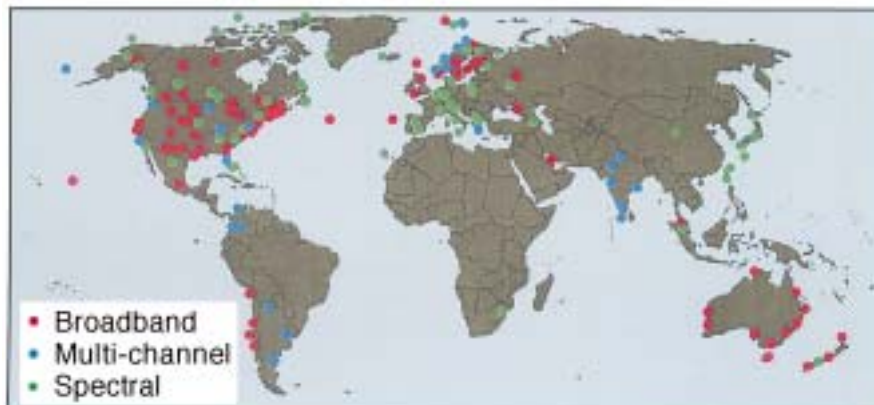
changes, it is also important to assess the impact of atmospheric changes by measuring the levels of solar UVR at the Earth's surface. It is the amount of solar UVR at ground level rather than the status of stratospheric ozone *per se* that will determine the effects on human health, marine organisms, and plant life. Even when stratospheric ozone depletion is indicated over a region of the Earth's surface, it will not necessarily result in significantly increased amounts of solar UVR at ground level. This is due to other atmospheric absorption and scattering processes, localised atmospheric pollution including, in particular, ozone in the troposphere, and cloud cover (Madronich *et al*, 1998).

- 5 Human exposure to solar UVR depends on geographical location, altitude, time of day, time of year and sky cover and behavioural protective factors (Bergmanson and Sheldon, 1997). El Paso, which is at the same latitude (around 33°N) as Atlanta, Georgia, receives 38% more UVR, because of its greater altitude. Hawaii (around 20°N) receives ten times more UVR exposure than Alaska (greater than 55°N) because it is closer to the equator (Scotto, 1996). Increased risks of UVR damage have been attributed in part to loss of the ozone layer from the stratosphere (Longstreth, 1987), first noted in the 1980s (Farman *et al*, 1985). In many parts of the world people spend more time in the sun and an increased lifespan gives a greater opportunity for UVR exposure (Bodhaine *et al*, 1996).
 - 6 The spectral UVR irradiance (at a wavelength of 300 nm) is theoretically at a maximum at noon, when the solar elevation is at its highest. This is at least about ten times higher than that over the period before 09:00 GMT or after 15:00 GMT. Seventy per cent of the global UVR exposure (the integrated total exposure dose of biologically weighted UVR falling on a horizontal surface) is delivered during the four hours centred around midday. It should be noted, too, that spectral irradiance varies with wavelength and increases more than 1000-fold, between 290 and 310 nm.
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MEASUREMENTS OF AMBIENT SOLAR UVR

- 7 Measurements of solar UVR have been made worldwide for many years. However, coordinated measurements have only been obtained over the past decade (WMO, 1998) (Figure 2.1) and therefore provide only a limited database for epidemiological studies and assessing personal exposure to solar UVR at ground level. Many new commercial and research UVR detectors have recently been developed increasing the number and general quality of solar UVR measurements. Calibration procedures have been improved and several national and international intercomparisons have been reported (Madronich *et al*, 1998). Results relating to published long-term measurement programmes worldwide (covering the period 1968 to 1993) were summarised previously (NRPB, 1995). This summary included both published spectral data (measurements made at wavelength intervals from above about 280 nm to which any suitable action spectrum may be subsequently applied) and broadband data (measurements over a wavelength range inherently incorporating a weighting function representative of a biological action spectrum). Some of the reported UVR trends, particularly those related to measurements which terminated in the 1980s, have been called into doubt due to calibration and measurement uncertainties (Blumthaler *et al*, 1990; Correll *et al*, 1992; Garadazha *et al*, 1987; Scotto *et al*, 1988).

FIGURE 2.1 Global distribution of solar UVR WMO coordinated measurement sites, showing the distribution of broadband, multichannel and spectral surface-based measurements (Weatherhead and Webb, 1997)



- 8 There is little evidence from UVR measurement data globally for long-term UVR changes in UVR levels, although some temporal variations have been reported (Kerr *et al*, 1993; McKenzie *et al*, 1999; Zheng *et al*, 1993). Madronich *et al* (1998) predicted trends derived from total ozone and cloud reflectivity measurements, but the uncertainties on these assessments are high. Some general patterns of geographical variations were also identified by these authors. For example, high levels of UVB radiation continue to be observed in Antarctica during the recurrent springtime ozone depletion. In addition, ground-based UVR measurements (Seckmeyer *et al*, 1995) have shown that erythemally weighted UVR irradiances in the Southern Hemisphere are up to 40% higher than those at comparable latitudes in the Northern Hemisphere, which may be explained in terms of atmospheric variations. Such variations may also explain differences between these measurements and corresponding satellite-based estimates, which indicate only 10% to 15% differences between the two hemispheres.
- 9 In the UK, both spectral and broadband ground-based solar UVR measurements are undertaken routinely. Spectral measurements at Reading (around 51.5°N) between 1993 and 1997 show a non-statistically significant increase in UVB of 4.3%, compared with a decrease in stratospheric ozone of 5.9% (Bartlett *et al*, 2000). The daily values of ozone vertical columns and the ratios of erythemally weighted UVR (UVR_{eff}) (which is affected by ozone depletion) to UVA (320–400 nm) (which is relatively unaffected by ozone depletion) for Reading are plotted in Figure 2.2. Broadband measurements (Driscoll *et al*, 2000) of erythemally weighted UVR (UVR_{eff}) at NRPB, Chilton (also around 51.5°N) from 1989 to 2000 show a non-significant trend in the annual UVR_{eff} (Driscoll *et al*, 2000). The mean annual UVR_{eff} (SED, or standard erythema dose*) (CIE, 1997) as a function of latitude across the UK is shown in Figure 2.3 for six measurement sites. The range of the standard deviation on these measurements is between 7% and 11%. The annual UVR_{eff} values at Chilton and Glasgow are shown in Figure 2.4 for the measurement periods.

* In this chapter, SED (standard erythema dose), which is a physical quantity (equal to 100 J m^{-2} effective), has been used instead of MED (minimum erythemal dose), which is a clinical measure that varies between individuals.

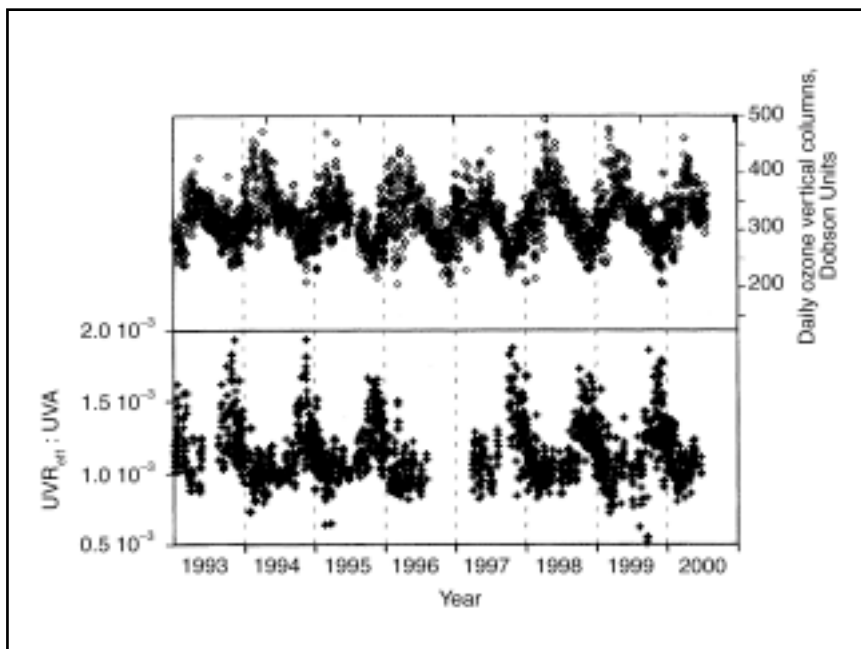


FIGURE 2.2 Daily ozone vertical columns (Dobson Units DU) measured in the south-west of England (top) and the ratio of UVR_{eff} (UV_{ee}) to UVA from measurements at Reading in the solar zenith angle range 75° – 80° (bottom) (Bartlett and Webb, 2000)

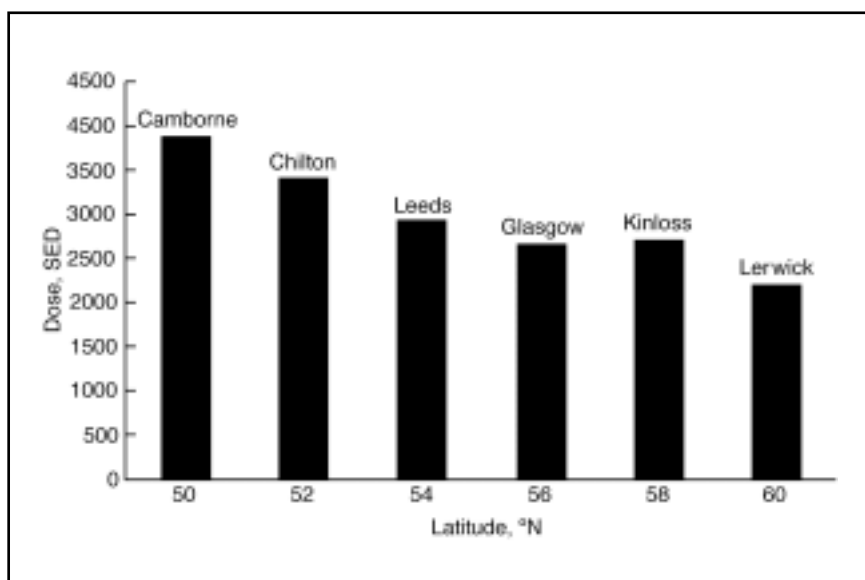
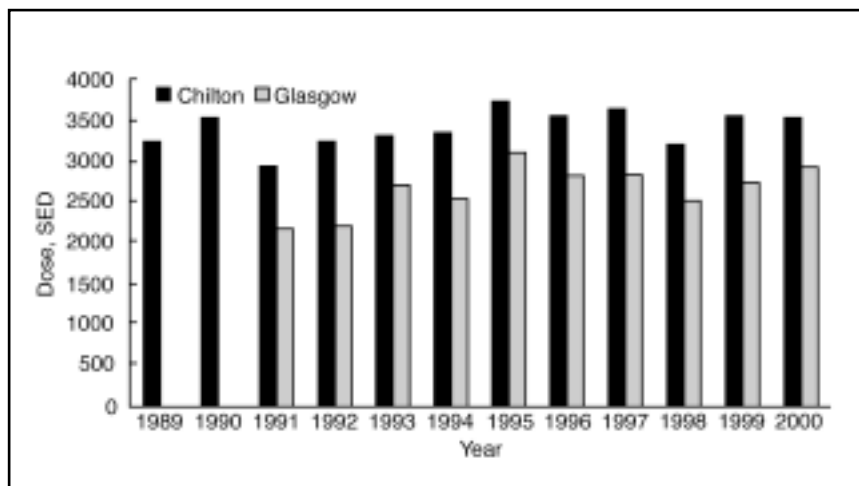


FIGURE 2.3 Mean annual erythemally weighted UVR dose (SED) at various latitudes across the UK from 1990 to 2000 (Driscoll, NRPB, Personal communication)

FIGURE 2.4 Annual erythemally weighted UVR dose (SED) at Chilton from 1989 to 2000 and at Glasgow from 1991 to 2000 (Driscoll, NRPB, Personal communication))



- 10 Erythemally weighted UVR levels can be expressed in terms of the UVR index (ICNIRP, 1995), which numerically equals 40 times the time-weighted average effective UVR irradiance ($\text{W m}^{-2} \text{eff}$). Estimates of the global geographical distribution of the UVR index for noon in January and July for clear skies are shown in Figure 2.5 (Vanicek *et al*, 2000). The index is quoted in the range from 1 (low risk) to 15 (very high risk). Very high indices are shown in the figure, particularly, for equatorial regions and high altitudes, central Australia, the west coast of America, central Asia and South Africa. The indices appropriate to clear skies at noon in June in Europe are shown in Figure 2.6, ranging from 4 in Scandinavia to 10 around the Mediterranean Sea. Typically, indices no greater than 7 are expected for northern Europe during the summer, in agreement with measurements. Reflectance data for different terrains are presented in Chapter 6.

ARTIFICIAL UVR SOURCES

- 11 Artificial sources of optical radiation that emit UVR are commonplace. UVR may be emitted from a source, either adventitiously or deliberately, for any one of many applications. There are few artificial sources that result in human exposure to UVR greater than that from solar radiation. However, exceptions are those used for medical therapy and diagnosis, cosmetic tanning and a few industrial sources, generally effectively enclosed, but where accidental exposure may occur. There are no statutory regulations in the UK covering the control of exposure from UVR. Where recommendations specifically limiting exposure to optical radiation (including UVR) exist they do so in the form of voluntary standards (ACGIH *et al*, 1999; ICNIRP, 1996). However, there is a general requirement under safety legislation to assess risks from work practices and equipment. Voluntary standards may be used as a measure of good practice.

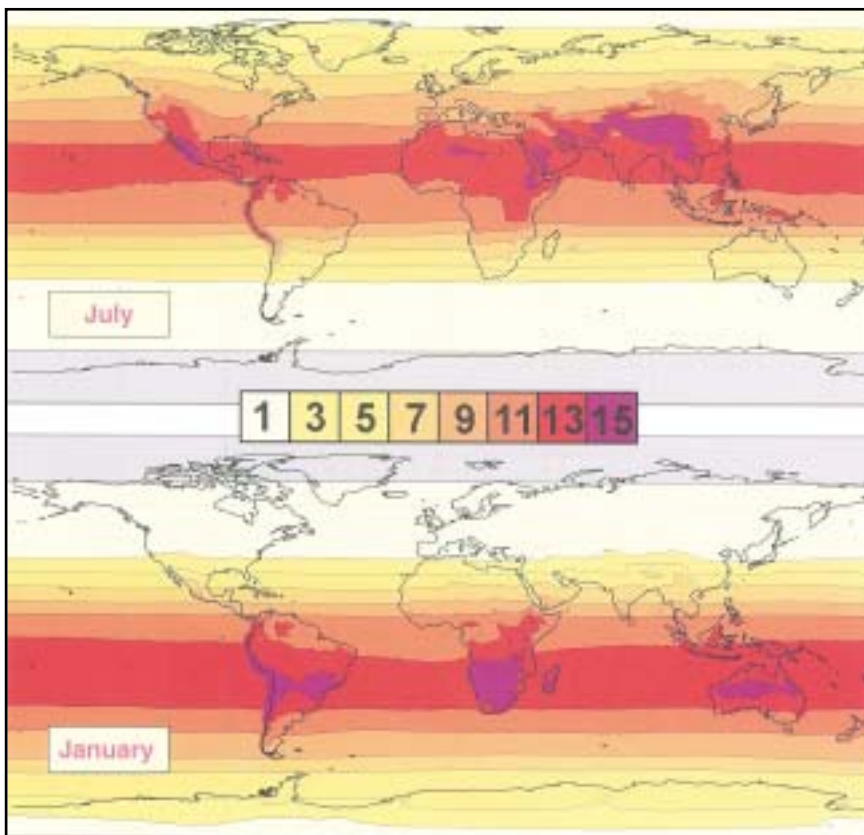


FIGURE 2.5 Estimation of the global geographical distribution of the UVR index (ICNIRP, 1995), ranging from 1 (low erythemal risk) to 15 (very high risk) for noon in January and July for clear skies (Vanicek et al, 2000)

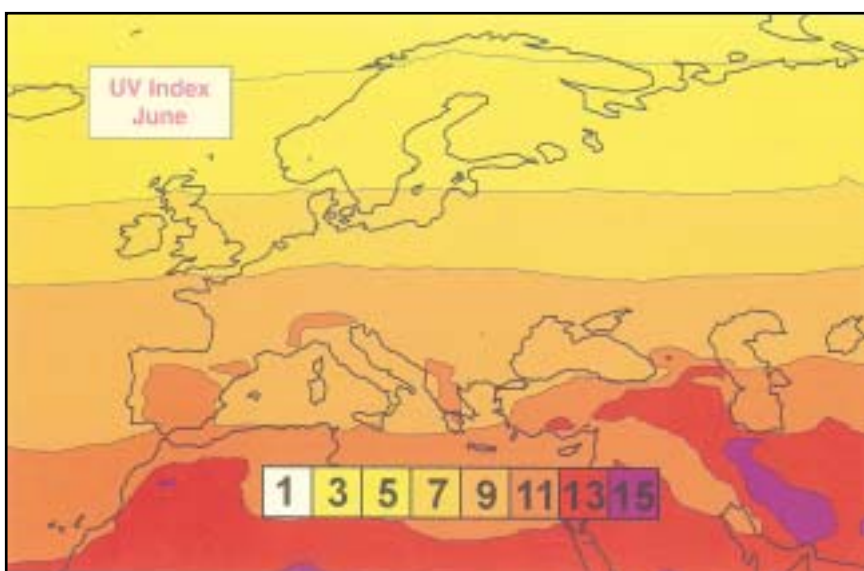


FIGURE 2.6 Estimation of the geographical distribution of the UVR index (ICNIRP, 1995) across Europe for a clear sky June day at noon. The UVR index values are colour coded ranging from 1 (low erythemal risk) to greater than 9 (high erythemal risk) (Vanicek et al, 2000)

- 12** In almost all non-laser optical sources the radiation is produced either by heating a material to incandescence, by an electrical discharge in a gas or vapour, by luminescence in a material or by a combination of these.
- 13** Any unfiltered optical source whose emissions are due to the heating of a material, eg a filament lamp, that emits significant quantities of UVR will also emit copious amounts of visible and infrared (IRR) radiations. In the case of high temperature tungsten halogen lamps, biologically significant amounts of shorter wavelength UVR (UVB 280–315 nm) are also emitted. Essentially the same holds true for high intensity (gaseous) discharge (HID) lamps. Some incandescent and HID lamps have sufficient intrinsic filtration in the construction of the lamp, eg 'hard glass' Wood's filter envelope lamps (black-light lamps), effectively to remove the unwanted radiation to the degree required for the purpose in hand. However, in most instances additional filtration, afforded by incorporation of the lamp in a suitably filtered luminaire, is necessary to reduce exposure to an acceptable level with respect to recommended exposure limits.
- 14** In the case of a source whose emissions derive from the fluorescence of a material, eg a fluorescent lamp, the UVR emission can be more specifically selected using an appropriate phosphor in conjunction with a suitably absorbing lamp envelope. However, as with the incandescent and high pressure discharge lamps, additional external filtration may be required for some purposes.

Incandescent lamps

- 15** The incandescent lamp is the oldest type of lamp in common use. Its durability has been due to its simplicity of construction enabling cheap mass-production methods. However, in the face of the requirement to save energy and the potential competition of 'compact' gaseous discharge fluorescent lamps, research and manufacturing efforts are still being made to increase both the comparatively short life and the low luminous efficacy of these lamps. Typical gas-filled incandescent filament lamps operate at filament temperatures between 2700 and 3000 K with powers up to 500 W and the peaks of their spectral emissions are in the infrared (IRA 700–1400 nm) region. Little UVR is emitted from such lamps.
- 16** In applications where a physically small source is required (eg for producing a focused beam) or where much more power (up to several kilowatt) is required, tungsten halogen lamps are often used. These are quartz envelope tungsten filament lamps to which a halogen vapour (iodine or bromine) is added. The presence of the vapour results in reversible cyclical chemical reactions between tungsten metal lost by evaporation from the filament and the vapour. As a result of their small size they operate at an increased gas pressure compared with 'conventional' incandescent lamps and evaporation from the filament is minimised. These features result in improved luminous efficacy and in longer life. In order to maintain the efficiency of the regenerative chemical reactions the temperature of the wall of the bulb must be maintained at not less than 530 K. The majority of the bulbs of tungsten halogen lamps are made from silica (quartz) whose thermal properties are most suitable. The combination of filament temperatures that are likely to be in the range 2900–3450 K and quartz bulbs, which readily transmit UVR, results in a significant emission of UVR. In addition, the emission of blue light, which is a measure of the potential retinal photochemical hazard of a lamp, is higher. The incorporation of suitable secondary

filtration to reduce UVR emissions to an acceptable level is an important feature of the design of any illumination system using tungsten halogen lamps. Such lamps are used safely in filtered luminaires for a diverse range of applications. However, some luminaires incorporating tungsten halogen lamps and particularly some desk-top luminaires have no protective secondary filtration (McKinlay *et al.* 1989). The induction of UVR erythema in people has been observed from exposure to unfiltered tungsten halogen lamps (Césarini *et al.* 1989). Data on occupational hazard weighted UVR and on erythemally weighted UVR emitted by unfiltered desk-top luminaires indicate the need for effective filtration in some cases (Table 2.1). Newer types of double walled tungsten halogen lamps are available. Here the potentially harmful emissions of UVR are effectively attenuated by the outer hard glass envelope. These lamps are fitted with standard screw or bayonet cap connectors, typically have a claimed life of 2000 hours, are 25% more efficient than 'conventional' tungsten filament lamps, and are available in clear and pearl (diffuse) forms. They are intended to replace conventional tungsten filament lamps for general lighting purposes. The range of UVR emission data for some such lamps is presented in Table 2.1.

| Lamps | Effective irradiance* (mW m ⁻² effective) | | UVA (315–400 nm) (mW m ⁻²) | Reference |
|--------------------------------------|---|--------------------------------|--|-----------------|
| | ACGIH [†] | Erythema [‡] | | |
| Desk-top 20 W tungsten halogen lamps | 1.2–6.3 | 1.9–10.0 | 54–220 | McKinlay (1992) |
| Halogen A lamps | 0.2–2.3 (x 10 ⁻³) | 0.7–10.3 (x 10 ⁻³) | 3–15 | NRPB (1995) |

TABLE 2.1 Range of UVR emissions from desk-top tungsten halogen lamps (normalised to 500 lux illuminance)

* 30 cm from lamps.

[†] ACGIH (1989): 1 maximum permissible exposure for an 8 h working day is equivalent to 1 mW m⁻² effective.

[‡] CIE reference erythema action spectrum (McKinlay, 1992).

Low pressure discharge lamps

- 17 The most common application of the low pressure discharge is in fluorescent lamps. The fluorescent lamp operates by means of a discharge between two electrodes through a mixture of mercury vapour and a rare gas, usually argon. Light is produced by conversion of 253.7 nm mercury emission radiation to longer wavelength radiations by means of a phosphor coating on the inside of the wall of the lamp. Lamps are available with many different phosphors and envelopes to produce a wide range of spectral emissions covering the visible (light), UVA and UVB regions. While the continuum emissions of fluorescent lamps are characteristic of the phosphors, the narrow peak spectral emissions are dominated by the characteristic line emission spectrum of the low pressure mercury vapour discharge. In relation to other light sources the fluorescent lamp is particularly efficient, with some 20% or so of the input energy resulting in useful light. Data from a study of the amount of UVR emitted by 'white' fluorescent lamps used in the UK for general lighting purposes are presented in Table 2.2. The UVA emission data are generally similar to those of Cole *et al.* (1986) obtained from measurements on general lighting lamps being used in the USA; however, the UVB emissions from the American lamps (up to 10⁻³ W m⁻² effective)

were significantly greater than that found in a British study ($7 \times 10^{-5} \text{ W m}^{-2}$ effective). The emissions from some of the so-called super high output (SHO) tubes examined in the American study displayed the presence of 253.7 nm radiation. It has been suggested that this might have been due to a low iron content in the glass envelope of these lamps. The spectral transmission of the glass envelope has been shown to be particularly important in attenuating UVR.

18 Frequently in office and industrial environments where fluorescent lamps are used, the luminaire assembly incorporates a diffuser or controller. Three materials are commonly used in the construction of diffusers: opal acrylic, opal styrene and opal polycarbonate. Controllers are luminaire covers that are figured with small prisms or lenses. Two commonly used materials are clear acrylic and clear styrene. Some luminaires incorporate opal (diffusing) sides and a clear figured (controller) base. The use of diffusers and controllers results in the absorption and reflection of the radiation emitted by the associated lamp. The UVR-attenuating properties of different diffusers are demonstrated by the measurement data in Table 2.3.

19 During the past few years the further development and improved design of general lighting fluorescent lamps has been evident in the production of compact fluorescent lamps. These lamps are essentially low wattage, small diameter fluorescent tubes folded in a compact form. They are most readily available commercially with cool-white phosphors but other phosphors are also available. For a given illuminance their spectral emissions of UVR are essentially no different from those of full size tubular fluorescent lamps (Whillock *et al.* 1990) (Table 2.2).

TABLE 2.2 Range of UVR emissions for some fluorescent lamps (normalised to 500 lux illuminance)

| Lamp | UVB (mW m^{-2}) | UVA (mW m^{-2}) | | | Reference |
|---|---------------------------------|----------------------------|------------|------------|-------------------------------|
| | | 315–400 nm | 315–340 nm | 340–400 nm | |
| General lighting fluorescent lamps (UK) | – | 27–40 | 1.0–1.5 | 26.0–38.5 | Whillock <i>et al.</i> (1988) |
| Compact fluorescent lamps | $0\text{--}31 (\times 10^{-3})$ | 200–5400 | – | – | Whillock <i>et al.</i> (1990) |

TABLE 2.3 Measurements of UVR irradiance from various diffusers/controllers with a white fluorescent lamp as the source (McKinlay *et al.* 1988)

| Diffuser type | Irradiance totals in each waveband (percentage in parentheses) | | | | | |
|---------------------------------|--|-------|----------------------------|---------|--|---------|
| | UVA (mW m^{-2}) | | UVB (mW m^{-2}) | | UVB [†] (mW m^{-2} effective) | |
| Bare lamp | 22.32 | (100) | 3.45 | (100) | 0.059 | (100) |
| Clear acrylic* | 16.35 | (73) | 2.91 | (84) | 0.048 | (81) |
| Clear styrene* | 2.87 | (13) | 0 | (0) | 0 | (0) |
| Opal styrene [†] | 0.92 | (4) | 0.003 | (< 0.1) | 0.00002 | (< 0.1) |
| Opal polycarbonate [†] | 0.20 | (< 1) | 0.012 | (< 1) | 0.00009 | (< 1) |

* Surface figured with small prisms.

[†] Reeded surface.

[†] ACGIH (1989): 1 maximum permissible exposure for an 8 h working day is equivalent to 1 mW m^{-2} effective.

20 As well as a number of special colour-rendering fluorescent lamps which are essentially variants of general lighting fluorescent lamps, a number of special-applications fluorescent lamps have been developed and are commercially available. An example is the so-called black-light lamp which uses a nickel/cobalt oxide (Wood's glass) envelope. The phosphor chosen for these lamps emits around 370 nm in the UVA. Wood's glass is almost entirely opaque to light and the lamps are used for a number of commercial, scientific, medical and industrial fluorescence purposes as well as for display and entertainment. Three types of fluorescent lamps that emit UVR in printing and copying merit mention, namely lamps suitable for diazo printing with a main emission around 360 nm, those intended for modern 'fast' diazo printing with a principal emission around 420 nm, and those used for 'photocopying' with predominantly green emissions.

21 The development of a range of phosphors with enhanced UVA emissions has led to the widespread use of fluorescent lamps in PUVA (psoralen plus UVA) treatment cabinets, and in sunbeds and solaria. Fluorescent lamps used for photochemotherapy (PUVA) of psoriasis are generally the same types as those widely used for cosmetic tanning. A summary of the range of UVR emissions of some UVA fluorescent lamps is presented in Tables 2.4 and 2.5. Changes can occur in the UVR spectral emissions in such lamps as a result of ageing during normal use. These can amount to reductions in UVB up to 50%, and reductions in UVA up to 45% after 1000 hours of use. Philips Lighting has recently introduced a new tanning lamp called the CLEO Natural in which the UVB output is 5% of the overall UVR output. Percentage UVR emissions from common sunlamps and specialist lamps are summarised in Table 2.6. Fluorescent lamps intended for UVB irradiation, such as the Q-Panel UVB313 and Philips QFS40, TL01 and TL12 lamps, are also available (Table 2.6).

| Fluorescent peak (nm) | Measurements on single tubes at 1 m | |
|-----------------------|-------------------------------------|---------------------------|
| | UVA (mW m ⁻²) | UVB (mW m ⁻²) |
| 348-354 | 1.18-1.86 (x 10 ³) | 8.6-21.9 |
| 366 | 1.35 (x 10 ³) | 10.6 |

TABLE 2.4 Emissions from UVA fluorescent lamps (Diffey and McKinlay, 1983)

| Lamp type | Measurements made at 50 cm (percentage emissions in parentheses) | | | | | |
|-------------------|--|---------------------------|------------|--------------|--|--|
| | UVB (280-315 nm) (mW m ⁻²) | UVA (mW m ⁻²) | | | | |
| | | 315-400 nm | 315-340 nm | 340-400 nm | | |
| Philips TL10R | 1.4 (0.07) | 2100 (99.9) | 1.1 (0.05) | 2110 (99.98) | | |
| Philips TL09 | 7.2 (0.7) | 1040 (99.3) | 210 (20.0) | 830 (79.3) | | |
| Philips TL03 20 W | 0.12 (1.5) | 7.65 (98.5) | 0.04 (0.5) | 7.61 (98.0) | | |
| GEC-UVA | 7.2 (0.7) | 970 (99.3) | 200 (20.6) | 770 (78.7) | | |
| Wolff Rapidsonne | 34.6 (3.0) | 1110 (97.0) | 330 (30.0) | 770 (67.0) | | |
| Wolff Fittsonne | 6.9 (1.0) | 690 (99.0) | 150 (22.0) | 540 (77.0) | | |
| Wolff Fotomed | 63.5 (6.0) | 1000 (94.0) | 390 (36.0) | 610 (58.0) | | |

TABLE 2.5 UVR emission data for unused UVA fluorescent lamps, (NRPB, 1995)

TABLE 2.6
Percentage UVR
emissions from
common sunlamps
and specialist lamps
(McKinlay, 1992, and
after Diffey,
Personal
Communication)

| Lamp type | % UVB (280–315 nm) | % UVA | | |
|-----------------------|-----------------------|------------|------------|------------|
| | | 315–400 nm | 315–340 nm | 340–400 nm |
| Philips TL01 | 88 | 12 | 6 | 6 |
| Philips TL09 | 0.5 | 99.5 | 15.5 | 84 |
| Philips TL10 | 0.05 | 99.95 | 0.02 | 99.98 |
| Philips TL12 | 56.5 | 43.5 | 34 | 9.5 |
| Philips Cleo Natural | 4.5 | 95.5 | 35.5 | 60 |
| Philips Cleo Performa | 0.8 | 99.2 | 20.3 | 78.9 |
| Philips QFS40 | 54 | 46 | 35 | 11 |
| Q-Panel FUVB313 | 56 | 44 | 35 | 9 |
| Wolff Bellarium | 2.7 | 97.3 | 27.1 | 70.2 |

High pressure discharge lamps

22 The designation 'high intensity discharge' (HID) lamps includes the families of lamps often called high pressure mercury vapour, metal halide and high pressure sodium vapour lamps. Only mercury vapour and metal halide lamps emit significant amounts of UVR. High pressure mercury vapour lamps are widely used for industrial and commercial lighting, street lighting, display lighting, floodlighting and a large number of printing, curing and other industrial applications. The light spectral emissions of the discharge are in the blue, green and yellow regions of the spectrum with major emission lines at 436, 546, 577 and 579 nm, and a large amount of UVR is also generated. The general construction of high pressure mercury lamps is a fused silica (quartz) discharge tube containing the mercury/argon vapour discharge mounted inside an outer envelope of soda-lime or borosilicate glass. The colour range of the lamp can be made more acceptably white by the addition of a red emitting phosphor on the inside wall of the outer envelope. Another similar type of lamp has an outer envelope that is additionally coated internally with a reflective layer designed to direct most of the light downwards. The outer glass envelope effectively absorbs most residual UVR; consequently the quantity of potentially harmful UVR emitted by such lamps depends critically on the integrity of this envelope. Data from measurements made at 2 m from a mercury HID lamp with the outer envelope removed illustrate the importance of this aspect of safety design (Table 2.7).

23 High pressure mercury vapour lamps were once commonly used (with little or no filtration) for cosmetic tanning purposes. Typically they were 80 to 300 W lamps used either singly or in groups in a sunlamp installation. These lamps are now little used, having been largely replaced by UVA fluorescent and filtered HID UVA cosmetic tanning systems. High pressure mercury vapour health lamps have also been used for many years for medical treatment purposes (see Chapter 7, paragraph 75), and predominantly in the treatment of certain skin diseases, notably psoriasis and acne, and of pressure sores and superficial ulcers. Another common range of medical applications of high pressure mercury lamps is their use with a Wood's filter for diagnosing such disorders as *tinea capitis* and erythrasma (Diffey, 1986) by UVA-induced fluorescence. The use of high pressure mercury lamps for the UVA-photopolymerising of dental resins was at one time common but has now been replaced by the combined use of tungsten halogen lamps and blue-light sensitive resins.

| Lamp type | Effective irradiance* (mW m^{-2} effective) | | | | | | | |
|---|---|--------------------|-----------------|--------------------|-----------------|--------------------|-----------------|--------------------|
| | Test condition [†] | | | | | | | |
| | A | | B | | C | | D | |
| | With outer bulb | Without outer bulb | With outer bulb | Without outer bulb | With outer bulb | Without outer bulb | With outer bulb | Without outer bulb |
| General Electric H400 A33-1 Clear | 2.5 | 110 [‡] | <0.1 | 160 | 12.5 | 3640 | 0.2 | 0.2 |
| Westinghouse H33 GL 400/DX White | <0.1 | 1040 | <0.1 | 190 | 0.2 | 3680 | <0.1 | 0.3 |
| General Electric H400D x 33-1 White | <0.2 | 75 [‡] | <0.1 | 180 | 0.5 | 3900 [‡] | <0.1 | <0.1 [‡] |
| General Electric MV400/BUH Metal halide | <0.3 | 122 [‡] | <0.1 | 6 [‡] | 1 | 510 [‡] | <0.1 | <0.1 [‡] |

TABLE 2.7 UVR emissions from 400 W HID mercury vapour general lighting (USA) lamps (Piltingsrud *et al.* 1978)

* ACGIH (1989): 1 maximum permissible exposure for an 8 h working day is equivalent to 1 mW m^{-2} effective.

[†] Test condition:

A - Lamp mounted vertically - measurements at 2 m on mid-line axis of lamp.

B - Lamp mounted horizontally - measurements at 2 m on central axis of lamp.

C - Lamp mounted horizontally in reflector shield with no face plate - measurements at 2 m on central axis of lamp.

D - Lamp mounted horizontally in reflector shield with glass face fitted - measurements at 2 m on central axis of lamp.

[‡] Lamps did not operate at normal intensity.

- 24** The family of metal halide lamps encompasses a number of different types of high pressure mercury lamps whose discharges all contain additives. The additives are most typically metal halides chosen either to produce a strongly coloured emission (usually a single halide), to produce a more broadly spectrally uniform emission (multi-halide) or to enhance the UVR (most often UVA) emission. Compared with ordinary high pressure mercury lamps the luminous efficacies of metal halide lamps are high. They are used for a range of industrial and commercial applications that includes photochemical processing, graphic and photographic illumination, studio lighting and reprography and are also used for UVA cosmetic tanning equipment, for some medical applications, and for solar radiation simulation. Metal halide lamps are also used in filtered industrial applications requiring an activating range of wavelengths between 320 and 440 nm, eg lithographic platemaking and printed circuit photoresist etching.

Welding arcs

- 25** Gas welding processes operate at relatively low black-body temperatures and their emissions of UVR are low (Moss *et al.* 1979). In comparison with gas welding processes, the emissions of optical radiations from arc welding are very high and many data on the optical radiation emissions associated with a variety of electric arc welding processes have been published (Lyon *et al.* 1976; Marshall *et al.* 1979). The spectral emissions from arc welding processes vary with the composition of the electrodes and the metals being joined, the plasma that is created and the shielding gas used (Table 2.8). Where an

optical source of very high radiance and of small size is required a very high pressure arc lamp may be used. Such lamps have a filling gas of mercury vapour, mercury vapour plus xenon gas, or xenon gas. Metal halide types are also available. Two physical types are commonly used: the compact (or short) arc and the linear arc. Typical applications of compact arcs include projectors, searchlights, modern headlamps and solar radiation simulators. The spectral emission of xenon lamps, which at wavelengths shorter than infrared closely matches that of a black-body radiator at about 6000 K, enables their use as solar radiation simulators in experimental studies. Their emission spectrum is continuous from the UVR through to the IRR region. Large amounts of UVA, UVB and UVC are emitted by unfiltered lamps to the extent that they can present a significant health hazard if incorrectly used. The luminance of compact xenon arcs may approach that of the sun (approximately 10^9 cd m^{-2} *) and in some lamps with greater than 10 kW rating the luminance of the brightest spot may exceed $10^{10} \text{ cd m}^{-2}$. They therefore present a potentially severe retinal hazard if viewed.

TABLE 2.8
Summary of UVR
emissions (at 1 m)
from a variety of
electric arc welding
processes (Slaney
and Wolbarsht,
1980)

| Process | Base metal | Current (A) | Gas | Arc gap (mm) | UVR* (mW m^{-2}) |
|---------|------------|-------------|-----------------------------|--------------|-----------------------------|
| TIG | Steel | 50-300 | Argon | 1.6-3.2 | 0.03-1.2 ($\times 10^3$) |
| MIG | Aluminium | 125-300 | Helium | 6.4 | 2-5 ($\times 10^3$) |
| PAW | Steel | 100-275 | 85% argon + 15% hydrogen | 4.8 | 0.28-1 ($\times 10^3$) |

* ACGIH (1989): 1 maximum permissible exposure for an 8 h working day is equivalent to 1 mW m^{-2} effective.

Lasers

- 26** The production of optical radiation by a laser is generally a process similar to that used in gaseous discharge non-laser sources. Emissions are the result of electronic transitions in the atoms or molecules of a material from low to high energy states (absorption and excitation) followed by transitions from the high to the low energy states (de-excitation and emission).
- 27** All lasers have three basic components: a laser (active) medium, an energy source (pumping system), and a resonant optical cavity. A pumping system is necessary to provide energy to electrons to raise them to excited states and achieve what is termed 'population inversion'. This is a condition where there are more atoms or molecules in a higher energy state than in a lower energy state and is a critical condition for the stimulated emission from a laser. The pumping system can be optical, using an intense source such as a xenon flashtube or another laser; electron collision pumping, using an electrical discharge or radiofrequency radiation; or chemical pumping, using the energy released from making and breaking chemical bonds. Mirrors placed at each end of the laser medium form a resonant cavity. The construction is such that the beam passes through the laser medium several times and the number of photons is amplified during each transit. One of the mirrors is chosen to be partially transmitting thus enabling part of the laser beam to be emitted from the cavity. The resultant emission is essentially monochromatic.

* The candela, cd, is the unit of luminous intensity, in a given direction, of a source emitting a given monochromatic radiation.

| Type | Name | Spectral emissions (nm) |
|-------------|---|-----------------------------|
| Excimer | Fluorine (F ₂) | 157 |
| | Argon fluoride (ArF) | 193 |
| | Krypton fluoride (KrF) | 248 |
| | Xenon chloride (XeCl) | 308 |
| | Xenon fluoride (XeF) | 351 |
| Dye | Excimer, solid state, gas laser pumped | Down to 197 (dye dependent) |
| Gas | Nitrogen (N ₂) | 337 |
| | Helium cadmium (HeCd) | 325 |
| Gas ion | Argon (Ar) | 364, 351 |
| | Krypton (Kr) | 356, 351 |
| | Ar or Kr with -barium borate non-linear crystal | 229-264 |
| Solid state | Neodymium:YAG (Nd:YAG) | 355 (frequency tripled) |
| | | 266 (frequency quadrupled) |

TABLE 2.9 Some lasers with UVR emissions

- 28** There are a number of lasers that emit UVR directly. However, UVR emissions can also be produced by adding non-linear crystals to the optical path of the laser beam to either double, triple or quadruple the frequency of the beam (ie producing radiation at a half, a third or a quarter of the original wavelength). Advances in laser technology have resulted in an increasing number of available UVR wavelengths, across the UVA, UVB and UVC regions - examples are shown in Table 2.9. The future development of semiconductor lasers will result in physically smaller UVR lasers increasing the range of applications. UVR emitting lasers are already extensively used in the semiconductor industry where shorter wavelengths generally mean greater precision of manufacture and higher component densities.

SUMMARY AND CONCLUSIONS

- 29** For most people the major source of UVR exposure is the sun. However, for some individuals, for at least some of the time, UVR from artificial sources may contribute significantly to their total exposure. Such sources include those used for medical therapy, cosmetic tanning and a few industrial sources.
- 30** Ground-level measurements of solar UVR have been made worldwide for many years. However, until recently, these measurements have not been coordinated internationally. They provide only a limited database for assessing personal exposure to solar UVR.
- 31** There is no convincing evidence from published measurement data worldwide for populated areas to indicate a global trend of changing solar UVR at the Earth's surface with time or with stratospheric conditions. This is likely to be due to dominant tropospheric variables, such as atmospheric absorption and scattering processes, localised atmospheric pollution and cloud cover.
- 32** Incandescent sources such as tungsten filament bulbs generally emit levels of UVR insignificant to human health, although some unshielded tungsten halogen lamps can emit amounts of UVR sufficient to cause erythema.

- 33** Fluorescent lamps for general lighting are specifically designed to emit light. They emit very small amounts of UVR at the levels of light exposure normally encountered in the home and in the workplace. However, special-applications fluorescent lamps, such as those used for cosmetic tanning, emit levels of UVR sufficient to cause skin and eye injury. The most potent artificial sources of UVR, and particularly of UVB and UVC, are those characterised as high intensity discharge (HID) lamps. These include high pressure mercury, mercury metal halide and xenon lamps. The spectral emissions of a xenon lamp enable its use as a solar radiation simulator for experimental studies but depend critically on the operating characteristics of the lamp and on the spectral filters incorporated in the irradiation system. The performances of such lamps change with time and frequent calibration of the irradiation system is required. HID lamps used for lighting purposes are double enveloped lamps whose outer envelope attenuates the UVR emitted and, when used within properly designed luminaires, do not present a UVR hazard. Any HID lamps used in an open situation without secondary containment are likely to constitute a UVR hazard.
- 34** Gas welding, brazing and cutting processes operate at temperatures insufficiently high to cause the emission of intense UVR, but advised limits for protection may be approached if exposures at short distances are very prolonged. Arc welding processes are particularly potent sources of UVR and even very short exposures may be hazardous to the eyes and to the skin. Both gas and arc welding also emit light and IRR which may be hazardous to the retina. Appropriate personal protection always needs to be worn during gas or arc welding.

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3 Cellular Studies

INTRODUCTION

- 1 The shorter UVB (290–320 nm) wavelengths are strongly absorbed by, and damage, DNA and are considered to be the primary photocarcinogenic wavelengths, at least with regard to non-melanoma skin cancer. For more than three decades cellular studies have therefore focused on the direct DNA damage caused by sunlight and DNA repair mechanisms. Considerable new information continues to emerge on DNA repair as the relevant genes are cloned. UVA (320–380 nm) radiation is also carcinogenic to animals and interacts with tissues by generating an oxidative stress. Recent studies have therefore focused on the type of oxidative DNA damage induced by UVA radiation and the modulation of UVA damage by endogenous antioxidants. The search has continued for the chromophore(s) for UVA radiation damage and, under certain conditions, melanin is clearly a chromophore that leads to photosensitisation. There have also been considerable advances in our knowledge of the modulation of gene expression by UVA and UVB radiation and there is current focus on the significance of these very marked acute changes.
-

OXIDATIVE DNA DAMAGE

Induction of oxidative DNA damage and action spectra

- 2 There has been an awareness for some time that the longer wavelength components of sunlight have oxidising properties and part of this evidence was the demonstration that UVA radiation causes DNA strand breaks in both procaryotic (Tyrrell *et al.* 1974) and eucaryotic cells (Roza *et al.* 1985). There has been renewed interest in this area as techniques to measure specific types of oxidative damage, in particular 8-hydroxy deoxyguanine (8-OHdG), have developed. UVA radiation clearly induces significant levels of 8-OHdG in mammalian cells (Kvam and Tyrrell, 1997a; Zhang *et al.* 1997a), although action spectra differ in their definition of the precise wavelength dependence for the induction (Kielbassa *et al.* 1997; Kvam and Tyrrell, 1997b). Although the measurements were made rather differently, the difference between a response peaking in the UVA (Kvam and Tyrrell, 1997b) versus a response peaking in the near-visible (Kielbassa *et al.* 1997) is almost certainly due to a difference in the chromophore profile between the two cell types (human skin fibroblasts versus Chinese hamster ovary cells). Analysing oxidative DNA damage after exposure to several types of broad-spectrum radiation (UVA, UVB, UVC and solar simulator), Douki *et al.* (1999) concluded that 8-OHdG damage was not involved in cell lethality and was unlikely to be involved in mutagenesis. The latter conclusion is based on the type of UVA-induced mutations which were characteristic of changes at bipyrimidine sites rather than oxidised guanines. Analysis of UVA-induced mouse skin tumours led to similar conclusions for the originating damage in photocarcinogenesis (Van Kranen *et al.* 1997). However, it is clear that until a more detailed picture of the spectrum of oxidative DNA damage emerges, no final conclusion can be drawn.

Modulation of UVR damage by antioxidants

- 3 Reduced glutathione has been shown to be the critical endogenous antioxidant in preventing potentially lethal oxidative damage in cells (Tyrrell and Pidoux, 1986, 1988). A lack of any single antioxidant enzyme (catalase, superoxide dismutase) does not appear to alter UVA lethality (Tyrrell and Pidoux, 1989). Various combinations of chemical and enzymatic antioxidants have been used in many studies to help elucidate the nature of the reactive oxygen species involved in UVR-induced oxidative damage, particularly the longer wavelengths (see Tyrrell, 1997). Various studies have indicated that singlet oxygen is a major player in UVA-induced lethality (Tyrrell and Pidoux, 1989), as well as oxidative DNA damage (Kvam and Tyrrell, 1997; Zhang *et al.*, 1997b) and UVA activation of gene expression (Basu-Modak and Tyrrell, 1993; see paragraphs 20 and 21).

UVR damage to antioxidant defence

- 4 Oxidative damage to proteins by UVR will undoubtedly contribute to a weakening of the enzymatic antioxidant defense system in skin. It has been shown that both UVB and particularly UVA radiations can destroy glutathione both in human skin (Wheeler *et al.* 1986) and in cultured human skin cells (Lautier *et al.* 1992). Catalase is rapidly destroyed by UVA radiation, presumably because the heme groups are powerful chromophores and highly susceptible to damage. Both acute and chronic irradiation of the skin of hairless mice will lead to strong suppression of catalase activity (eg Okada *et al.*, 1994; Shindo *et al.*, 1994). Although superoxide dismutase activity is induced by acute and repeated exposures to UVB, the overall chronic effect of irradiation is likely to be a suppression. In later studies (Podda *et al.*, 1998) human skin equivalents were used to investigate destruction of various non-enzymatic antioxidants and ubiquinol and ubiquinone were clearly the most sensitive of the compounds tested.

Multidrug resistance, overexpression of P-glycoprotein and resistance to UVR radiation

- 5 A recent study showed that a multidrug resistant cell line which overexpressed P-glycoprotein was resistant to UVA radiation (but not UVB or UVC) relative to a cell line not expressing P-glycoprotein (Trindade *et al.*, 1999) Since MDR modulators did not effect resistance to UVA radiation, this result is likely to reflect direct damage to the P-glycoprotein itself and be unrelated to its activity as an efflux pump.
-

MELANIN – A ROLE IN DAMAGE ENHANCEMENT AND PROTECTION

Enhancement and protection from damage *in vitro* by melanin and its precursors

- 6 Melanin and certain precursors can sensitise biomolecules to photodamage (Koch and Chedekel, 1987; Routaboul *et al.*, 1995). More recently it has been shown that in the presence of Cu(II), L-DOPA (a precursor of melanin) and melanin can cause strand breakage and exposure to eumelanin alone can enhance strand breaks (Hill and Hill, 1987; Husain and Hadi, 1998) and induce oxidative DNA damage 8-OhdG (Kvam and Tyrrell, 1999) in pure DNA and such damage is strongly enhanced by low doses of UVA radiation. In contrast, lipid peroxidation in a UVR-exposed model liposome system is

substantially reduced in the presence of the melanin precursors, 5,6-dihydroxyindole and 5-S-cysteinyldopa (Schmitz *et al* 1995).

Melanin and UVR damage to cultured cells

- 7 Various studies have addressed the question as to whether melanin can act as a photosensitiser of DNA damage particularly in cultured melanoma cells. Kobayashi *et al* (1993) used melanoma cell types with differing melanin levels and showed that the melanin actually protected against DNA damage induced directly by UVR exposure (cyclobutane-type pyrimidine dimers and 6-4 photoproducts). Indeed, the melanin in the skin of living fish has been shown to decrease the dimers induced in the epidermis by monochromatic UVB radiation at 290, 302 and 313 nm (Ahmed and Setlow, 1993). However, where oxidative-type DNA damage has been measured, there is evidence that melanin can act as a photosensitiser (Wenczl *et al* 1998; Kvam and Tyrrell, 1999). By using melanocytes derived from different skin types and modulating melanin levels, Wenczl and co-workers were able to show that melanocytes contained chromophores that sensitised them to UVA-mediated strand breakage and that this appears to involve either pheomelanin or melanin precursors. Marrot *et al* (1999) also used normal human melanocytes and modified melanin levels and could show that the levels of UVA-induced strand breakage, as assessed by the 'comet assay', were dependent on the level of pigment. Similar conclusions were reached by Kvam and Tyrrell (1999) for the specific oxidative DNA damage 8-OHdG using different melanoma cell lines in studies in which cells were used with altered eumelanin/pheomelanin levels.
- 8 In a related study in keratinocytes, Kipp and Young (1999) added the eumelanin precursor 5,6-hydroxyindole-2-carboxylic acid to cultured human keratinocytes and showed that UVA-induced strand breakage (as estimated by the comet assay) was enhanced by the pre-treatment. It is not clear how the concentrations employed relate to *in vivo* concentrations of the precursor.

Melanin and cell death or mutation

- 9 Studies from Hill's laboratory (Hill *et al*, 1997) which have used melanocyte lines derived from pigmented and albino mice have indicated that an albino cell line was protected against UVB and FS20 (broad-spectrum) irradiation as a result of the lack of pigment and that there was a corresponding increase in pyrimidine dimers (cyclobutane-type and 6-4 photoproducts) in a highly pigmented cell line (but see Kobayashi *et al*, 1993, above). However, in studies from the same group (Li and Hill, 1997) using the Cloudman S91 mouse melanoma line, it was reported that both killing and mutation induction after irradiation with monochromatic UVB was reduced in pigmented cells and there was also protection against killing (but not mutation) induced by UVB + UVA (FS20) irradiation. Overall the studies are indicative that melanin may sensitise to UVA-mediated cell death. In contrast, Barker *et al* (1995) showed that cultured human melanocytes derived from skin types I to VI had similar UVB sensitivity regardless of melanin content but the more pigmented cells showed a greater capacity to resume proliferation after the irradiation treatment.

UVR and melanogenesis

- 10 The mechanism by which UVR stimulates melanogenesis is still not fully understood. However, the following three recent findings in the area are particularly worthy of note.

- 11** Fairly convincing data have now accumulated to support the concept that DNA damage or the repair that follows UVR damage is critically involved in the process of melanogenesis (Eller *et al.* 1996; Gilchrest and Eller, 1999). The dinucleotide pTpT mimics most of the effects of UVR on induction of pigmentation and tyrosinase mRNA regulation and, in addition, enhances repair of UVR-induced DNA damage in human cells.
- 12** The synthesis of alpha-melanocyte stimulating hormone and adrenocorticotrophic hormone are both stimulated by exposure to UVR and these proteins act on the recently cloned melanocortin-1 receptor (MC1R), which in turn stimulates cAMP formation – a major factor in inducing melanogenesis (for review, see Hearing and Abdel-Malek, 1999). There are many allelic variants of the MC1R gene and several of these are expressed in individuals with skin type I or II, red hair and poor tanning ability.
- 13** Another important finding in the area of UVR-induced melanogenesis is that normal human keratinocytes secrete nitrate oxide (NO) in response to UVA and UVB radiations (Romero-Graillet *et al.* 1997) and this NO can stimulate melanogenesis in the melanocyte fraction of a keratinocyte/melanocyte co-culture, suggesting that NO may play an important role in paracrine mediation of UVR-induced melanogenesis.
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DNA REPAIR

- 14** DNA repair is critically involved in the carcinogenesis process and DNA damage is continuously removed from cellular DNA as a result of this repair. The main pathway for removal of UVR damage is excision repair (Lindahl and Wood, 1999). Approximately 130 repair genes have been described to date (Wood *et al.* 2001). Patients with the disease xeroderma pigmentosum (XP) are highly susceptible to solar radiation induced skin cancer (Arlett and Lehmann, 1996; Bootsma *et al.* 1998) because of DNA repair defects. The majority are deficient in one of several steps in nucleotide excision repair and fall into seven genetically distinct complementation groups. XP variant patients have defects in post-replication repair, more specifically on an alteration in DNA polymerase involved in translesion synthesis (Masutani *et al.* 1999).
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UVR MODULATION OF GENE EXPRESSION

Cellular level

- 15** Strictly speaking, altered gene expression implies an alteration in the level/activity of the final protein product. However, the term is currently used to describe changes at the level of signal transduction, promoter activity and in mRNA accumulation as well as post-transcriptional regulation. Under this wide definition, UVR in the solar range has been observed to modulate the expression of many genes depending on the wavelength range of UVR employed, the dosage level and the cell type (Tyrrell, 1996a,b). Despite numerous publications on the topic, the functional consequences of this altered expression are rarely known. The effects of UVB radiation are usually similar to those documented for the non-solar UVC wavelengths. The expression of numerous genes has been shown to be modified following UVC/UVB irradiation of cells. The explanation of this large number almost certainly lies in well-documented

observations that three major classes of transcription factor (AP-1, NF κ B and p53) are either activated (AP1 or NF κ B) or stabilised (p53) by short wavelength UVR. Several of the stress-responsive signalling pathways, notably jun kinases and p38MAP kinases (both stress-activated protein kinases, SAPKs), and ERK kinases, are activated by short wavelength UVR, although the early events that trigger the response are still controversial. Since literally hundreds of eucaryotic promoters have cis-acting elements that will bind these factors, it is not surprising that the expression of a considerable number of genes can be modulated. However, it is crucial to note that a majority of the studies have been done at very high (supra-lethal) UVR doses and, while they have been extremely informative about the signalling cascades involving protein kinases phosphatases, many of the effects observed are not relevant to normal, physiological exposures. However, there are important exceptions and both metallo-proteinases and the jun component of the AP-1 complex are activated both in cultured human skin cells and in human skin irradiated *in vivo* (Scharfetter *et al* 1991; Fisher *et al*, 1996, 1998) at physiologically relevant dose levels. Furthermore relatively low levels of UVB radiation and normal levels of UVA radiation can activate cytokine production (eg IL-1, IL-6 and TNF- α) in both primary and transfected human keratinocyte cell lines (for review, see Ullrich, 1995).

- 16** Studies with UVA radiation have usually been designed to involve physiologically relevant doses. UVA radiation significantly up-regulates expression of several genes in cultured human skin fibroblasts including collagenase, intercellular adhesion molecule 1, CL100 phosphatase and heme oxygenase 1 (HO-1), the last being the most dramatic oxidant-mediated up-regulation of any higher eucaryotic gene so far observed. In recent studies strong up-regulation of both c-fos and c-jun expression by UVA radiation of cultured fibroblasts has been observed (Bose *et al* 1999; Soriani *et al*, 2000) These proteins are nuclear oncogenes as well as transcription factor components of the AP-1 complex.
- 17** UVB can mimic growth factor responses, eg by causing dimerisation of growth factor receptors (Miller *et al* 1994), and the proteins that are increased after UVB treatment are often involved in growth stimulation. UVB radiation can also interact with STAT 1 (an important cytoplasmic transcription factor that is phosphorylated by Janus kinases in response to interferon gamma and translocated to the nucleus) and inhibits activation of STAT 1 dependent genes (Aragane *et al*, 1997). Recent studies have indicated that formylated indolocarbazoles (tryptophan photoproducts) are potent Ah-receptor agonists and that UVB radiation can activate CYP1A1 (cytochrome P 450) gene expression in several human cell types (Wei *et al* 1999). Clearly there are many ways in which UVB radiation can modulate gene expression.

The skin

- 18** For the most part, the patterns of UVR modulation of gene expression observed in cells are also reflected in studies with skin irradiated *in vivo* (Tyrrrell, 1996a,b). Much of this work has been done with solar-simulated radiation, which is predominantly UVB and information is available for both rodents and humans. Increases in p53 protein, collagenase and ornithine decarboxylase have all been observed in skin after exposure to broadband UVB radiation and increases in HO-1 protein and ferritin have been observed in human skin following broad-spectrum UVA radiation. Although there are

several studies showing that the AP-1 components that include fos and jun, are increased to some extent in skin following UVR treatment, recent studies using shave biopsies of human skin treated with radiation *in vivo* have shown that only the jun protein shows significant increases and that fos is expressed constitutively at significant levels (Fisher *et al.* 1998). The induction is inhibited by retinoic acid, but this is not an effect on signal transduction and occurs at the post-transcriptional level. Work from the same group (Fisher *et al.* 1996) has convincingly shown that metalloproteinases are strongly induced in human epidermis at UVB doses as low as 0.2 of a minimum erythemal dose. The transcriptional regulation of the metalloproteinase enzyme, collagenase, involves the AP-1 cis-acting response element in the promoter of the gene which corresponds to the DNA sequence originally observed as a phorbol ester responsive element (Angel *et al.* 1987).

- 19 Both collagenase and heme oxygenase 1 (HO-1) are clearly up-regulated in the dermis following exposure to UVA radiation. It is likely that chronic stimulation of collagenase will be involved in the photoageing process. The bulk of evidence suggests that HO-1 induction is a protective response against oxidative damage and that this involves both the capacity of HO-1 to break down heme and its involvement in iron homostasis and re-utilisation (Vile *et al.* 1994; Poss *et al.* 1997; Kvam *et al.* 1999).

Oxidative stress and UVR-induced gene expression

- 20 UVA inducibility of HO-1 gene expression (as monitored by mRNA accumulation) can be enhanced several-fold in human fibroblasts by depleting cellular glutathione (Lautier *et al.* 1992). Similar observations have been made with other UVA-inducible genes that have been tested including the two AP-1 transcription factor components, c-fos and c-jun (Bose *et al.* 1999; Soriani *et al.* 2000). Interestingly the basal level of expression of HO-1 is also reproducibly enhanced five-fold under conditions of glutathione depletion. This is consistent with the possibility that intermediates generated during cellular metabolism and normally quenched by cellular reducing equivalents may actually be triggering the expression of constitutive levels of the mRNA.
- 21 Another factor common to oxidant (UVA)-inducible gene expression is that the generation of singlet oxygen appears to be a crucial early event in the activation response. Again, this was first postulated for the HO-1 gene (Basu-Modak and Tyrrell, 1993) and it has now been shown that singlet oxygen is involved in the UVA activation of other genes such as collagenase (Wlaschek *et al.* 1997) and intercellular adhesion molecule 1 (ICAM1) (Grether-Beck *et al.* 1996).
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SUMMARY AND CONCLUSIONS

- 22 Several lines of evidence show convincingly that UVB radiation causes damage to DNA by direct absorption. UVA radiation also leads to potentially mutagenic base damage (eg 8-OHdG) but via oxidative pathways. DNA repair processes are critical for removal of all types of base damage. The role of antioxidant enzymes is still being elucidated. Glutathione is known to be the major endogenous antioxidant that protects against UVA damage. Both glutathione and the antioxidant enzyme, catalase, are progressively destroyed by UVA radiation. While UVR is intimately involved in the process of melanogenesis, melanin can act as a photosensitiser and generate both

oxidative damage and cytotoxicity under certain conditions. UVB and UVA radiations activate expression of a wide variety of genes, the functional significance of which is still under investigation. UVB and UVA radiations can activate oncogene and metallo-proteinase expression in skin, both of which are implicated in carcinogenesis.

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4 Animal Studies of Photocarcinogenesis

INTRODUCTION

- 1 Animal studies of the carcinogenicity of UVR have been summarised by IARC (1992), WHO (1994), de Gruijl (1995, 1999), de Laat and de Gruijl (1996) and Longstreth *et al* (1998), as well as by the Advisory Group (NRPB, 1995). In particular, in its previous report on health effects from exposure to UVR, the Advisory Group noted that numerous experiments have taken place using a variety of different UVR sources, many with a broad spectral output, emitting in the UVB and UVA regions and sometimes in the visible wavelength region. Skin tumours have been elicited after single exposures to UVR, but more often result from experimental protocols in which irradiation is given daily for weeks or months. Carcinogenicity has been investigated mostly in mice, less often in rats, and infrequently in other species. Squamous cell carcinomas (SCC) are readily induced in rodents by exposure to solar radiation or to UVR. IARC (1992) considered that the evidence was sufficient to conclude that solar radiation, broad-spectrum UVR, and UVA, UVB or UVC radiation were all carcinogenic to experimental animals. Melanoma-like tumours have been induced in hybrid fish and in a marsupial following UVR exposure, but not in rodents unless applied in conjunction with a chemical carcinogen. Basal cell carcinoma (BCC), the most common human malignant skin tumour, has rarely been observed in experimental animals exposed to UVR. Interesting new lines of research using transgenic or knockout mouse models for both melanoma and BCC as well as SCC are described below.
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SQUAMOUS CELL CARCINOMA

- 2 Many quantitative studies of the induction of squamous cell carcinomas (SCC) have used the hairless mouse model to determine action spectra and dose dependence. More recently, the generation of transgenic or knockout mice bearing functionally disabled tumour suppressor genes such as *Tp53* (previously known as *p53*) or genes encoding DNA repair proteins have enabled the investigation of their role in skin carcinogenesis following UVR exposure at a more fundamental level.

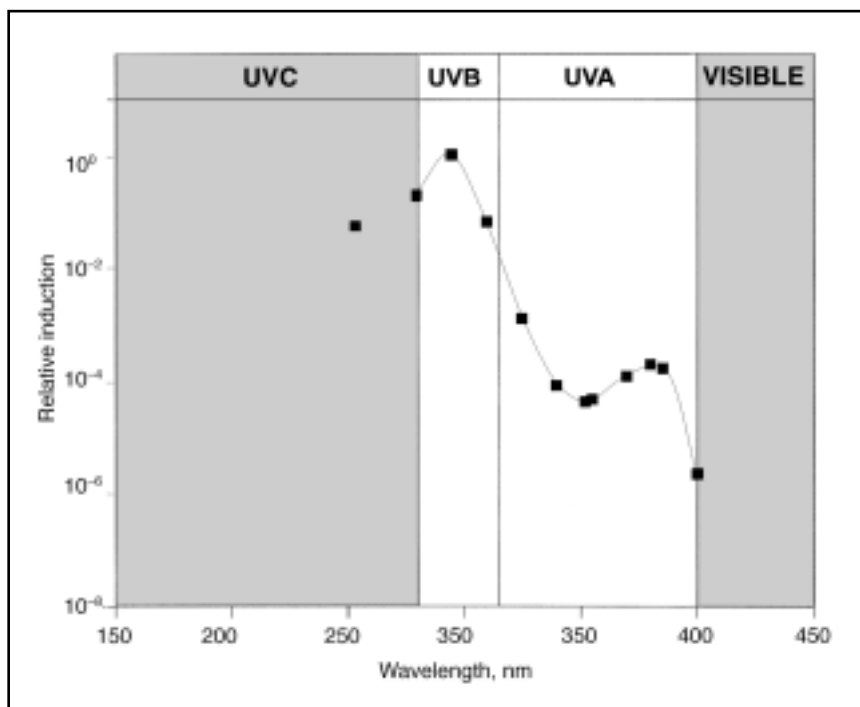
'Natural' animal models

- 3 The induction of SCC in albino (Skh:h-1) or lightly pigmented (Skh:h-2) mice provides most of the recent quantitative data available on experimental photocarcinogenesis *in vivo*. These tumours are readily induced by exposure to UVC, UVB and UVA radiation. However, the daily dose of UVR required to induce carcinoma following repeated exposure is usually well below typical outdoor values, probably reflecting a greater sensitivity of the relatively thin mouse epidermis to UVR damage compared to humans. Recent data (Mitchell *et al*, 1999) indicate that chronic exposure to UVB results in DNA damage that persists for weeks after exposure in a small number of heavily DNA damaged cells at the dermal-epidermal boundary. In addition, DNA repair was significantly reduced, suggesting an enhanced predisposition to UVR-induced carcinogenesis.

Action spectrum and dose dependence

- 4 The most rigorous action spectrum for SCC in the mouse has been derived by de Gruijl *et al* (1993), combining data on chronic UVR-induced tumours from experiments carried out between 1978 and 1991 at the University of Utrecht in the Netherlands (de Gruijl and van der Leun, 1992), and at the Photobiology Unit of the former Skin and Cancer Hospital in Philadelphia in the USA (Cole *et al*, 1986). Data were collected from a total of 1100 hairless albino Skh:h-1 mice exposed each day to UVR from one of 14 different broadband UVR sources covering the spectral range 253 nm to more than 400 nm. The mice were exposed to one of several doses from each source and, for UVA sources, exposure times were increased to 12 hours per day in order to generate an effective dose. A SCUP (Skin Cancer Utrecht-Philadelphia) action spectrum (Figure 4.1) was derived over the wavelength range 270–400 nm by calculation, based on goodness-of-fit, from the t_{50} (time in days until 50% of the mice bear 1 mm tumours) data for carcinomas resulting from each UVR source. The action spectrum was well defined in the UVB region, but had increasing uncertainty in the UVA and UVC regions. It shows a minimum around 350 nm and a secondary peak at longer wavelengths. Interestingly in this context, Kielbassa *et al* (1997) observed UVR-induced oxidative DNA damage in Chinese hamster ovary cells exposed *in vitro* to show a minimum around 350 nm and a secondary peak at longer wavelengths, in this case extending into the visible region. Perhaps more pertinently, Kvam and Tyrrell (1997) reported that UVR-induced oxidative guanine base damage in human skin fibroblasts peaked at around 365 nm. Both studies suggest a probable role for oxidative DNA damage in the aetiology of UVA carcinogenesis.

FIGURE 4.1 SCUP action spectrum for SCC induction in hairless albino mice: the relative induction at 254 nm is shown separately (from de Gruijl *et al*, 1993)



- 5 The dose–time dependence of SCC induction, particularly following exposure to long wavelength (365 nm) narrowband UVA (UVA-1) radiation has been explored in detail by de Laat *et al* (1997a,b). The experimental data fell within the anticipated range based on the SCUP action spectrum; however, the median induction time (t_{50}) was found to be inversely proportional to the daily dose (D) to the power 0.35; a less steep dose dependency than previously demonstrated for UVB (proportional to $D^{-0.62}$) suggesting that, compared to UVB, the carcinogenicity of low doses of long wavelength UVA could be higher than previously expected.

***Tp53* tumour suppressor gene mutations**

- 6 UVR-induced *Tp53* tumour suppressor gene mutation is clearly implicated in the aetiology of SCC in humans and mice. Following chronic UVB exposure of mice, patches of epidermal skin cells revealed elevated *Tp53* levels, over 70% of which reacted with mutant-specific monoclonal antibodies, for at least several weeks following exposure but decreasing in number over time (Berg *et al*, 1996). In contrast, brief exposure resulted in a uniform but transient increase in *Tp53* which did not react with mutant specific antibody. Similar results have been reported in humans. Ren *et al* (1996) found that a large fraction of sun-exposed skin contained mutated *TP53*. Cells of each *in situ* or invasive tumour carried the same mutation, in contrast to adjacent patches of skin cells that carried variable *TP53* mutations, suggesting that *TP53* mutation is an early event in the development of SCC. Since cells with mutant *TP53* show a diminished capacity to undergo apoptosis, the results of Berg *et al* (1996) suggest that repeated sun exposure may preferentially enhance their survival compared to normal keratinocytes, whereas the decrease in the number of *TP53*-positive patches following exposure indicates that regression may occur once such exposure ceases.
- 7 Mutations with clear 'UVB fingerprints' have been observed in the *TP53* tumour suppressor gene of human non-melanoma skin cancers and UVB-induced murine SCC. In mice, over 95% are found at dipyrimidine sites in the non-transcribed strand (Dumaz *et al*, 1997); such strand bias does not exist in humans. The majority were C→T transitions with 5% CC→TT tandem double mutations. Four distinct UVB mutation hotspots were identified: two major ones at codons 267 (33%) and 272 (19%) and two minor ones at codons 146 (10%) and 173 (4%). UVA I is much less effective in inducing these mutations (van Kranen *et al*, 1997; de Laat *et al*, 1997a,b); only 14% of 365 nm-induced skin tumours carried *Tp53* mutations compared to 54%–73% identified in UVB-induced tumours, suggesting that the *Tp53* gene does not play an equally important role in UVA-driven skin carcinogenesis.
- 8 Li *et al* investigated further the role of the *Tp53* tumour suppressor gene in the aetiology of UVR-induced skin tumours using transgenic mice carrying multiple copies of a mutant allele of the *Tp53* gene as well as wild-type alleles (Li *et al*, 1995, 1996) or homozygous *Tp53*-deficient (*Tp53*^{-/-}) knockout mice (Li *et al*, 1998). More SCC developed in the transgenic mice following UVB exposure (8 kJ m⁻² three times per week) than in the control wild-type mice, suggesting that mutation of the *Tp53* gene is an important step in the development of SCC. In the *Tp53* knockout mice, exposure to UVB (3.6 kJ m⁻² three times a week) resulted in tumour development in the knockout mice within 12 weeks, considerably earlier than the 21–37 week latency seen in other studies following the exposure of wild-type mice, confirming the view that loss of *Tp53* function leads to the accumulation of mutations and skin cancer.

Nucleotide excision repair defective mice

- 9** In humans, inherited defects in nucleotide excision repair (NER) are associated with at least three distinct photosensitive disorders: xeroderma pigmentosum (XP), Cockayne's syndrome (CS) and trichothiodystrophy (TTD). Complementation studies with patient cell lines have revealed the existence of seven potentially affected genes in xeroderma pigmentosum (*XPA* through to *XPG*), two in Cockayne's syndrome (*CSA* and *CSB*), and three in trichothiodystrophy (*TTDA*, *XPB* and *XPD*). Knockout mice which carry genetic defects which mimic these disorders have been used to investigate the role of nucleotide excision repair in UVR-induced skin tumorigenesis. One of the immediate effects of DNA damage is to block transcription. A specialised NER sub-pathway preferentially directs DNA repair to the transcribed strand of active genes (transcription-coupled repair) which is important for the removal of lesions for which the global genome repair process is too slow. All XP and TTD complementation groups are deficient in global genome repair and, with the exception of XPC, are also deficient in transcription-coupled repair. A specific defect in transcription-coupled repair is encountered in Cockayne's syndrome which results from mutations in the *CSA* or *CSB* gene. Fibroblasts from Cockayne's syndrome patients exhibit normal global repair but are UVR sensitive and are unable to recover RNA synthesis after UVR exposure.
- 10** In one experiment (van der Host *et al.*, 1997), *CSB*-deficient mouse knockouts (*CSB*^{-/-}) exposed to low levels of UVB (1 kJ m⁻² per week) developed SCC significantly earlier than the heterozygous (*CSB*^{+/-}) or wild-type (*CSB*^{+/+}) litter mates. The absence of such a clear oncogenic predisposition in human Cockayne's syndrome probably results from the more effective removal of pyrimidine dimers by global genome repair in man compared to that in mice (de Grujil, 1999), a murine characteristic that renders even normal mice more sensitive to UVB-induced skin tumours than humans through the accumulation of mutations on the non-transcribed DNA strand.
- 11** Xeroderma pigmentation patients are characterised by a dramatic, 2000-fold, increase in the risk of skin cancer. Recently, the mouse homologue of the human genes responsible for XP complementation group A (*XPA*), which are defective in global genome and transcription-coupled DNA repair, and complementation group C (*XPC*), defective only in global genome repair, have been cloned and knockout mice have been generated. Berg *et al.* (1997) found that skin tumours appeared approximately four times earlier in *XPA*^{-/-} mice exposed to broadband UVR for 500 days compared to their heterozygote or wild-type littermates. The authors calculated that the risk of skin cancer was increased by more than 10⁴ times in these mice, which is in line with data for human xeroderma pigmentosum.
- 12** Berg *et al.* (1998) reported that, whilst both *XPA* and *XPC* knockouts show increased susceptibility to epithelial hyperplasia and SCC, *XPA*^{-/-} mice had a minimum erythral dose (MED) about ten times lower than their heterozygote and wild-type littermates, whereas *XPC*^{-/-} mice had similar MED values to their heterozygote and wild-type littermates. Interestingly, *XPA* patients are prone to skin cancer and have a low MED, whereas *XPC* patients have early skin cancers and MEDs in the normal range. Hence, defective global genome repair appears to lead to skin cancer susceptibility but does not influence erythral sensitivity. The latter was enhanced by defective transcription-coupled repair which suggests that blockage of RNA synthesis is a key event in the development of UVR-induced erythema. In addition, the results imply that sensitivity to UVR-induced

sunburn is not necessarily a quantitative clinical marker of an individual's susceptibility to skin cancer. Interestingly, similar studies with NER defective mice also indicate that acute sunburn is not predictive for systemic immunosuppression (see Chapter 5).

BASAL CELL CARCINOMA

- 13** Basal cell carcinoma (BCC) is the most common skin cancer in the white-skinned population, constituting 75% of non-melanoma skin cancers, and the incidence is rising (Dava-Grosjean and Sarasin, 2000). The cell of origin is probably a pluripotential epidermal stem cell, and there is a range of histologic subtypes (Gailini and Bale, 1997). Exposure to sunlight, particularly UVB, is a strong risk factor, but there is only a modest association with cumulative exposure. A number of different studies point towards UVR-induced mutations in the 'sonic hedgehog' (SHH) signalling pathway, particularly of the patched (*PTCH*) gene, as implicated in BCC aetiology. *PTCH* codes for a developmental regulator protein involved in the SHH signalling pathway which plays an important role in embryonic development but also carries the potential for involvement in oncogenic transformation. Germ-line mutations of *PTCH* are responsible for the nevoid BCC syndrome (or Gorlin's syndrome), characterised by multiple skin cancers, internal cancers and severe developmental abnormalities (Dava-Grosjean and Sarasin, 2000). Inactivating mutations in *PTCH* have also been identified in both familial and sporadic BCC; analysis of *PTCH* mutations in sporadic BCC revealed many C→T substitutions at dipyrimidine sites supporting a role for UVB in their genesis (Evans *et al* 2000).
- 14** The hedgehog signalling pathway was first identified in *Drosophila* as an important regulator of larval development and has been shown to be highly conserved in vertebrate evolution (Goodrich *et al* 1996; Hahn *et al* 1999). SHH is the best characterised of three mammalian homologues and plays a central role in the patterning of limbs, the axial skeleton and central nervous system (Hahn *et al* 1999). Binding of SHH to a membrane receptor complex of *PTCH* and *SMO* (smoothened) proteins releases *SMO* by conformational transformation from the inhibitory effect of *PTCH*, leading to the downstream activation of various genes including *GLI1*, which has been shown to have oncogenic potential, and *PTCH*. Overexpression of *GLI1* and *PTCH* has been demonstrated in all sporadic BCC, in contrast to normal keratinocytes (Undén *et al* 1997; Aszterbaum *et al* 1999a; Hahn *et al* 1999; Nagano *et al* 1999), and is thought to be a common denominator for tumours with mutations in this pathway. Loss-of-function mutations in *PTCH*, regarded as a tumour suppressor gene, or activating mutations in the proto-oncogenes *SHH* and *SMO*, would all lead to overexpression of *GLI1* and *PTCH*. The overexpression of *SHH* in transgenic mice, for example, leads to the development of many features of nevoid BCC (Oro *et al* 1997).
- 15** Aszterbaum *et al* (1999b) report the development of a *Ptch* heterozygous knockout (*Ptch*^{+/-}) mouse that is thought to be representative of human nevoid BCC (*PTCH*^{+/-}) syndrome and develops small baseloid cell tumours on skin protected from UVR. On chronic exposure to UVR (at 3 MED, three times per week for a year), all *Ptch*^{+/-} mice developed on exposed skin larger and more numerous trichoblastoma and BCC-like tumours which, when examined by *in situ* analysis, were shown to have detectable Gli

mRNA. The deletion from *Ptch*^{+/-} mice exposed to UVR of the wild-type *Ptch* gene in almost all cells from some trichoblastoma or BCC-like tumours indicates that the *Ptch* gene is an important target for UVR-induced mutagenesis and that the *Ptch*^{-/-} cells may undergo clonal expansion. The evidence suggests that UVR-induced dysregulation of the SHH signalling pathway and target gene activation are essential events in the initiation of BCC tumourigenesis.

MALIGNANT MELANOMA

- 16** The evidence relating to experimental models for primary melanoma has been previously summarised (Epstein, 1992; IARC, 1992; WHO, 1994; NRPB, 1995; Bardeesy *et al* 2000). Despite many concerted attempts, there are at present no natural animal models of human malignant melanoma. Animal models for UVR-induced melanomas described in the previous Advisory Group report (NRPB, 1995) comprised a marsupial (a South American opossum) and certain hybrid fish (platyfish and swordtail fish hybrids), the latter being well understood genetically. More recently, a number of transgenic mouse models of melanoma have been developed; effects have also been studied in knockout mice deficient in the *p16* tumour suppressor gene, which is implicated in familial melanoma. In addition, studies have been carried out of melanomas induced in human skin grafted on to immunologically tolerant mice by a single exposure to a chemical carcinogen followed by UVR exposure.

'Natural' animal models

- 17** The development of an adequate animal model of human malignant melanoma is clearly important. The hairless pigmented mouse model may be unsatisfactory in this respect since, in contrast to human skin, the primary location of active melanocytes in untreated skin is in the hair follicle and only an occasional active melanocyte is found in the epidermis. Various animal models of melanoma have been reviewed by Kusewitt and Ley (1996). These authors note that the aetiology, behaviour and appearance of these tumours vary considerably among species and that the extent of similarity between animal and human melanomas is also quite variable. No animal model, however, precisely mimics all features of human melanomas. Spontaneous melanoma is generally rare in animals except for Sinclair swine and certain hybrid fish. In contrast to common melanomas in humans, melanomas in animals generally arise in the dermis and there is negligible epidermal involvement; melanomas in fish may arise from specialised melanocytes (macromelanophores) not found in humans. Swine melanomas do, however, resemble human melanomas histologically. A strong genetic predisposition for melanoma development such as that seen in perhaps 10% of patients with melanoma can be identified only in fish and swine. In addition, regression, which can be a prominent feature of human melanoma, is seen only in swine.
- 18** The induction of melanoma by UVR has been investigated by Setlow *et al* (1989) using hybrids of the platyfish *Xiphophorus maculatus* and the swordtail *Xiphophorus helleri*; irradiation of five day old fish with broadband UVR induced invasive melanomas. However, the applicability of this model to humans may be limited due to the evolutionary divergence between these organisms (Bardeesy *et al* 2000). The melanomas that develop in *Xiphophorus* may arise from cells other than

typical melanocytes and thus do not resemble human melanomas (Kusewitt and Ley, 1996). In addition, the malignant tumours that develop in fish are generally more aggressive and invasive than the tumours that develop in humans, and regression is not reported to occur.

- 19** The genetic basis of melanoma induction in this animal model is, however, well understood. Tumour formation depends on a single oncogene, designated *Tu*, which is regulated by a tumour suppressor gene, designated *DIFF* (otherwise, known as R_{DIFF} or *R*). In the platyfish, *Tu* is associated with a locus that determines pigmentation patterns, which is located on the sex chromosomes, whilst *DIFF* is associated with a locus believed to regulate macromelanophore pigment cell differentiation and is located on an autosome (Witbrodt *et al*, 1989); neither gene is present in the swordtail. Serial backcrossing of platyfish and swordtails results in the stepwise replacement of the *DIFF*-bearing chromosomes with *DIFF*-free chromosomes and is accompanied by deregulation of the *Tu* oncogene, leading to either benign or malignant melanoma, depending on the number of functional *DIFF* alleles remaining. UVR probably serves to inactivate the tumour suppressor gene thereby deregulating *Tu*.
- 20** A functionally normal *Tu* proto-oncogene, designated *INV*, was found close to the *Tu* locus on the sex chromosomes (Schartl and Adam, 1992; Adam *et al*, 1993). Sequence database searches (Witbrodt *et al*, 1989; Schartl and Adam, 1992) revealed significant homology with receptor tyrosine kinases, particularly human epidermal growth factor (EGFR) and the gene has been designated *Xmrk* - *Xiphophorus* melanoma receptor tyrosine kinase. The authors suggest that *Xmrk* acquired oncogenic potential from a gene duplication event, non-homologous recombination resulted in a second copy of *Xmrk* located nearby but under different transcriptional control. The mapping of a *CDKN2*-like gene to linkage group V, a region containing the *DIFF* locus, suggests that this is a likely candidate for *DIFF* (Nairn *et al*, 1996). Comparative sequence analysis suggests that the *Xiphophorus* *CDKN2* gene (termed *CDKN2X*) is related to all four members of the mammalian *CDKN2* gene family* (Kazianis *et al*, 1999) and may represent an ancestral prototype. However, RT-PCR analysis reveals that both *Xmrk* and *CDKN2X* are highly expressed in fish melanoma (Kazianis *et al*, 1999), in contrast to the inactivation or loss of heterozygosity of *p16* (*CDKN2A*) reported in human melanoma.
- 21** The South American opossum, *Monodelphis domestica*, which develops foci of dermal melanocytic hyperplasia in addition to squamous epithelial hyperplasia following repeated exposure of the shaved animal to broadband UVR (Kusewitt *et al*, 1991; Ley *et al*, 1989), is one of the most well-characterised animal models. Van de Berg *et al* (1994) noted that the benign melanocytic lesions induced by exposure to UVB in these animals shared some features with both common and dysplastic naevi in humans; they are usually irregular in outline and may exceed 5 mm in diameter. However, they are dermal in origin and do not readily transform into a malignant metastasising state. Robinson *et al* (1996) reported that the repeated suberythral exposure of newborn opossums to broadband UVR resulted in widespread metastatic melanoma, an interesting parallel with epidemiological studies which show that moving to sunnier areas before 15-20 years of age increases the risk of melanoma far more than such a move after 20 years of age (see Chapter 7, paragraph 128).

* The *CDKN2* family are otherwise known as the *INK4* family of cyclin-dependent kinase inhibitors and include *p16^{INK4a}*, *p15^{INK4b}*, *p18^{INK4c}* and *p19^{INK4d}* (Roussel, 1999).

- 22 Other animal models include a stock of hairless pigmented Guinea pigs developed by Bologna *et al* (1990) which possess a pigmentary system similar to human skin with active melanocytes present in the basal layer of the epidermis. Green *et al* (1996) noted that the Angora goat may also be a potentially useful animal model in this context.

Wavelength dependence of melanoma induction

- 23 An action spectrum for the induction of melanoma in the fish melanoma model has been determined using *Xiphophorus* hybrids exposed to monochromatic radiation at wavelengths between 302 and 435 nm (Setlow *et al*, 1993). The effectiveness of UVR in inducing melanoma appeared to decrease by less than two orders of magnitude over this wavelength range, contrasting strongly with action spectra for various types of DNA damage and suggesting the presence of an efficient sensitiser in the target melanocytes, possibly melanin itself or one of its precursors. However, there was some heterogeneity in the background levels of melanoma in the control groups of unexposed fish, particularly in the experiments carried out at longer wavelengths, indicating a need for confirmation of these potentially important observations.
- 24 The wavelength dependence of the induction of melanocytic hyperplasia compared to the induction of non-melanoma skin cancers in the South American opossum was investigated by Ley (1997). Following exposure to broadband UVR at 250 J m^{-2} three times a week for 81 weeks, the prevalence of non-melanoma skin tumours and melanocytic lesions was found to be 71% and 31%, respectively. However, the same regime of exposure to UVA radiation at 25 kJ m^{-2} resulted in a higher incidence of melanocytic lesions (22%) compared to non-melanoma lesions (4%). The author noted that, as in the fish model described above, the data implied that UVA radiation was more efficient in inducing melanoma precursor lesions than in inducing non-melanoma skin tumours. In contrast to the fish model, however, UVA did not cause conversion to malignancy in the opossum. Further study by Robinson *et al* (2000) confirmed this observation. Only one of almost more than 800 suckling young opossums exposed to UVA radiation at up to 140 kJ m^{-2} developed a melanocytic lesion which subsequently regressed with age. The authors concluded that in this animal model, the potency of UVA for melanoma induction was extremely low compared with that for UVB.

Transgenic mouse models

- 25 Epstein (1992) suggested that transgenic mice which are predisposed to develop malignant skin melanoma would provide useful animal models for investigating the aetiology of melanoma. A transgenic mouse model (Tyr-SV40E) of malignant skin melanoma has been developed (Bradl *et al*, 1991; Mintz and Silvers, 1993) in which the series of changes and types of lesion parallel those in human disease in many respects, including the tendency to metastasise (Mintz *et al*, 1993). The transgene is comprised of a simian virus 40 early-region, including the large tumour antigen transforming gene, under the transcriptional control of the tyrosinase promoter expressed in melanocytes. In this model, mice of the more susceptible lines die young of early-onset eye melanomas; it is necessary to graft skin from high susceptibility lines to longer-lived Tyr-SV40E hosts of a low susceptibility strain in order to enable the development of skin melanomas, limiting the usefulness of this animal model.

- 26 Kato *et al* (1998) reported the development of a novel metallothionein-I (MT)/ret transgenic mouse line in which skin melanosis, benign melanocytic tumour and malignant melanoma metastasising to distant organs developed. The authors suggest that the process of tumour development and its malignant transformation in this model may resemble that of the human giant congenital melanocytic nevus that is present at birth and frequently converts to malignant melanoma during ageing.
- 27 Zhu *et al* (1998) also reported the development of a transgenic mouse model (TG-3) with a strong tendency to develop melanoma; pigmented lesions originating in the dermis appear as multi-focal lesions resembling dysplastic naevi which were progressive, increasing in size and invading nearby tissue. Transfection with a fragment of genomic DNA resulted in five independent transgenic mouse lines, one of which spontaneously developed malignant melanoma. The lesions were considered to resemble human cuboid cell melanoma.
- p16 tumour suppressor gene knockout mice**
- 28 The involvement of *p16^{Ink4a}* in the development of human tumours is implied by the observation that the *INK4a* locus (also called the *CDKN2A* or multiple tumour suppressor 1 locus) is mutated in many tumour-derived cell lines and maps to a chromosomal region frequently altered in human malignancies including familial melanoma. In the particular case of Dutch and Australian families with hereditary melanoma, most of the *INK4a* predisposing mutations affect exclusively *p16^{Ink4a}*. However, Habglan *et al* (1998) noted other evidence that suggested that loss of *p16^{Ink4a}* did not play a major role in the genesis of melanoma and speculated that it may be a late event.
- 29 Serrano *et al* (1996) generated an *Ink4a^{-/-}* knockout mouse that eliminated both *p16^{Ink4a}* and *p19^{ARF}*. The mice are viable but develop spontaneous tumours at an early age and are highly sensitive to carcinogenic treatments. The authors reported that 60% of such mice treated with DMBA followed by repeated UVB exposure (three exposures per week beginning on postnatal day 4–8 at up to 7 kJ m⁻²) developed clinically apparent and histologically confirmed malignancy compared to only 17% of the heterozygote knockout mice and none of their normal littermates. The main tumour types were (fibro) sarcomas and (B-cell) lymphomas. The group of mice treated with UVB alone developed tumours that were indistinguishable from untreated mice, suggesting that UVB potentiates the carcinogenicity of DMBA but, when used alone under the conditions employed in the study, was not tumorigenic. These findings are consistent with the view that *Ink4a* deficiency may accelerate progression to more malignant tumours. Serrano *et al* (1996) suggested that the absence of skin melanomas might be explained by a longer latency but noted that, in general, mice were relatively resistant to the development of this tumour.
- 30 Kiyokawa and Koff (1998) note that the contribution from the overlapping *p19^{Arf}*, which also has growth suppressive properties and is disrupted in *p16* knockouts, remains to be clarified and speculate that the clinical spectrum of cancers resulting from the deletion of *p16*, which is different to that observed in the mouse knockouts, may also involve deletion of *p15^{Ink4b}*, located only 25 kb away from the *p16* gene.
- 31 Some of these issues were addressed by Chin *et al* (1997). In this study, *Ink4a^{-/-}* (*p16*) knockout mice were crossed with *tyr-ras* transgenic mice carrying an activated *H-ras*

mutation*. Mice bearing the activated *ras* mutation that were homozygous for *Ink4a* deletions developed cutaneous and ocular melanomas which were non-metastatic but locally invasive. In contrast, the occasional loss of *p15^{Ink4b}* probably reflects its status as a bystander in deletions extending beyond the *Ink4a* gene. Interestingly, Tp53 levels were low in all melanomas. The authors noted that this transgenic mouse model recapitulated some of the prominent genetic features observed in human melanomas, namely activation of the Ras pathway, deletion of the *Ink4a* tumour suppressor, and absence of Tp53 mutation and suggested that it may provide a suitable animal melanoma model for further study. Metastasis, however, was not observed. Chin *et al* (1998) pointed particularly towards further study involving receptor tyrosine kinases, noting the overexpression of EGFR in some late-stage human melanomas.

Carcinogenesis in grafted human skin

- 32** Atilasoy *et al* (1998) have developed an experimental model in which full thickness human skin is grafted on to SCID (severe combined immunodeficiency disease) mice or RAG-1 (recombinase activating gene-1) knockout mice. The xenografts survive indefinitely with anastomoses between murine and human vasculatures and a characteristically human histological architecture and antigenic phenotype. The grafts can be serially transplanted to younger hosts to facilitate long-term studies. However, initial studies have indicated that with SCID mice, the grafted human skin is much less susceptible to UVR-induced skin cancer than the surrounding host skin because of an inherent DNA repair defect that makes them more sensitive to DNA-damaging radiation (Soballe *et al*, 1996). RAG-1 mice, which have dark pigmentation and intact DNA repair mechanisms, are used preferentially.
- 33** Sauter *et al* (1998) found that the exposure of human newborn foreskin grafted to RAG-1 mice to DMBA followed by UVB exposure (500 J m^{-2} three times weekly for up to a year) resulted in the development of squamous precancer of human origin in 83% of the mice and melanocytic hyperplasia or melanoma in 44% of the mice. Atilasoy *et al* (1998) noted that exposure to UVB, DMBA or UVB + DMBA resulted in the development of human melanocytic lesions ranging from hyperplasia to malignant melanoma. Histologically, 68% of UVB-treated xenografts and 77% of those treated with DMBA and UVB displayed melanocytic hyperplasia; 23% and 38%, respectively, developed solar lentigo (pigmented macules). In one skin graft treated with DMBA and UVB, a nodular pigmented tumour with the characteristics of nodular malignant melanoma developed. Further experiments are planned using skin from patients with sporadic or familial melanoma.
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SUMMARY AND CONCLUSIONS

- 34** The carcinogenicity of solar radiation and UVR in experimental animals, mostly mice, is well established. Squamous cell carcinomas are readily induced in rodents. Melanomas, or melanoma-like lesions, have only been readily induced in two animal models, a hybrid fish and an opossum. Basal cell carcinomas have rarely been observed.

* Jansen *et al* (1996) indicated that about 15% of melanomas carried *ras* mutations, predominantly N-*ras* but including H-*ras*.

- IARC (1992) considered that the evidence was sufficient to conclude that solar radiation, broad-spectrum UVR, and UVA, UVB or UVC radiation were all carcinogenic to experimental animals. Mice are more sensitive than humans to UVB-induced SCC because of their thinner skin and less efficient repair of pyrimidine dimers on the non-transcribed DNA strand. An action spectrum has been produced for the induction of SCC in mice showing the greatest sensitivity to be around 290 nm in the UVB region. A lower, secondary peak around 380 nm in the UVA region may be indicative of increased levels of oxidative DNA damage in this region. In addition, the carcinogenicity of low doses of long wavelength UVA could be higher than previously expected.
- 35** Mutation of the *TP53* tumour suppressor gene seems to occur as an early event in the development of UVB-induced SCC in both humans and mice but may be less important in UVA-driven skin carcinogenesis. Cells with mutant TP53 show a diminished capacity to undergo apoptosis to form 'sunburn cells', suggesting that repeated sun exposure may preferentially enhance their survival compared with normal keratinocytes.
- 36** Studies have been carried out of the roles of transcription-coupled repair and global genome repair in UVB-induced skin tumourigenesis using various nucleotide excision repair defective (knockout) mouse models of various heritable photosensitivity disorders in humans. Knockout mice deficient in both repair processes were approximately 10^4 times more sensitive to UVR-induced skin tumours than normal littermates and showed an increased sensitivity to erythema; similar observations have been made in patients. Interestingly, mouse knockouts deficient only in global genome repair were equally sensitive to skin tumour induction but had normal erythema sensitivity. The results suggest that sensitivity to UVR-induced sunburn is not necessarily quantitatively indicative of skin cancer susceptibility.
- 37** Mutations of the *PTCH* tumour suppressor gene, part of the 'sonic hedgehog' signalling pathway, are thought to be responsible for the nevoid BCC syndrome and are implicated in the aetiology of familial and sporadic BCC. Mutational analysis of *PTCH* in sporadic BCC also supports a role for UVR in their aetiology. Recently, a *Ptch*^{+/-} heterozygous knockout mouse model has been developed. Chronic exposure to UVR results in the development of BCC-like tumours, supporting the view that UVR-induced dysregulation of the sonic hedgehog signalling pathway and target gene activation are essential events in the initiation of these tumours.
- 38** There are few natural animal models of melanoma. Most UVR-induced animal melanomas arise in the dermis with negligible epidermal involvement; spontaneous melanomas and the strong genetic predisposition to melanoma seen in humans have been identified only in Sinclair swine and certain hybrid fish. In the latter, the relevant tumour suppressor gene and proto-oncogene have recently been shown to have significant homology with two human genes implicated in the aetiology of human melanoma. Nevertheless, significant differences in tumour aetiology and growth remain, suggesting caution in extrapolating these results to humans. The other common experimental animal melanoma model is the South American opossum. In young animals, metastasising tumours develop following exposure to UVB radiation but not following UVA exposure.
- 39** A number of transgenic mouse melanoma models have been developed of which the most promising is one in which mice homozygous for *Ink4a* deletions and bearing

an activated *H-ras* mutation developed locally invasive melanomas. Another way of investigating UVR effects in melanoma induction is through studies in which full-thickness human skin is grafted on to immune compromised mice, of which the most promising seems to be the RAG-1 (recombinase activating gene 1) knockout mouse.

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5 Immune Response

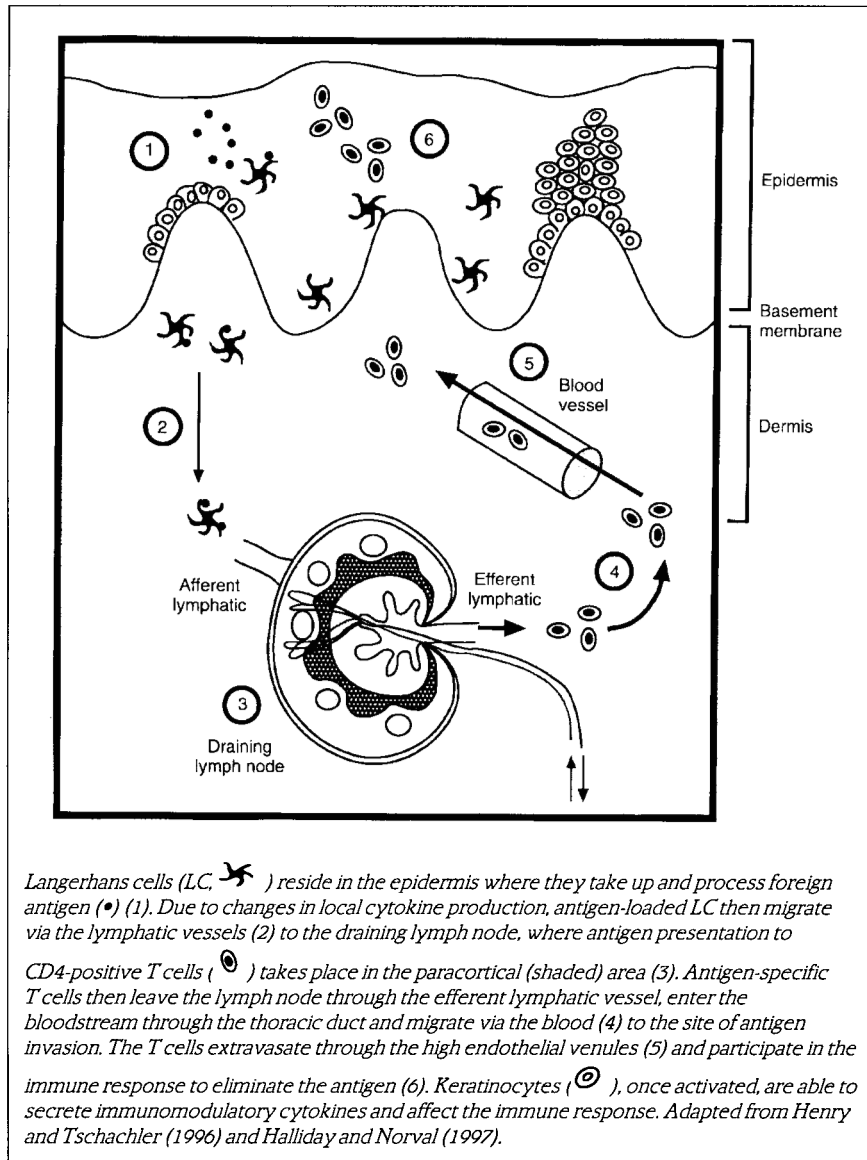
INTRODUCTION

- 1 The results of a seminal experiment were published nearly 25 years ago (Fisher and Kripke, 1977); these led to the development of photoimmunology as an area of intense interest, research activity and progress. Tumour cells from mice which had developed highly antigenic skin cancers as a result of chronic UVB exposure were transplanted into syngeneic mice. As might be expected, the cells were rejected but, if the recipient mice were UVB-irradiated with suberythral doses for three weeks prior to transplantation, the cells were not rejected and behaved as though they were in an immunosuppressed animal. A further study revealed that T suppressor cells were generated in the spleens of the irradiated transplanted mice which were capable of mediating the down-regulation in immunity towards the tumour cells (Fisher and Kripke, 1982). Following these initial observations, work has focused on elucidating the cutaneous and systemic changes which occur after UVR exposure and which result in immunosuppression. Such modulation may have implications not only for tumour rejection but also for the ability to control microbial infections, autoimmune diseases and allergic responses. Most information has been provided thus far for carcinogenesis and infectious diseases, although there is considerable current research interest in the other areas also. In this chapter, a short introduction to the skin immune system and an overview of the effects induced by UVR on immunity can be found immediately below. The following sections will then describe *in vitro* systems, animal models, human studies, and the immunoprotective properties of sunscreens. A final section summarises this information and indicates areas which require investigation.
-

SKIN IMMUNE SYSTEM

- 2 The skin immune system contains contributions from many cell types, some resident in the dermis or epidermis, and others highly mobile, frequently connecting the cutaneous environment with the blood or lymph. Following contact with an antigen, the Langerhans cells (LC), the major antigen presenting cells of the epidermis which form a dendritic network, internalise and process it. Changes in local cytokine production in the epidermis, particularly tumour necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), lead to the migration of the LC to the draining lymph node via the afferent lymph. During this process, the LC become mature, as indicated by the altered expression of various adhesion and co-stimulatory molecules on their surfaces. After arriving in the lymph node as dendritic cells, they present the processed antigenic peptides to specific T cells which are stimulated to proliferate and to express a particular cytokine profile. T helper (Th) cells are divided into Th1 and Th2 subsets on the basis of the cytokines they produce: Th1 cells secrete cytokines such as IL-2 and interferon- γ (IFN- γ), while Th2 cells secrete cytokines such as IL-4 and IL-10. In some cases, the activated T cells can home preferentially to the skin and extravasate into the tissues to act as effector cells. The skin immune system is shown in Figure 5.1.

FIGURE 5.1
Schematic diagram
of the skin immune
system during the
course of an immune
response



UVR AND THE SKIN IMMUNE SYSTEM

- 3 The sequence of events leading to immunomodulation following UVR exposure is now known to be complex and is most likely to involve a series of events commencing with the absorption of UVR by a chromophore or chromophores located in the outermost layers of the skin. The end result is the dysregulation of selected systemic and local immune responses. The outline of this cascade is shown below and illustrated in Figure 5.2.

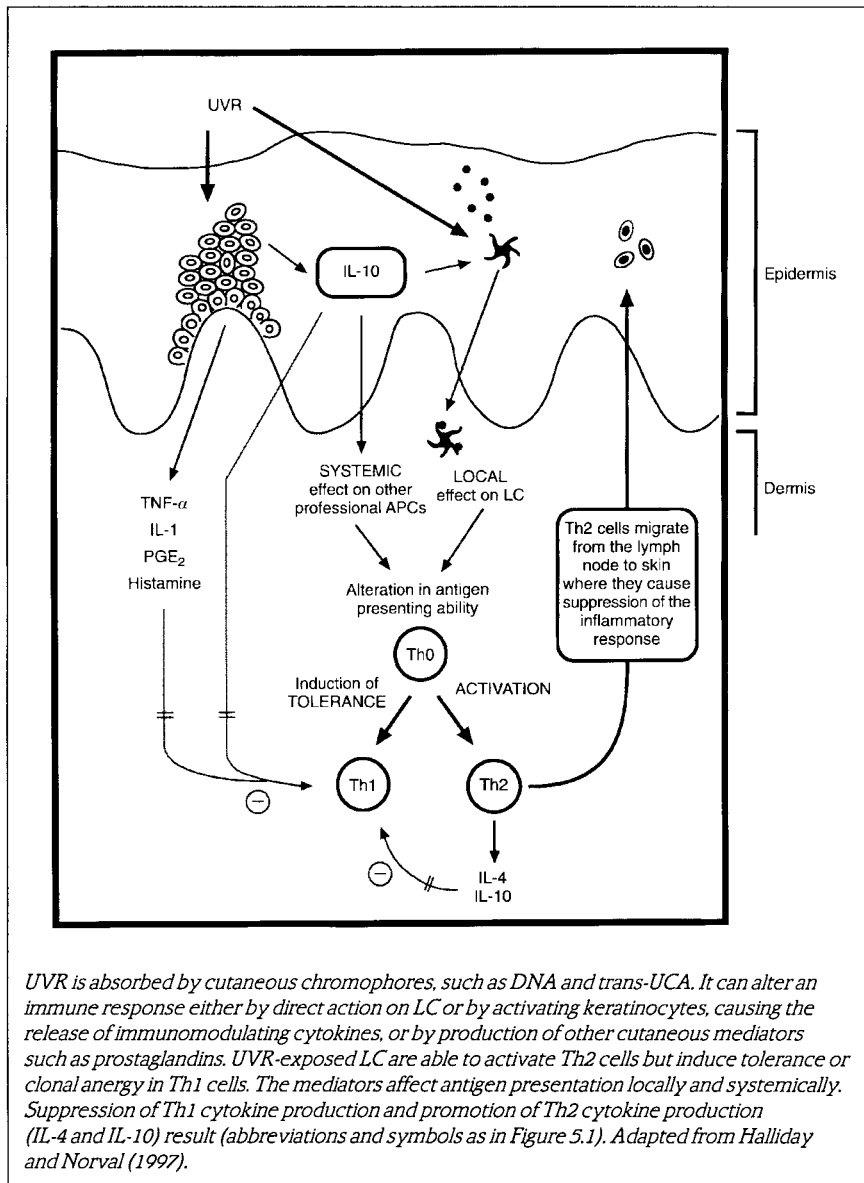
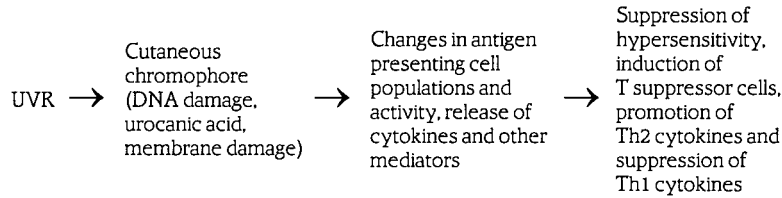


FIGURE 5.2 Effect of UVR on the generation of an immune response

UVR is absorbed by cutaneous chromophores, such as DNA and trans-UCA. It can alter an immune response either by direct action on LC or by activating keratinocytes, causing the release of immunomodulating cytokines, or by production of other cutaneous mediators such as prostaglandins. UVR-exposed LC are able to activate Th2 cells but induce tolerance or clonal anergy in Th1 cells. The mediators affect antigen presentation locally and systemically. Suppression of Th1 cytokine production and promotion of Th2 cytokine production (IL-4 and IL-10) result (abbreviations and symbols as in Figure 5.1). Adapted from Halliday and Norval (1997).

CELLULAR STUDIES

- 4 As indicated above, a complex series of events follows UVR exposure *in vivo* which ends in immunosuppression. One method by which each step can be elucidated is to study the response of individual cell types *in vitro* and then to relate the results to the *in vivo* situation. These cellular approaches can be divided into three categories:
- (a) chromophores involved in the initial absorption of UVR are examined,
 - (b) mediators such as cytokines which promote pro- and anti-inflammatory responses are assessed,
 - (c) changes in the properties of adhesion and co-stimulatory molecules, of particular importance in antigen presentation, are studied.

Chromophores and UVR *in vitro*

- 5 DNA and *trans*-urocanic acid (*trans*-UCA) are major absorbers of photons in the epidermis and have been shown to act as important chromophores for immunomodulation. In addition, membrane damage and induction of cytoplasmic transcription factors may play critical roles (see Chapter 3, paragraph 15).

DNA

- 6 Several recent experiments have shown that DNA damage can act as a trigger for UVR-induced immunosuppression in mouse models *in vivo* (see below) and a direct association between the induction of specific cytokines and the formation of cyclobutane pyrimidine dimers (CPD), which represent one of the major changes to DNA following UVB irradiation, has been revealed *in vitro*. First Petit-Frere *et al* (1998) demonstrated the production of IL-6 in human keratinocytes as a result of UVR exposure. IL-6 is readily inducible in a variety of cell types, acting as a multi-functional pro-inflammatory cytokine. The wavelength dependence of the IL-6 release was investigated and was found to be similar to that of DNA absorption or the induction of CPD, with a maximum effect at 250 nm and only minor effects above 313 nm. The reliance of the IL-6 production upon CPD formation was shown by treating the keratinocytes with photosomes (photolyase encapsulated in liposomes) plus photo-reactivating light. This procedure led to a reduction in IL-6 release and the specific repair of the CPD. A previous study followed a similar protocol but used a line of murine keratinocytes (PAM-212) which were irradiated with UVB *in vitro* (Nishigori *et al*, 1996). This was shown to result in the production of cytokines able to suppress the delayed type hypersensitivity (DTH) response to alloantigens when tested in mice. One such cytokine was identified as IL-10. The link with DNA damage was demonstrated by treating the cells with liposomes containing T4 endonuclease V immediately after the exposure, which repaired the defect and led to a very reduced amount of IL-10 being released. IL-10 is an important suppressor of both T lymphocyte and antigen presenting cell effector function, affecting, for example, the ability of LC to present antigen so that only the Th2 subset is stimulated (Enk *et al*, 1993). Finally Kitibel *et al* (1998) have shown that UVB could induce the expression of TNF- α in PAM-212 cells by damage to DNA. These publications mark the first time that DNA damage in keratinocytes has been associated with the production of specific immunomodulatory molecules and the mechanism is thought to involve DNA-dependent protein kinases (Yarosh *et al*, 2000).

Cis-UCA

- 7** *Cis*-UCA, formed from the naturally occurring *trans*-isomer of UCA on exposure of the skin to UVR, initiates many of the suppressive effects of UVB on the immune system (reviewed most recently by Mohammad *et al.* 1999). However, its mechanism and site of action are unknown at present. As cytokines are induced by UVR exposure of keratinocytes and as UCA isomerisation takes place in the same layer of the skin, various *in vitro* experiments have been performed to monitor the expression of cytokines following treatment of keratinocytes with *cis*- and *trans*-UCA. Using Northern blotting, Redondo *et al.* (1996) found no increase in the mRNAs of IL-1 α , IL-1 β , IL-6, IL-8, TGF- β and TNF- α after incubation of human keratinocytes with *cis*-UCA. Similar results were found using murine keratinocytes and the more sensitive RT-PCR method of detecting levels of mRNA (Zak-Prelich *et al.* 2001). These results agree with earlier studies (Yarosh *et al.* 1992) and do not substantiate the hypothesis of Kurimoto and Streilein (1992) that *cis*-UCA may act by inducing the production of TNF- α .
- 8** There is interest currently in the interaction between UVR and neuropeptide release in the skin which might influence the type of immune response generated (see paragraph 26). *Cis*-UCA has been shown recently to bind to γ -amino butyric acid (GABA) receptors present on rat cortical membranes (Laihia *et al.* 1998). GABA is an inhibitory neurotransmitter. No such binding to histamine (H₁, H₂ or H₃) receptors was revealed. This may be an important finding as GABA receptor activity is known to modulate calcitonin gene-related peptide (CGRP) release. CGRP is a vasodilating neurotransmitter, closely associated with LC and produced by keratinocytes on UVB exposure. However, GABA receptors remain to be detected in the skin.
- 9** One final *in vitro* approach to determine the mechanism of action of *cis*-UCA has demonstrated that, in human keratinocytes, there is synergy between *cis*-UCA and histamine resulting in increased prostaglandin production (Jaksic *et al.* 1995). Prostanoids are known to mediate some of the effects of UVB-induced erythema by increasing vascular permeability and are implicated in UVB-induced systemic immunosuppression in mice (Chung *et al.* 1986; Schreedhar *et al.* 1998).

Cytokines and UVR *in vitro*

- 10** UVR induces changes in the cytokine profile of several cutaneous cell types which have both pro- and anti-inflammatory activities. Changes occur in other mediators also, such as histamine, neuropeptides and prostanoids, with equal importance in determining the type of immune response generated. Some of these are listed in Table 5.1 and further details can be found in Takishima and Bergstresser (1996).
- 11** In addition to the changes in cytokines, the regulation of some of their receptors may be altered by UVR exposure. The receptor for IL-1 is one such example which is thought to play a major role in inflammatory reactions in the skin. Human keratinocytes express two receptors for IL-1: RI acts as a signalling receptor and RII as a decoy receptor by binding to IL-1, thus suppressing IL-1-mediated tissue responses. Grewe *et al.* (1996) showed that UVB affected the expression of these two receptors differently. RII was induced very quickly but RI was decreased initially, then gradually increased. Inflammation may be controlled by this differential effect. The down-regulation of a signalling receptor is not confined to IL-1 α but has also been demonstrated for TNF- α (Trefzer *et al.* 1993).

TABLE 5.1
Cutaneous
mediators whose
expression is
up-regulated by
UVR (from Norval,
2000)

| Mediator | Produced by | Function |
|------------------|---|---|
| TNF- α | Keratinocytes, mast cells, dermal fibroblasts, Langerhans cells | Langerhans cell migration, sunburn cell formation, stimulates PG synthesis, changes in adhesion molecule expression |
| IL-1 α | Keratinocytes, Langerhans cells | Stimulates PG synthesis, increases TNF- α and IL-6, inhibited by IL-1 receptor antagonist |
| IL-1 β | Keratinocytes, Langerhans cells | Langerhans cell migration |
| IL-6 | Keratinocytes, Langerhans cells | Fever |
| IL-10 | Keratinocytes (mouse) macrophages (human) melanocytes | Decreases IL-1, TNF- α , IFN- γ , IL-12, decreases antigen presentation, increases IL-1 receptor antagonist |
| IL-12 | Keratinocytes, dendritic cells, Langerhans cells | (Increase IL-12p40, decrease bioactive IL-12p70) Decreases antigen presentation, decreases Th1 responses |
| PGE ₂ | Keratinocytes, mast cells | Erythema, decreases antigen presentation, increases IL-4, decreases IL-12 |
| Histamine | Mast cells | Increases PG |

Adhesion and co-stimulatory molecules and UVR *in vitro*

- 12** Adhesion molecules, such as ICAM-1, and co-stimulatory molecules, such as the B7 family, require to be expressed on the surface of particular cells to allow the generation and maintenance of a variety of immune responses in the skin. UVR has been shown to alter their expression by mechanisms which are not understood but which may be of therapeutic importance in certain skin diseases with inflammatory components; for example, psoriasis and atopic dermatitis.
- 13** ICAM-1 is not normally expressed on human keratinocytes but is induced in inflamed skin on stimulation with pro-inflammatory cytokines, such as IFN- γ and TNF- α . It has been found that this cytokine-induced up-regulation in ICAM-1 expression can be inhibited by UVB or UVA irradiation of keratinocytes *in vitro* (Krutmann *et al.* 1990). The regulatory mechanisms involved are not known at present but are likely to include intracellular signal transduction. This finding may have relevance *in vivo* as demonstrated by Ahrens *et al.* (1997), who cultured fibroblasts from patients with xeroderma pigmentosum complementation group D (XPD), trichothiodystrophy (TTD) and normal subjects. Both XPD and TTD individuals are deficient in the excision repair of UVR-induced DNA damage but only the former show an increased risk of skin cancer. The ability of UVB to inhibit the expression of ICAM-1 following treatment of the fibroblasts with IFN- γ was measured. The cells from the XPD patients had a two- or three-fold increased susceptibility to the UVR-induced inhibition of ICAM-1 expression compared with the TTD and normal cells. Perhaps, therefore, particular defects in DNA repair and the consequent effects on the immune system following UVR exposure can be linked to the risk of skin cancer.
- 14** UVB is able to alter the expression of adhesion and co-stimulatory molecules on antigen presenting cells such as monocytes and epidermal LC cultured *in vitro* (Simon *et al.* 1990, 1991). This effect is likely to be of functional significance as it results in the energy of the Th1 cytokine response whilst promoting the Th2 cytokine response. Thus cytokines such as IL-2 and IFN- γ are no longer produced and others, such as IL-10

and IL-4, are found preferentially. This change would lead to immunosuppression *in vivo* with an inability to deal effectively with, for example, many viral infections which require a Th1 response for control. The mechanism whereby the adhesion molecules are down-regulated is not known at present but is unlikely to be a direct effect of UVR on the antigen presenting cell itself. The cytokine milieu of the antigen presenting cell may be critically important in this context.

- 15** Finally *cis*-UCA has not been shown in *in vitro* experiments to alter the antigen presenting ability of human monocytes (Higaki *et al.* 1986), human LC (Rattis *et al.* 1995) or murine dendritic cells (Lappin *et al.* 1997), although it had a marginally suppressive effect on human epidermal cells, as measured in a mixed epidermal cell lymphocyte reaction (MECLR) (Hurks *et al.* 1997a).
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ANIMAL STUDIES

- 16** In rodent models it has been known for several years that exposure to UVR followed by exposure to an antigen leads to the generation of CD4⁺ T cells in the spleen and lymph nodes which are specific for the particular antigen and which can transfer the suppression to syngeneic animals. More recently, when the subdivision of T cells on the basis of their cytokine profiles became apparent, several *in vivo* experiments have indicated that there could be a differential effects of UVR on these subsets. One such study noted promotion in the production of the Th2 cytokines, such as IL-10, with a concomitant abrogation in the production of the Th1 cytokines, such as IL-2, IL-12 and IFN- γ (Araneo *et al.* 1989). However in another report, down-regulating effects on both types of T cells were demonstrated (Garssen *et al.* 1999a).
- 17** One dramatic phenotypic change occurs in the epidermis on exposure to UVR, even at suberythemal doses, which is a decrease in the number of LC (Toews *et al.* 1980). The interdigitating network is lost and the remaining cells round up. If a contact sensitizer is applied to the skin during this time, no induction of CHS occurs. It is thought that some LC migrate to the draining lymph nodes (see Figure 5.2) while others, perhaps depending on the dose and wavelength, are trapped in the skin or undergo apoptosis. TNF- α , produced locally by keratinocytes and mast cells, is involved in the migration (Moodycliffe *et al.* 1994), and possibly IL-1 β also (Duthie *et al.* 2000). The dendritic cells, which arrive in the lymph node bearing antigen, cluster abnormally with T cells in the paracortex. Changes in the expression of adhesion and co-stimulatory molecules are likely, leading to the preferential production of particular down-regulatory cytokines. However such modulations in the surface markers for effective antigen presentation have been difficult to show experimentally, and there may be important changes in antigen internalisation and processing which have not been studied as yet. Shortly after the LC migrate from the skin in response to UVR, a new population of antigen presenting cells enters the dermis (reviewed by Cooper, 1996). They may express co-stimulatory molecules and produce cytokines which are different from the resident LC, thereby promoting immunosuppression.

Animal models of carcinogenesis

- 18** Skin cancers in hairless and in shaved haired mouse strains can be induced by chronic suberythemal UVR over a period of approximately six months. Such tumours

are highly antigenic. Kripke (1981) has hypothesised that a neoantigen is formed in the skin, due to the mutagenic effects of UVR, at a time when the antigen presenting cells are altered, resulting in the activation of T cells which down-regulate the immune response to the tumour. Therefore the modulation of the normal host defence by UVR may be critical in allowing the tumour to progress, and this has been shown experimentally in mice. For example, pre-irradiation of one site led to enhanced primary tumour growth at a second irradiated site, with the promotion phase of the carcinogenesis being most affected (de Gruijl and van der Leun, 1982). Another approach showed that mice which had received T suppressor cells prepared from animals irradiated during the course of chronic UVR exposure, developed skin tumours earlier than mice receiving T cells from control unirradiated mice (Fisher and Kripke, 1982). These effects of UVR are systemic, affecting tumours at sites other than the irradiated ones, and are antigen-specific. There are also local effects on immunity at the irradiated site itself which are non-specific. Thus, if mice were irradiated for three weeks before being injected in the ears with melanoma cells, a higher number of tumours developed compared with the unirradiated control animals (Donawho and Kripke, 1991). The mechanism involved here is not known but may depend on a cytokine imbalance in the cutaneous site of injection, perhaps triggered by DNA damage or UCA isomerisation (Donawho *et al* 1998).

Animal models of infectious diseases

- 19** Although the local and systemic effects of UVR on immune responses are well described, not so much information is available regarding immunomodulation during infection. However, at least 13 such models in rodents have now been established; these are summarised in Table 5.2 and recent reviews can be found in Halliday and Norval (1997) and Norval *et al* (1999). The protocols have varied from one experimental model to another regarding UVR dose and source, the type of microorganism, the route of inoculation and whether the infection occurs at a UVR-exposed or non-exposed site, the timing of the infection with respect to UVR exposure, and what parameter is being measured as an endpoint. Assays have ranged from clinical symptoms, resistance to re-infection and counting the organisms in the irradiated animals to measurement of specific immune responses, most commonly DTH and *in vitro* lymphoproliferation. As a result of these differences between one study and another, it is not easy to reach a general conclusion but, in almost all the models examined thus far, irradiation caused suppression of resistance to the organism in question. It is particularly interesting to note that UVR can affect both skin-associated infections such as that caused by herpes simplex virus (El-Ghorr and Norval, 1996; Norval and El-Ghorr, 1996; Yasumoto *et al* 1994), and others which are systemic with no skin involvement at any stage such as those caused by *Listeria monocytogenes* (Goettsch *et al* 1996a) and *Trichinella spiralis* (Goettsch *et al* 1996b). This implies that the changes induced by the irradiation, although initiated in the epidermis, can alter the type of immune response generated in sites other than the cutaneous environment through, perhaps, aberrant antigen presentation or cytokine expression. It might be speculated that microorganisms controlled by mainly Th1 cytokine responses would be most affected by exposure to UVR which is thought to down-regulate such responses preferentially.

TABLE 5.2 Effect of UVR exposure on immune response in animal models of infection (adapted from Halliday and Norval, 1997)

| Microorganism | Route of infection | Species | Timing of UVR exposure | Antigen-specific effects of UVR | Reference |
|-----------------------------------|-------------------------------------|---------|------------------------------|--|--|
| Herpes simplex virus | Subcutaneous or epicutaneous | Mouse | Before infection | Lesions unaffected, suppressed DTH | Norval and El-Ghorr (1996) |
| | Epicutaneous following immunisation | Mouse | Before challenge | Lesions more severe, DTH unaffected, decreased lymphoproliferation | El-Ghorr and Norval (1996) |
| | Intradermal | Mouse | Before infection | Lesions more severe, suppressed IFN- γ , enhanced IL-4 production | Yasumoto <i>et al.</i> (1994) |
| Murine leukaemia virus | Intraperitoneal | Mouse | Before and after infection | Decreased lymphoproliferation, greater spleen histopathology, decreased MLR | Brozek <i>et al.</i> (1992) |
| Reovirus | Intraperitoneal or intragastric | Mouse | Before infection | Suppressed DTH, decreased lymphoproliferation, decreased cytotoxic T cell activity, clearance of virus unaffected | Letvin <i>et al.</i> (1981) |
| Rat cytomegalovirus | Intraperitoneal | Rat | Before infection | Decreased viral clearance, increased tissue necrosis | Garssen <i>et al.</i> (1995) |
| <i>Mycobacterium bovis</i> BCG | Subcutaneous | Mouse | Before or after infection | Decreased clearance of bacteria and enhanced dissemination, decreased phagocytic function, suppressed DTH (temporary) depending on UVR dose and site | Jeevan and Kripke (1989, 1990, 1992a, 1996) |
| <i>Mycobacterium lepraemurium</i> | Subcutaneous | Mouse | Before infection | Decreased clearance of bacteria, increased local inflammatory response, suppressed DTH (temporary) | Jeevan <i>et al.</i> (1992b) |
| <i>Listeria monocytogenes</i> | Intravenous | Rat | Before infection | Decreased clearance of bacteria, decreased lymphoproliferation | Goettisch <i>et al.</i> (1996a) |
| <i>Borrelia burgdorferi</i> | Subcutaneous (inactivated) | Mouse | Before immunisation | Suppressed DTH, suppressed IgG2a and 2b, elevated IgG1 (after secondary challenge) | Brown <i>et al.</i> (1995) |
| <i>Candida albicans</i> | Subcutaneous (inactivated) | Mouse | Before or after immunisation | Suppressed DTH depending on UVR dose | Denkins <i>et al.</i> (1989); Jeevan <i>et al.</i> (1992a) |
| | Intravenous following immunisation | Mouse | Before challenge | Decreased survival time | Denkins and Kripke (1993) |
| <i>Leishmania major</i> | Intradermal | Mouse | Before and after infection | Less severe skin lesions, no effect on numbers of organisms, suppressed DTH, no protection against re-infection | Giannini (1992) |
| <i>Trichinella spiralis</i> | Oral | Rat | After infection | Decreased clearance of larvae, suppressed DTH, suppressed lymphoproliferation | Goettisch <i>et al.</i> (1996b) |
| <i>Schistosoma mansoni</i> | Percutaneous | Mouse | Before infection | No effect on clearance, no effect on tissue necrosis | Jeevan <i>et al.</i> (1992a); Noonan and Lewis (1995) |
| <i>Plasmodium chabaudi</i> | Intraperitoneal | Mouse | Before infection | Increased mortality, decreased interferon- γ and increased IL-10 in serum | Yamamoto <i>et al.</i> (2000) |

- 20** In the most recent of these models, this concept was confirmed (Yamamoto *et al* 2000). The malaria parasite *Plasmodium chabaudi* was inoculated intraperitoneally into mice which had been irradiated with a single erythral broadband UVR dose one day previously. The exposure resulted in the death of the irradiated, infected animals, whereas, without the UVR exposure, the infection was sublethal. It was revealed that the concentration of plasma IFN- γ induced by the parasite was markedly reduced while that of IL-10 increased in the irradiated, infected mice compared with the unirradiated, infected mice, indicating that the enhanced susceptibility following UVB exposure was mediated by a switch from a Th1 to a Th2 cytokine profile. The United Nations Environment Assessment Panel suggested in 1989 (Van der Leun *et al*) that there may be a particular risk of greater incidence or severity of malaria if the terrestrial UVR exposure of human subjects continued to increase.

Role of DNA as an initiator of UVR-induced immunosuppression

- 21** UVR absorption by cellular DNA results in various types of damage of which the formation of cyclo-butane pyrimidine dimers (CPD) is the most common. CPD have been located in keratinocytes and LC following UVB exposure and also in dendritic cells in lymph nodes draining the irradiated sites (Sontag *et al*, 1995). In the marsupial *Monodelphus domestica*, repair of the CPD is carried out by an endogenous photolyase. Applegate *et al* (1989) showed that suppression of CHS, induced by exposure to UVR, was prevented if the enzyme was activated by exposure to visible light following the UVR exposure. A series of experiments in mice was then carried out in which the CPD were repaired either *in vivo* or *in vitro* after UVR exposure (reviewed in Vink *et al*, 1998). This resulted in the CHS response, suppressed by the UVB radiation, being restored. An outline of the protocols used for these experiments may be found in Figure 5.3. It is not known how the DNA damage affects antigen presentation and how antigen-specific naive cells are directed to suppress the CHS. There could be a reduced level of transcription of the genes required for effective presentation, or there could be indirect effects by activation of cytokines or regulatory genes. There is evidence currently for the latter possibility as DNA damage, induced by UVB radiation, has been shown to up-regulate the production of particular cytokines in *in vitro* studies (see paragraph 6 above).
- 22** Additional evidence for a significant role of DNA damage in UVB-induced immunosuppression has been provided by experiments in transgenic mice, deficient in some aspect of nucleotide excision repair (see Chapter 4, paragraph 12). Miyauchi-Hashimoto *et al* (1996) reported that a XPA mutant mouse exhibited enhanced local and systemic immunosuppression following UVB exposure compared with the normal littermates. In addition, epidermal LC were affected at lower UVR doses than the normal mice. Recently four more mutant mouse strains (XPA, XPC, CSB, TTD) were created to study the sensitivity of UVR-induced systemic suppression and acute skin effects, and to compare these parameters with susceptibility for the development of UVR-induced skin cancer. XPA and CSB mice were highly sensitive to sunburn/erythema, TTD mice were moderately sensitive, and XP-C had the same sensitivity as the wild-type mice. XPA mice were very susceptible to suppression of CHS and DTH responses following UVR, while CSB mice were not. Therefore these preliminary results indicate that the acute effects of UVR exposure on the skin are not predictive for immunosuppression (Garssen *et al*, 2000).

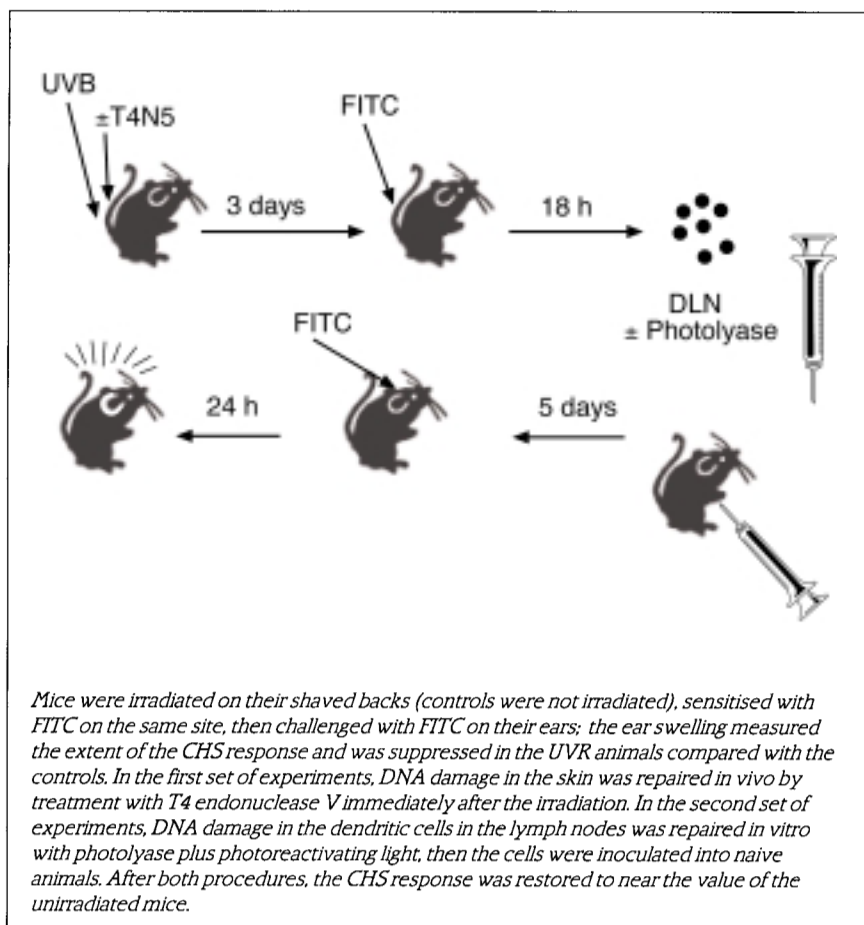


FIGURE 5.3 Outline of the protocol used by Vink *et al* (1996, 1997) to show that DNA damage mediates UVR-induced local suppression of CHS

Role of *cis*-UCA as an initiator of UVR-induced immunosuppression

- 23** A variety of approaches have examined the role and mode of action of *cis*-UCA *in vivo* as an initiator of the cascade of responses following UVR exposure which results in immunosuppression. One such method has been to assay changes in immune function on treating experimental animals with *cis*-UCA; another has been to assay the abrogation of the changes in immune function on administration of an antibody with specificity for *cis*-UCA (Moodycliffe *et al*, 1993) to animals exposed to UVR. For example, if such an antibody is injected intraperitoneally into mice two hours prior to UVR exposure, it significantly reversed the UVR-induced down-regulation in DTH responses, the accumulation of dendritic cells in lymph nodes draining the irradiated site, the loss of epidermal LC, and the suppression in the MECLR (El-Ghorr and Norval, 1995; Moodycliffe *et al*, 1996). In some systems it could also reverse the UVR-induced suppression in local (Kondo *et al*, 1995) and systemic CHS (Hart *et al*, 1997), although not in others (El-Ghorr and Norval, 1995; Moodycliffe *et al*, 1996). In an interesting

study, the enhancement in melanoma growth in mice as a result of a three week UVB irradiation protocol could be inhibited significantly by treatment of the animals with the *cis*-UCA monoclonal antibody, whereas enzymatic repair of DNA damage had no effect (Donawho *et al.* 1998). The antibody has also been used in a model of infectious disease, namely *Trichinella spiralis* in the rat (Garssen *et al.* 1999b). It was found that the UVB-induced suppression of DTH to *Trichinella* antigen and the increase in larvae counts in the muscles were significantly reversed in animals treated with the monoclonal antibody. Therefore with regard to both infections and tumours, *cis*-UCA acts as an important mediator of the suppression in immune responses which follow UVR exposure.

24 *Cis*-UCA has been shown to affect antigen presentation *in vivo* in mice. Epidermal cells were incubated with *cis*-UCA for two to three hours and this resulted in the inhibition of their ability to sensitise mice for CHS or DTH (Dai and Streilein, 1997). Furthermore, if epidermal cells were pulsed with tumour-associated antigens and treated with *cis*-UCA, then injected into mice which were challenged subsequently with tumour cells, outgrowths of the tumours occurred; normally tumour growth was prevented by the epidermal cell immunisation (Beissert *et al.* 1997). In contrast to these findings, Holan *et al.* (1998) showed that the main immunomodulating effect of *cis*-UCA was on the CD4⁺ population rather than on the antigen presenting cells themselves. They found that IL-10 was produced from the CD4⁺ cells on incubation with *cis*-UCA which inhibited the Th1 cytokine response, thus leading to down-regulation in immune responses.

25 Evidence to link *cis*-UCA with histamine and prostaglandin (PGE₂) release has been obtained in several mouse models. Most recently, Hart *et al.* (1999a) have demonstrated a relationship between *cis*-UCA and mast cell activity in the initial phase of UVB-induced systemic immunomodulation. In mutant mice depleted of mast cells (*Wf/Wf*), *cis*-UCA was unable to alter CHS, analogous to the situation with UVB. Reconstitution of the mice with bone-marrow-derived mast cell precursors enabled the mice to respond to the immunosuppressive effects of *cis*-UCA. Moreover, *cis*-UCA has been shown to cause mast cell degranulation in human skin organ cultures (Wille *et al.* 1999). The histamine released from mast cells is likely to act downstream of *cis*-UCA and to stimulate prostanoid production, leading to an enhancement in the release of Th2 cytokines, such as IL-4 and IL-10 (Schreedhar *et al.* 1998). A further study in support of this sequence of events is provided by Reeve *et al.* (1999) who showed that *cis*-UCA-induced immunosuppression of CHS could be prevented by IFN- γ , a Th1 cytokine.

Role of neuropeptides in UVR-induced immunosuppression

26 In addition to the cytokines, prostanoids and histamine induced in the skin as a result of UVR exposure, it is recognised that a range of neuropeptides and neurohormones are also produced which can act as mediators of immunity and inflammation. For example, CGRP is released which has immunosuppressive properties by altering adhesion molecule expression and antigen presenting cell function (Niizek *et al.* 1997). It is also vasodilatory, thus contributing to the oedema and erythema which follow UVR exposure. The role of the sensory nervous system in controlling cutaneous immune responses after UVR exposure has been reviewed by Scholzen *et al.* (1999).

Susceptibility of mouse strains to UVR-induced immunosuppression and wavelength considerations

- 27** It has been recognised for several years that mouse strains can be divided into those that are susceptible to the immunosuppressive effects of UVR on CHS, and those that are resistant, requiring a much larger dose of UVR to be affected. These strains differ between local (contact sensitiser applied to the irradiated site) and systemic (contact sensitiser applied to non-irradiated distant site) models of CHS. With regard to the local model, TNF- α has been reported to have critical importance in regulating susceptibility (Yoshikawa and Streilein, 1990), and a recent report defines the region on the murine chromosome 17 which contains the susceptibility locus within the MHC region (Handel-Fernandez *et al.* 1999). With regard to the systemic model, there is good evidence that mast cell prevalence is one critical factor determining susceptibility. Thus a strain considered highly UVR-susceptible (C57BL/6) contained a large number of dermal mast cells, while a strain considered UVR-resistant (BALB/c) had about half that number (Hart *et al.* 1999b). The *Uvs1* locus has been identified as being of major importance in UVB-induced systemic immunosuppression but other loci are also involved (Noonan and Hoffman, 1994).
- 28** Most UVR studies to date in mice have used lamps which emit broadband UVB, but a few are beginning to address the waveband dependency of the immunosuppressive effects of the exposure. Reeve *et al.* (1994) irradiated hairless mice with different sources which incorporated successively greater short-wavelength cutoffs, thereby increasing the proportion of UVA. It was found that only the wavebands richest in the short wavelengths induced suppression of systemic CHS; a correlation was established between the oedematous response and the suppression. El-Ghorr and Norval (1999) reported that a comparatively high dose of UVA-1 (340–400 nm) equivalent to 1 MED ($500\,000\text{ J m}^{-2}$) was required to cause suppression of local CHS in C3H/HeN mice but a much reduced dose of broadband UVB (5000 J m^{-2}) was sufficient. With regard to DTH, a minimum dose as small as 100 J m^{-2} broadband UVB was required for significant suppression, while a minimum dose of 1000 J m^{-2} UVA-1 was needed. Thus, not only does the UVR waveband matter, but different immune responses may be affected in different ways by these wavelengths. Recently it was shown that UVA irradiation led to the inhibition of the antigen presenting function of epidermal cells with no up-regulation of co-stimulatory molecules on culture, as would normally be expected (Iwai *et al.* 1999). This effect resulted in the suppression of the induction phase of CHS, and could be reversed by application of glutathione to the skin during the irradiation. Therefore reactive oxygen species may be involved in UVA-induced immunomodulation.
- 29** In an interesting series of experiments, Reeve *et al.* (1998, 1999) found that sub-erythemal exposure of mice to UVA radiation protected them from the suppression in systemic CHS induced by UVB exposure alone. The UVA could be administered either before or after the UVB and may induce the formation of a photoproduct, suggested to be IFN- γ , a major Th1 cytokine, from experiments in IFN- γ gene knockout mice. It was shown that, while both wild-type and mutant mice were suppressed to the same extent by UVB radiation, if UVA followed the UVB exposure, then responses were restored in the wild-type mice but remained suppressed in the mutant mice. A further publication revealed the importance of heme oxygenase in the UVA-induced restoration of CHS responses (Reeve and Tyrrell, 1999). It was suggested that IFN- γ may regulate the production of this enzyme in the dermis.

HUMAN STUDIES

- 30** As indicated above, many experiments have been carried out in rodent models to test the effects of UVR exposure on the immune system. Fewer have been designed to examine the situation in human subjects but, in general, they have produced similar results to those obtained in rodents. For example, suppression of the induction of CHS and tolerance correlates with the migration of LC from the skin and the influx of a specific subset of macrophages into the dermis, and then the epidermis (Meunier *et al.* 1995). These cells produce IL-10 and activate CD4⁺ suppressor-inducer T lymphocytes. A recent review summarises human UVR-induced changes in antigen presentation by LC and macrophages, in natural killer cell and T cell activity, and in cytokine production (Duthie *et al.* 1999). The complex interactions which may occur between the cellular and cytokine components of the human epidermis as a result of UVR exposure are shown in Figure 5.4.

Susceptibility and resistance to the immunosuppressive effects of UVR

- 31** Following exposure of a small area of human skin to 1440 J m⁻² on each of four consecutive days, a protocol which reduces LC numbers in the epidermis from 656 to 17 per mm², 40% of volunteers demonstrated suppressed CHS responses to DNCB applied epicutaneously to the site of exposure, followed by challenge at a distant unirradiated site (Yoshikawa *et al.* 1990). In parallel with mouse studies, these subjects were designated as UVB-susceptible and the others, in whom the CHS response was unaltered by the UVR exposure, were called UVB-resistant. It was also revealed that 92% of skin cancer patients and 100% of malignant melanoma patients fell into the UVB-susceptible category (Yoshikawa *et al.* 1990). It was concluded that UVB-induced suppression of CHS may therefore act as a risk factor/indicator for the development of skin cancers. However, it should be noted that the proportion of black people with the UVB-susceptible trait is similar to that in Caucasians, despite the lower incidence of skin cancer in those with black skin (Vermeer *et al.* 1991). Skov *et al.* (1998b) also reported that 56% of human subjects exhibited suppressed CHS following 3 MED UVB and local sensitisation. Tolerance was not induced in the unresponsive individuals. However, susceptibility to the immunosuppressive effects of UVB could not be attributed easily to changes in epidermal antigen presenting cell populations as there was no difference between the susceptible and resistant groups with regard to LC and macrophage cell numbers, or their ability to activate autologous T cells following the exposure (Skov *et al.* 1998b).
- 32** The clear division into UVB-susceptible and UVB-resistant has not been found in all studies. Cooper *et al.* (1992) reported that almost all subjects had a reduced ability to respond to DNCB if the sensitiser was applied to the irradiated site. The down-regulation was dose dependent to some extent as, at the lowest exposure used (0.75 MED UVB daily for four days to a small area of skin), non-responsiveness was induced in 68% of individuals, while at the highest (2 MED UVB daily for four days), non-responsiveness was induced in 95% of individuals. The most susceptible people exhibited tolerance to DNCB on repeated challenge with the sensitiser. There was a modest suppression in CHS if the sensitiser was applied at a distant unirradiated site after 4 MED UVB was given as a single dose. UVA did not alter CHS responses in any subject, indicating a possible wavelength dependence of the immunosuppressive effect

(Skov *et al* 1997). Another study has demonstrated that solar-simulated UVR exposure, corresponding to 3 MED, followed by sensitisation on the irradiated site, led to suppressed CHS in 50% of subjects (Serre *et al* 1997). However, in contrast, Kelly *et al* (1998) showed that solar-simulated radiation was highly suppressive in every person tested. A single exposure of a small area of skin to 3 MED was followed by sensitisation with DNCB at the irradiated site and diphenylcyclopropanone at a distant site, and elicitation with both sensitisers occurred three weeks later. The CHS was completely suppressed locally in 100% of individuals, and systemically in 83%.

- 33** It is difficult to draw firm conclusions at the present time. However, in all studies, at least a proportion of human subjects demonstrate suppressed CHS if the sensitiser is applied to the irradiated site. The effect is more marked if small quantities of the sensitiser are used. UVR-induced tolerance and systemic immunosuppression are not consistently observed and may depend on the contribution of different UVR wavelengths and doses. The most recent paper in this area examined the association between sunburn and UVR-induced suppression of local CHS responses (Kelly *et al* 2000). It was noted that people with skin types I/II who are sun-sensitive and tan poorly are at greater risk of developing skin cancer than people with skin types III/IV who are sun-tolerant and tan well. It was found that CHS could be suppressed in all subjects by exposure to solar irradiation equivalent to one hour of midday summer sunlight one day before the application of the sensitiser. A linear relationship was demonstrated between erythema and suppression of CHS. However, if the UVR dose was reduced to 1 MED or below, it was revealed that skin types I/II were two- to three-fold more susceptible to immunosuppression than skin types III/IV. Therefore the greater sensitivity of pale skinned people for a given level of sunburn may play a role in their increased risk of developing skin cancer.

Human diseases and UVR

- 34** For ethical reasons it is obviously not possible to perform experiments in people similar to the ones described above in animal models. In addition, few epidemiological studies have been completed in which the incidence and severity of disease have been correlated with personal sun exposure, season or latitude. However, some information is now available which includes a variety of infections, cancers and autoimmune diseases where the effect of sunlight exposure on the immune system may play an important role.
- 35** With regard to microbial infections, knowledge of this aspect of UVR effects has a long history – Finsen (1901) demonstrated 100 years ago that 'light' could be used successfully in the healing of skin tuberculosis (lupus vulgaris), although it had the opposite effect on smallpox lesions and on lung tuberculosis. Leprosy has been called the 'sunshine' disease as lesions occur most frequently on areas of the body exposed to sunlight (see paragraphs 44 and 45). In addition, three viral infections are influenced in different ways by natural exposure to sunlight: those caused by herpes simplex virus (HSV), human papillomavirus (HPV) and, more controversially, human immunodeficiency virus (HIV), each of which is now described in more detail.
- 36** HSV type 1 typically causes vesicular 'cold sores' in the orofacial region of the body and type 2 in the genital area. Following the primary infection, latency is established in the ganglia for life. The virus can reactivate at intervals, appear in an infectious form in

the skin again and replicate there to induce recrudescence lesions at the same site as the initial lesions. UVR exposure of this area is one commonly reported triggering factor for reactivation. This was first shown experimentally by Wheeler (1975) when recurrent cutaneous HSV type 2 infections in three patients were reactivated following exposure to UVR from an artificial source. Since then several other studies have confirmed the role of UVR exposure in this disease. For example, five patients with a history of herpes labialis provoked by sun exposure were irradiated on the usual site of their lesions with various doses from a cosmetic sunlamp (Spruance, 1985). Six of ten such treatments resulted in the development of vesicles. The frequency of the induced lesions was dose related and infectious virus could be cultured in most instances following the largest exposures of 5 to 6 MED. Furthermore, Rooney *et al* (1991) described a double-blind, placebo-controlled crossover trial in which 38 subjects who suffered from recurrent herpes labialis were exposed on two occasions to 4 MED UVB on the area where lesions had previously occurred. On one occasion a placebo cream was applied before the irradiation, and on the other occasion a sunblock was applied. It was reported that 71% of the patients treated with the placebo cream developed HSV lesions while none developed lesions when treated with the sunblock. These findings further substantiate the direct contribution of UVR to altering the balance between HSV and its host which occurs during latency.

37 The exact events occurring here are not understood but are thought to be two-fold. First, the virus has to reactivate in the ganglia, perhaps due to the transactivation of regulatory UVR-responsive elements, and then it replicates in the periphery (although there is some evidence that infectious HSV constantly circulates between the ganglia and the skin). The second event may be controlled primarily by the immune system of the host. It is known that T cells are critical in curtailing the viral replication and spread, as is indicated by the severe HSV infections suffered by subjects with T cell deficiencies or taking immunosuppressive drugs. It is possible that UVR may suppress local immune responses sufficiently to allow the generation of clinically apparent lesions. Local antigen presentation may be affected (Gilmour *et al*, 1993) and perhaps HSV-specific T cell immunity also (Miura *et al*, 1994), although not all studies confirm the latter possibility (Neill *et al*, 1998). It is very interesting to note a recent report by Gallerani and Manfredini (2000) indicating a seasonal variation in the incidence of shingles associated with another human herpesvirus infection, namely herpes zoster, in north-east Italy. This virus causes chicken-pox, most frequently in childhood, then remains latent in the ganglia until it reactivates causing shingles, often many years later. The frequency of disease was higher in the late spring/early summer months than in the winter months. The authors speculate that this could be due to the longer day length and more sunlight in the former period of the year, leading to interference with the immune response to the virus and consequent reactivation.

38 Over 100 genotypes of HPV have been identified, some of which are associated with the development of squamous cell carcinomas in immunosuppressed individuals. These subjects fall into two categories: renal allograft recipients (Proby *et al*, 1996) and people with the rare genetic disease epidermodysplasia verruciformis who have an underlying defect in cell-mediated immunity (Majewski and Jablonska, 1995). In both groups, the tumours develop almost totally on areas of the body exposed naturally to sunlight, especially the face and the backs of the hand (Hartevelt *et al*, 1990); the same

distribution is found for almost all squamous cell carcinomas and about 66% of basal cell carcinomas in immunocompetent individuals (Pearl and Scott, 1986). In addition, the prevalence of tumours is highest in sunny climates. The interactions between HPV and UVR have not been defined and are likely to be complex. It is recognised that HPV infections are frequently protracted and the virus is likely to have evolved various mechanisms to evade local immune responses within the infected site (reviewed by Fraser *et al*, 1999). Exposure to the sun induces damage to DNA in the epidermis and such mutations could be perpetuated and amplified as HPV causes abnormal proliferation of epidermal cells. On top of this, immune responses locally could be down-regulated by UVR which may be of significance even in subjects who are already considerably suppressed by taking drugs or genetically. One practical outcome is to advise immunocompromised subjects to avoid UVR exposure, either from the sun or from artificial sources. See Chapter 7, paragraphs 50–52, for more details regarding papillomaviruses and skin cancers.

- 39** The situation for the third virus, HIV, regarding UVR is very unclear but on theoretical grounds the progression to AIDS could be affected. First, the skin is involved as a major organ in HIV infections and a large majority of patients develop disorders of the skin or mucous membranes at some stage of the disease. Secondly, exposure to UVR has been shown to activate HIV in several transgenic mouse models (Vogel *et al*, 1992) and *in vitro* by damage to DNA and alteration in cellular transcription factors which are critical in controlling the symptomatic phase of AIDS (Stanley *et al*, 1989). Thirdly, as the disease progresses, there may be a shift from a Th1 to a Th2 cytokine profile (Clerici and Shearer, 1993), a change thought to be enhanced by UVR. Finally, HIV has been shown to infect LC and, when these move from the epidermis to the draining lymph node in response to UVR, they could then transmit the virus to T cells during antigen presentation, leading to cytolysis of the T cells or to T cells carrying the virus homing to the skin, thereby infecting other dendritic cells (Henry and Tschachler, 1996). Cruz *et al* (2000) have demonstrated very recently that a single dose of UVB led to an increase in viral RNA in the skin of HIV-positive patients with psoriasis or eosinophilic folliculitis, while UVA-1 had no effect on viral RNA expression. However, at present, there is no clinical evidence to substantiate a role for solar UVR in the exacerbation of HIV infections, despite many individuals with the virus using sunlamps cosmetically, taking sunshine holidays or undergoing phototherapy for various skin diseases (Adams *et al*, 1996). This conclusion is substantiated by one very recent study in which the association between sun exposure, as assessed by questionnaires, and disease progression to AIDS in a cohort of homosexual men in Amsterdam over a two year period was monitored. No correlation was established and no link was made with several immune parameters in the patients, such as CD4 counts and T cell reactivity (Maas *et al*, submitted for publication)
- 40** If UVR modulates immune responses to microbial antigens significantly, then the situation regarding vaccination requires consideration. It is necessary to determine, for example, if immunity to vaccines administered in the summer months is as effective as to vaccines administered in the winter months, and if it is advisable to vaccinate an obviously sun-exposed individual or someone who is about to depart for, or has recently returned from, a sunshine holiday. One study based in Utrecht has begun to investigate this important issue by assessing antibody titres to hepatitis B surface

antigen, after a standard immunising protocol. If the first and second vaccines were given during the winter months, the titres were higher than if given during the summer months (Termorhuizen *et al.* 1999). Currently an experimental human trial with controlled exposure to UVB prior to hepatitis B vaccination is being performed in the Netherlands, with subsequent measurement of antibody and T cell responses (Termorhuizen and Van Loveren, personal communication). It was noted in a report of the US Environment Protection Agency in 1995 (Selgrade *et al.* 1997) that priority required to be given to studying UVR in the context of vaccine effectiveness. It was proposed that Bacillus Calmette-Guerin (BCG) could be used for this purpose as it is given to most children shortly after birth; newborns with hyperbilirubinaemia are treated with solar UVR, while normal children are more or less UVR-protected, so comparisons could be made between these two groups. In addition, immune responses to measles vaccine administered in countries where large seasonal differences in climate occur could provide good data. Such studies have not been undertaken as yet.

41 It has been suggested that several diseases, other than those with a straightforward infectious aetiology, may be affected by UVR exposure. One such category is the autoimmune diseases. Here it is possible that the effects of UVR on immunity could be either beneficial, by down-regulating Th1 activity where this is critical, such as in the organ-specific insulin-dependent diabetes mellitus, or be adverse, by up-regulating Th2 activity where this is critical, such as in systemic lupus erythematosus (SLE). The former category has been demonstrated in a mouse model of experimental allergic encephalomyelitis where whole body UVR exposure prevented clinical and pathological signs of the autoimmune disease (Hauser *et al.* 1984). The latter may be indicated by the increase in disease activity in 50% of photosensitive patients with SLE following exposure to fluorescent lamps which emit some UVB ($15 \text{ mJ cm}^{-2} \text{ h}^{-1}$) (Richner and McGrath, 1992). If the lights were covered, no such effect occurred.

42 Several studies over the past 40 years, such as that by Kurland and Reid (1964), have pointed out a marked positive correlation in the incidence of multiple sclerosis in the Caucasian population with latitude. More recently McMichael and Hall (1997) have suggested that this could be due to solar UVR levels which are negatively correlated with latitude. For example, in Australia, the prevalence of multiple sclerosis per 100 000 people is 12 in North Queensland at latitudes of 12–23°S and 76 in Tasmania at a latitude of 43°S (Martyn, 1991). Multiple sclerosis is known to have an immunological basis with increased Th1 cells specific for myelin base protein and disturbances in DTH responses. Therefore increased UVR exposure could perhaps ameliorate this disease by suppressing Th1 function. This suggestion has gained support recently in a report where a negative association of deaths from multiple sclerosis and residential and occupational solar radiation in the USA was found (Freedman *et al.* 2000). In contrast, deaths from malignant melanoma in the same population were positively associated with both types of UVR exposure. The age at which the sunlight exposure occurs may be a factor as earlier studies found that the risk of developing multiple sclerosis in people who moved to a new country with a different multiple sclerosis incidence rate was only altered to the rate in the adopted country if the immigration occurred in early childhood (Dean and Kurtzke, 1971; Alter *et al.* 1978). Lastly, a more speculative study asked whether the rise in incidence of non-Hodgkin's lymphoma could be accounted for by population-based increases in solar UVR exposure (McMichael and Giles, 1996).

Here the risk of developing the tumour rose with decreasing latitude, even in migrants. See Chapter 8 for more details regarding non-Hodgkin's lymphoma.

- 43** Finally there is interest currently in assessing UVR in the context of respiratory allergens such as house dust mite where it is known that Th2 cytokine responses are responsible for the hypersensitivity in the airways that occurs. Hence UVR has the potential to exacerbate the symptoms by promoting Th2 activity, particularly the production of IL-10. Animal models exist in which this hypothesis can be tested, and it would be useful in addition to gather epidemiological data regarding the exposure of young children to sunlight and the development of allergic responses.

Suppression of DTH to microbial antigens in human subjects

- 44** Several studies have monitored changes in DTH to microbial antigens following UVR exposure of human subjects. Thus, in this case, alterations of memory responses are being assessed which may affect the resistance to re-infection or affect the balance between the microbe and the host, in the case of persistent infections. Cestari *et al* (1995) irradiated healthy contacts of leprosy patients who were lepromin-positive and tested their antigen-specific responses by injecting lepromin (a heat-killed suspension of *Mycobacterium leprae*) into the irradiated site. The size of the lepromin-induced granuloma, characterised by tissue necrosis and fibrosis, was reduced in the irradiated site, together with a lower number of infiltrating CD4⁺ cells. It is noteworthy that an increased incidence of leprosy lesions has been reported to occur in areas of the body exposed to sunlight (Patki, 1991). Damian *et al* (1998) irradiated subjects who had previously been vaccinated with BCG and were Mantoux-positive. Their mycobacterial DTH responses were then tested in exposed and unexposed sites. Suppression of DTH was found in the irradiated site, but not in the distant unirradiated site. A suberythral UVR dose (each day for five days) was sufficient to induce the effect. However, if the exposure to UVR was continued for four to five weeks, no significant suppression occurred, indicating that, perhaps, adaptive mechanism may have been generated to counteract the UVR effects. O'Dell *et al* (1980) tested the DTH to the yeast *Candida albicans* by intradermal injection into sun-damaged skin in the neck of volunteers. The response was suppressed compared with that elicited in normal back skin of the same person. *C. albicans* was included as one of several microbial antigens to test whether chronic solar-simulated radiation suppressed DTH, either locally or systemically. The others were tetanus toxin, diphtheria toxin, *Streptococcus* antigen, tuberculin, *Trichophyton* and *Proteus* antigens, prepared as a standard multitest kit. Following ten incremental UVR doses, the overall DTH score on challenge was reduced by 60%–70%, both at the exposed site and at an unexposed site, compared with the response in the same individual before irradiation (Moyal *et al*, 1997).
- 45** Therefore, as assessed by the elicitation stage of DTH, these studies overall show a general down-regulation of memory immune responses to a variety of microbial antigens resulting from UVR exposure.

UVR-induced changes in cutaneous antigen presenting cells, natural killer cells and T cells

- 46** One of the first changes to be recognised in the epidermis following UVB radiation was the reduction in LC numbers. This was shown originally in murine skin but has also been found in human skin (see, for example, Skov *et al* (1998b)). UVR may act differently

on the LC in people of different racial origins (Hollis *et al* 1998). Thus, whereas LC were depleted by apoptosis in the darker skin of Aborigine and Asian Australians, cells in Celtic Australians were even more reduced in number and died as a result of membrane disruption and organelle damage.

- 47** The function of human LC has been investigated in several studies. For example, low dose long-term UVB (300–500 J m⁻² three times weekly for four weeks) resulted in a marked suppression in the ability of epidermal cells from skin biopsies or blisters of healthy volunteers to act as stimulators in the MECLR (Van Praag *et al* 1994). This down-regulation was not paralleled by a change in LC number or of HLA Class II expression. Barr *et al* (1999) found that, following exposure of human skin to 3 MED solar-simulated radiation, the activity of the epidermal cells in a MECLR was suppressed by 69% from 4–15 hours later but recovered to control levels by 24 hours. From time-course studies of the expression of the cytokines TNF- α , IL-1, IL-1 receptor antagonist, IL-10, and TNF receptors, TNF- α was proposed to be the key mediator of UVR-induced damage in irradiated human skin (Barr *et al* 1999). Investigation of epidermal cell suspensions, derived from skin which had been subjected to erythemagenic UVB each day for four days, showed a doubling in numbers of CD36⁺ macrophages compared with unirradiated skin (Hurks *et al* 1997c). This increase correlated with the recovery, and the enhancement, of the MECLR (Hurks *et al* 1997c; Cooper *et al* 1985). There was not only infiltration of macrophages into the epidermis but also expansion of the dermal macrophages subset, which is phenotypically identical (Meunier *et al* 1995).
- 48** Results which appear contradictory to those just outlined above have been obtained by Kremer *et al* (1997). They used human skin organ cultures which were UVB irradiated with a single dose, up to 800 J m⁻², followed by a phenotypic and functional analysis of the cells which migrated out of the tissue. The number of HLA-DR⁺ LC was reduced in comparison with unirradiated skin. Furthermore the LC showed the same ability to stimulate allogeneic T cells on a per cell basis as those from unirradiated skin, despite evidence of DNA damage. It was concluded that the migrating cells are not altered in their antigen presenting capacity by UVR exposure, although it is possible that the cytokine environment in this experiment does not mimic the *in vivo* situation accurately.
- 49** Although there are probably no effects on numbers of circulating T cell subsets as a result of UVR exposure and no alteration in cytotoxic T cell activity specific for HSV was revealed during broadband UVB therapy (Neill *et al* 1998), changes in T cells do occur locally in irradiated skin. Biopsies showed an initial decrease, or depletion, of intraepidermal T cells, perhaps due to phototoxicity, within two days of a single erythemal UVR dose of solar-simulated light (Di Nuzzo *et al* 1996). Meanwhile dermal T cell numbers increased. One week after the irradiation, T cells had migrated into the epidermis and were almost exclusively of the memory phenotype (CD45RO⁺) and lacked activation markers (Di Nuzzo *et al* 1998).
- 50** Natural killer (NK) cells are HLA-unrestricted and play an important part in the recognition and lysis of both virally infected cells and tumours cells. They also aid the development of a Th1-like immune response through the release of IFN- γ . UVR exposure causes a dose-dependent inhibition of NK cell activity *in vivo* probably without causing a change in numbers, and, from *in vitro* experiments, UVA is likely to have an equivalent immunosuppressive effect to that of UVB (Hersey *et al* 1993). The exposure does not prevent NK cells recognising and binding to their target cells, but

acts at the apoptosis or lysis stage, perhaps by the production of reactive oxygen species (Toda *et al.* 1986). A study using solarium exposure as a source of UVR concluded that NK cell function was reduced during the course of the tanning (Hersey *et al.* 1983). The suppression was particularly significant two weeks after the last irradiation. Measurement of NK cell activity after various UVR therapies used for the treatment of psoriasis showed depression during, and up to four weeks after, the irradiation course (Gilmour *et al.* 1993). The precise timing and extent of the down-regulation varied between the groups (PUVA, broadband UVB and narrowband UVB) and may be related to dose.

Action spectra for UVR-induced changes

- 51** It is likely that various wavelengths throughout the UVR spectrum will affect different immune responses differently due, perhaps, to the initiating action of the photoreceptor most involved and the subsequent induction of a distinct profile of epidermal cytokines. Therefore there is considerable interest in defining action spectra in human skin for the immunomodulating effects of UVR. Thus far, limited information has been obtained regarding the isomerisation of UCA, the formation of thymine dimers, suppression of the MECLR and TNF- α release.
- 52** The action spectrum for production of *cis*-UCA in mouse skin is not consistent with the action spectrum for systemic UVR suppression of CHS (Gibbs *et al.* 1993). Similar experiments on UCA isomerisation were carried out in human skin irradiated with monochromatic light from 260 to 340 nm. The resulting action spectrum had a broad, flat peak from 280 to 310 nm, which was red-shifted from both the absorption peak of UCA and the action spectrum for immunosuppression (Gibbs *et al.* 1997). Kammeyer *et al.* (1995) demonstrated that isomerisation from *trans*- to *cis*-UCA occurred in human skin up to a wavelength of at least 363 nm, in the middle of the UVA waveband.
- 53** Young *et al.* (1998) carried out a study in which human skin was irradiated with various doses of monochromatic light ranging from 280 to 360 nm which was then assessed for thymine dimers as a measure of DNA damage. The maximum effect occurred at 300 nm in all layers of the epidermis and, at this wavelength or longer wavelengths, there was induction of dimers in dermal nuclei. The epidermal dimer action spectrum was compared with the erythral action spectrum in the same volunteers and the conclusion was reached that DNA is a major chromophore for erythema in the 280–340 nm waveband.
- 54** Hurks *et al.* (1997b) also measured thymine dimer formation after irradiation of human skin obtained by plastic surgery, with monochromatic light (254, 297, 302 and 312 nm) and compared the dose–response curve with that obtained for the suppression in the MECLR using epidermal cells from the biopsies as stimulators. Both action spectra showed a small reduction from 254 to 302 nm, followed by a steep decline to 312 nm. It was concluded that DNA damage was a major factor in suppression of immune responses following UVR exposure. However, as wavelengths above 312 nm were not included and the experiments were not done *in vivo* so that any movement of cells from the blood into the epidermis would be impossible, perhaps this result is not definitive.
- 55** The induction of TNF- α and IL-10 was compared in suction blister fluid prepared from human skin irradiated with 3 MED UVB or UVA-1 (Skov *et al.* 1998a). It was found

that the concentration of TNF- α rose rapidly (within six hours) following the UVB exposure but there was a slight decrease after UVA-1 exposure. The concentration of IL-10 rose very slightly after UVB but not after UVA-1. Differences in cytokine induction may help to explain the variation in immune responses which follow irradiation with these wavebands; for example, similar doses of UVR, as judged by erythema, resulted in suppression of CHS after UVB but not after UVA-1 (Skov *et al.* 1997).

UCA analyses in human subjects

- 56** Absorption of UVR photons causes the naturally occurring *trans*-isomer of UCA in the skin to convert to *cis*-UCA in a dose-dependent manner until the photostationary state is reached with approximately equal quantities of the two isomers. Human subjects vary considerably, up to ten-fold, in the concentration of UCA they contain in their skins, a parameter which does not correlate with stratum corneum thickness, pigmentation, body site or photosensitivity (Olivarius *et al.* 1997b). Bacteria which are able to convert *trans*- to *cis*-UCA and to degrade both isomers of UCA have been found as part of the commensal flora of the skin of some individuals (Hug *et al.* 1999). Following UVR exposure the isomerisation of UCA from *trans*- to *cis*-UCA is higher in lightly pigmented subjects compared with more pigmented subjects, indicating that people with fair skin may be at relatively higher risk of immunosuppression when exposed to a low dose of UVB (Olivarius *et al.* 1999). The UCA concentration of the isomers in each individual varies with the season of the year: the maximum percentage of *cis*-UCA is observed in the summer months, with a small reduction in the total amount of UCA at this time (Olivarius *et al.* 1997a).
- 57** Two studies have assessed UCA levels in subjects with cutaneous malignant melanomas and basal cell carcinomas in comparison with healthy controls (Olivarius *et al.* 1998; Snellman *et al.* 1999). In both, there was no difference between the patients and the controls in the total concentration of UCA or in the percentage of the *cis*-UCA isomer: therefore no indication was obtained to link UCA with an increased risk of developing skin cancer. In one report, the rate of isomerisation after UVR exposure from *trans*- to *cis*-UCA was slightly higher in the patients than in the controls (Olivarius *et al.* 1998), while, in the second report, the opposite result was obtained (Snellman *et al.* 1999).

Risk assessment for suppression of immune responses in human subjects by extrapolation from rodent models

- 58** In view of the difficulty of obtaining experimental data regarding UVR exposure and its effect on human subjects, and the lack of epidemiological information especially with regard to infectious diseases, it may be possible to use the immunological results obtained in animal models and to extrapolate these to the human situation (Selgrade *et al.* 1995). A start has been made to this so-called 'parallelogram' approach (Garssen *et al.* 1996, 1998). A UVR dose response was constructed for the suppression of T cell lymphoproliferation in rats infected intravenously with *Listeria monocytogenes* (Goettsch *et al.* 1996a). It was found that a dose of 6800 J m⁻² inhibited the response by 50% and the same dose also inhibited the clearance of bacteria from the spleen. A comparison of human and rat skin for susceptibility to the immunosuppressive effects of UVB exposure followed, as assessed by the MECLR. Rats were demonstrated to be about four times more sensitive than humans (Garssen *et al.* 1996), and this figure was

taken as a measure of interspecies variation. A figure of 0.5 was added to account for possible differences in individuals in their susceptibility to UVR-induced immunosuppression (intraspecies variation). Thus the estimated UVB dose required to suppress T cell immunity to *Listeria* by 50% in human subjects was $6800 \times 4 \times 0.5 = 13600 \text{ J m}^{-2}$. This calculation was then extrapolated to solar exposure using an action spectrum for the suppression of CHS in mice and the biological effective irradiance at certain latitudes (De Fabo *et al.* 1990). Thus, for example, it was predicted that exposure for about 100 minutes at 40°N (Spain, Italy or Japan) around noon in July on a clear day would suppress cellular immunity to *Listeria* by 50% (Garssen *et al.* 1998). Should the ozone layer decrease by 5% at some stage in the future, then the exposure time would shorten to approximately 97 minutes. Similar calculations have been carried out using the absorption spectrum for UCA, the action spectrum for DNA damage, and the action spectrum for the suppression of the MECLR (Norval *et al.* 1999). All gave similar results.

- 59** Several studies have examined the suppression in CHS to simple chemicals in human subjects due to UVR exposure and have found that the effective dose is about the same order as the theoretical assessment outlined above (Cooper *et al.* 1992; Kelly *et al.* 1998). One of the most recent of these used a single dose of solar-simulated radiation and showed that suppression of CHS occurred, both locally and systemically, after exposure to 3 MED (Kelly *et al.* 1998). Such a dose would be achievable in the UK with one hour of summer sunlight around noon on a clear day. These findings validate the parallelogram approach as a means of estimating human susceptibility to UVR, but, of course, do not account for the possible development of adaptive mechanisms such as tanning and epidermal thickening which may provide protection.
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SUNSCREENS AND IMMUNOPROTECTION

- 60** Despite much interest in this important area, many uncertainties remain, partly due to the variables which are being assessed. For the sunscreens themselves, there are many formulations with a range of sun protection factors (SPF) based on their ability to prevent erythema or oedema. Most sunscreens scatter or absorb UVR wavelengths. Sunscreens are tested frequently in haired mice in which erythema is difficult to determine, although hairless mice are used on occasion, allowing accurate measurement of oedema, and there is merit in using human subjects for testing, as much as is ethically permissible. In many protocols the lamps emit a spectrum which is very different from that of the sun. Therefore the consensus view currently is that solar-simulated light should be employed, whenever possible. Furthermore the action spectrum for immunosuppression in human subjects is not known. Until this is established, sunscreens will have to be tested empirically – no small undertaking. Finally and very importantly, there is no single recognised endpoint for immunomodulation. Assays have included local and systemic suppression of the induction phase (effect of UVR on primary immune responses) of CHS and DTH, suppression of the elicitation phase (effect of UVR on primary immune responses) of CHS and DTH, the ability to reject tumour cells, the depletion of epidermal LC, the isomerisation from *trans*- to *cis*-UCA in the epidermis, the suppression of the MECLR, the suppression of antigen presentation in the MLR, the induction of IL-10 in the serum, and the suppression of NK cell activity. Each of

these systems is likely to have differing UVR-dependencies: for example, NK cells are affected by UVA, whereas the production of IL-10 is unlikely to be so.

- 61** In whatever system is being used to assess the immune protection factor (IPF) of a sunscreen, it is essential to determine the UVR dose which gives 50% immunosuppression with and without the sunscreen and to compare this value with the SPF (Young and Walker, 1998). At the present time, there is uncertainty about whether the SPF necessarily relates to the IPF and therefore, in this respect, UVR exposure may never be considered 'safe'. IPF values, where they have been reported, are lower than SPF values (see, for example, Whitmore and Morison, 1995; Moyal *et al.* 1997; Serre *et al.* 1997), although not in all cases (Roberts and Beasley, 1995, 1997). To provide good immunoprotection, it may be necessary to include a UVA protection factor in the sunscreen, as is indicated in one recent study (Fourtanier *et al.* 2000); indeed, in general, formulations with broad absorption spectra may be most effective. More details regarding sunscreens and immunoprotection are provided by Ullrich *et al.* (1999) and Elmetts and Anderson (1996).
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SUMMARY AND CONCLUSIONS

- 62** Exposure to UVR results in suppression of immune responses. The chain of events leading to the immunomodulation is known to be complex. It is initiated by chromophores in the skin such as DNA and *trans*-UCA which, on absorption of UVR, change their properties and trigger the production of various mediators, particularly cytokines, both locally and systemically. There are associated changes in the populations of antigen presenting cells in the skin and in their function. The final step is the induction of T cells capable of down-regulating immunity and in a probable imbalance in T cell subsets with promotion of those synthesising Th2 factors, such as IL-4 and IL-10, and concomitant abrogation of those synthesising Th1 factors, such as IFN- γ .
- 63** Details of the above steps have been elucidated both in cellular systems *in vitro* and in animal models, generally rodents. It has been demonstrated that modulation of the normal host defences by UVR in mice may be important in allowing a tumour to progress and in causing a significant suppression of resistance to several microbial diseases, both skin-associated infections and systemic infections with no skin involvement. The chromosomal loci involved in genetic susceptibility to the local and systemic immunosuppressive effects of UVR on CHS responses in mice are beginning to be identified. Attempts have been made to derive a risk assessment for the suppression of immunity in human subjects by extrapolation from the rodent models. These show that measurable immunological changes are caused by UVR doses encountered easily in natural sunlight. Indeed it is noteworthy that in many instances immunosuppression is induced by exposures of less than 1 MED.
- 64** Fewer studies have been published examining the effects of UVR on immunity in human subjects, but, where done, generally they have produced results similar to those obtained in rodents. There is some evidence to indicate that there may be UVR-susceptible and UVR-resistant individuals, as in mice, with the former group more prone to develop skin cancers than the latter. With regard to infectious diseases, a link has

been demonstrated between recrudescence of HSV and sun exposure in a proportion of latently infected individuals, and a high risk of conversion of benign papillomas caused by various HPV types to squamous cell carcinomas in immunocompromised subjects on areas of the body naturally exposed to the sun. Evidence to associate solar irradiation with several other diseases, such as progression from the latent phase of HIV infection to AIDS, exacerbation of systemic lupus erythematosus, and a rise in the incidence of non-Hodgkin's lymphoma, is more controversial.

65 There is interest currently in determining the IPF of sunscreens and to investigate whether this value relates to the SPF where oedema/erythema is the endpoint assessed. At present the IPF, where reported, is generally lower than the SPF.

66 Much remains to be determined in this interesting and rapidly progressing area, not least to address critical questions regarding the impact of UVR on vaccine effectiveness and the resistance to re-infection, and the possibility of adaptation to UVR-induced immunosuppression on chronic exposure as may occur during the summer months.

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6 Ocular Effects

INTRODUCTION

Anatomy and optical features of the eye

- 1 The eyeball is suspended in the orbit, protected from direct exposure to optical radiation by the lids. Anteriorly, the transparent cornea is covered by an epithelium, which is continuous with that of the bulbar conjunctiva. Posteriorly, the sclera completes the outer, corneoscleral coat. When the eyes are open, almost the whole cornea is exposed, together with two small wedges of conjunctiva, overlying the subjacent sclera. The anatomy of the eye is shown in Figure 6.1.
- 2 Light entering the eye passes through the cornea, aqueous, pupil, lens and vitreous to be focused on the retina. The iris is pigmented and completely absorbs incident ultraviolet radiation (UVR), while the pupil regulates the amount of light reaching the retina. When the amount of light falling on the retina increases, the pupil constricts reflexly and the radiant energy reaching the lens and retina is reduced. UVR alone does not induce this protective response. Pupil constriction also occurs when a near object is viewed.
- 3 The lens of the eye is avascular and grows throughout life. It is housed in a collagenous capsule, deep to which, anteriorly, is the epithelium. This divides continuously at its periphery to produce elongated, lens fibre cells, which are added consecutively to the lens surface. Since these cells are never shed, the lens grows throughout life. Only the epithelium and the young, outer cortical fibres retain metabolic activity. The deeper cortical fibres and those of the lens nucleus are devoid of intracellular organelles. Transparency of the lens is dependent on the regular arrangement of the lens fibres and the degree of order of the lens crystallins, which are the major structural proteins of the lens. There is a negligible renewal of protein in the nucleus.
- 4 The retina consists of an inner neuroretina and an outer, retinal pigment epithelium (RPE) (Figure 6.2).

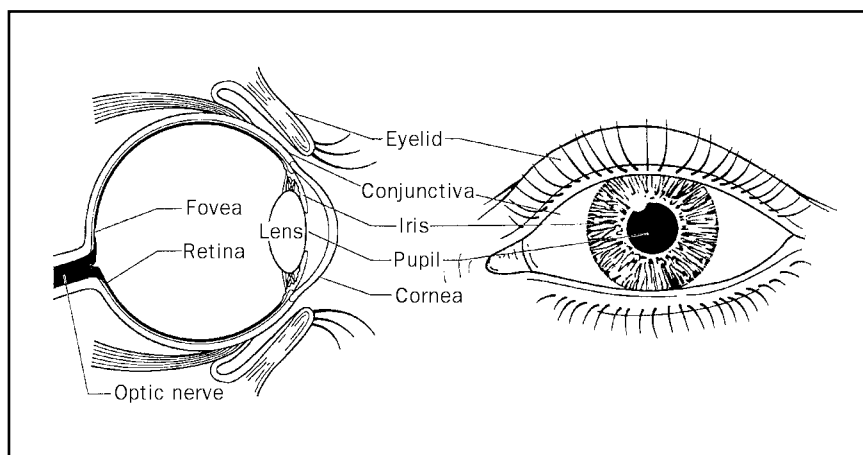
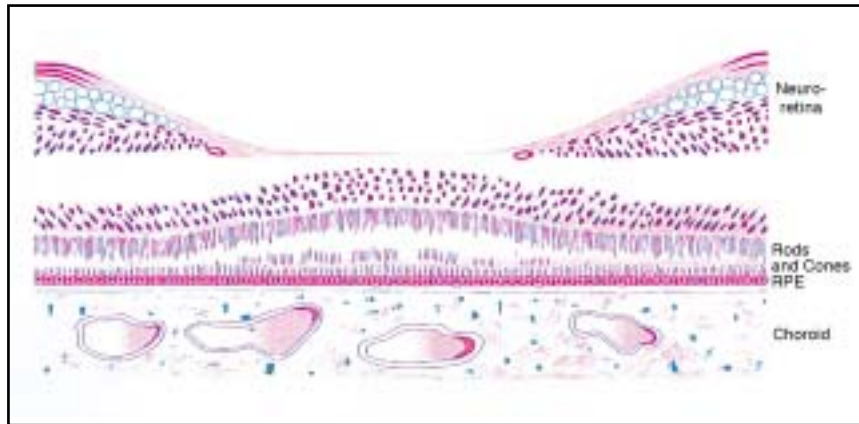


FIGURE 6.1 The eye

FIGURE 6.2 Cross-section of the retina, the centre of the retina, the fovea



- 5 Light is transmitted through two layers of neural cells to reach the photoreceptors, which are directly applied to the RPE. Within the neuroretina, the photoreceptor layer consists of the cones, which are responsible for daylight vision, visual acuity and colour sense, and the rods, which are responsible for night vision. In the human retina, the rods outnumber the cones by 25 to 1 and are about 1000 times more sensitive to light. Cones reach a maximum population at the fovea, a region of the retina specialised for visual acuity. The fovea lies on the visual axis at the centre of the macula. Photons not absorbed by the inner, neural layer of the retina, or by the photoreceptors, are captured by the melanin containing RPE, thereby reducing scatter and improving visual definition. The retina has a dual blood supply, a rich supply to the inner retina by retinal vessels and a further supply to the outer retina and RPE via the choroid, which lies outside the retina. The RPE plays an essential role in photoreceptor visual pigment turnover and in the recycling of vitamin A.

OCULAR EXPOSURE TO SOLAR UVR

- 6 As noted in Chapter 2, human exposure to solar UVR depends on geographical location, altitude, time of day, time of year and sky cover, and behavioural protective factors, ie avoidance of exposure (Bergmanson and Sheldon, 1997). A variable but important amount of solar radiation is reflected or scattered from the ground (albedo) and varies with the composition of the surface, as reported by Sliney (1995a,b; 1999). At its extremes, reflectance varies from 0.8% from grass, to 88% from fresh snow. The range of reflectances from various terrains, is shown in Table 6.1.
- 7 Sliney (1995a,b) has summarised the factors influencing ocular exposure, emphasising the importance of reflected radiation and of behavioural and geometric factors.

Solar geometry

- 8 Ocular exposure to visible radiation and UVR out of doors varies with time of day, but because of the ability of the human eye to adapt to changes in illumination levels and because of the differing reflectance of visible radiation compared with UVR, from different environmental surfaces, it is not possible for individuals to judge their UVR exposure intuitively from the brightness of the day (see below).

| Representative terrain surfaces | Diffuse reflectance ACGIH-weighted solar UVB (%) |
|---------------------------------|--|
| Green mountain grassland | 0.8–1.6 |
| Dry, parched grassland | 2–3.7 |
| Wooden boat dock | 6.4 |
| Black asphalt | 5–9 |
| Concrete pavement | 8–12 |
| Atlantic beach sand (dry) | 15–18 |
| Atlantic beach sand (wet) | 7 |
| Sea foam (surf) | 25–30 |
| Aged, 'dirty' snow | 59 |
| Fresh snow | 88 |

TABLE 6.1
Reflectance of
ACGIH effective
solar UVB from
different terrains
(from Sloney, 1995a)

Aversive behaviour

- 9** Ocular exposure is far more affected by aversive behaviour than is skin. Although the cornea is more sensitive than skin to UVR injury, photokeratitis does not occur in situations where sunburn occurs. This is because of aversive actions, which direct the eyes away from the sun or protect the ocular surface by narrowing the lid aperture ('squinting') (Sloney, 1995a). At sunset, atmospheric filtering is so great that squinting is not attempted.
- 10** On a clear sunny day, an individual will avoid looking directly at the sun (Sloney, 1986). When the sun is overhead and UVR irradiance is at its greatest, the cornea is shielded by the brow, upper lid and lashes. If the eyes are turned away from the sun, the more intense, scattered UVR from overhead strikes the corneas obliquely, so that most is reflected and little is absorbed. When looking towards the sun when it is lower in the sky, say 10° above the horizon (eg. when walking towards the sun) it is usual to 'squint', or narrow the palpebral aperture. This narrows the field of view above the line of sight. When walking, the eye is further protected from direct exposure or from the 'sky-light', by directing the eyes towards the ground, by about 15° (Sloney, 1983, 1986). These factors normally reduce corneal UVR exposure to a maximum of about 5% of that falling upon the top of the exposed head (Sloney, 1987). On an overcast day, and in the absence of a hat, the eye is exposed to an effective irradiance of 0.03–0.5 $\mu\text{W cm}^{-2}$. In the absence of protection, including aversive behaviour, the dose falling on the eyelids, is about 18%–20% of that falling upon a horizontal surface (Rosenthal *et al*, 1985, 1988a,b; Sloney, 1987; Sloney and Wolbarsht, 1980). However, when the sun's rays are incident along the line of sight, the eye absorbs up to 98% of radiation (Figures 6.3 and 6.4).
- 11** On a lightly overcast, cloudy or hazy day, when the total luminous flux is less, the eyelids are more widely open than on a bright, sunny day, so that there is a greater acceptance angle for UVR falling on the eye and a greater exposure of the ocular surface. In this situation, the UVB dose rate to the eye from sky scatter near the horizon may be increased by a factor of two or more, compared with a bright, sunny day. Ground reflectance makes an important contribution to ocular UVR exposure (Table 6.1). On looking at a snow-covered surface, UVR is reflected directly into the eye. In certain geographical locations where solar radiation is high, special protective measures are employed by the indigenous people to reduce exposure. In Iceland, eye protectors are used by the Inuits or Eskimos, consisting of slitted whalebone or seal-skin masks, and certain desert nomads employ slitted cloth masks or veils around midday (Sloney, 1995a).

FIGURE 6.3 Degree of lid opening varies greatly with different conditions of skylight and terrain luminance (from Slaney, 1995a)

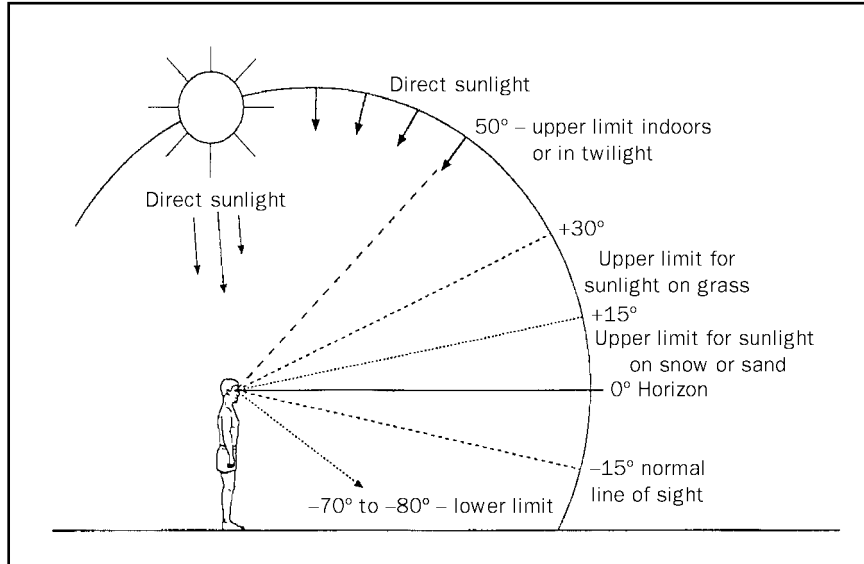
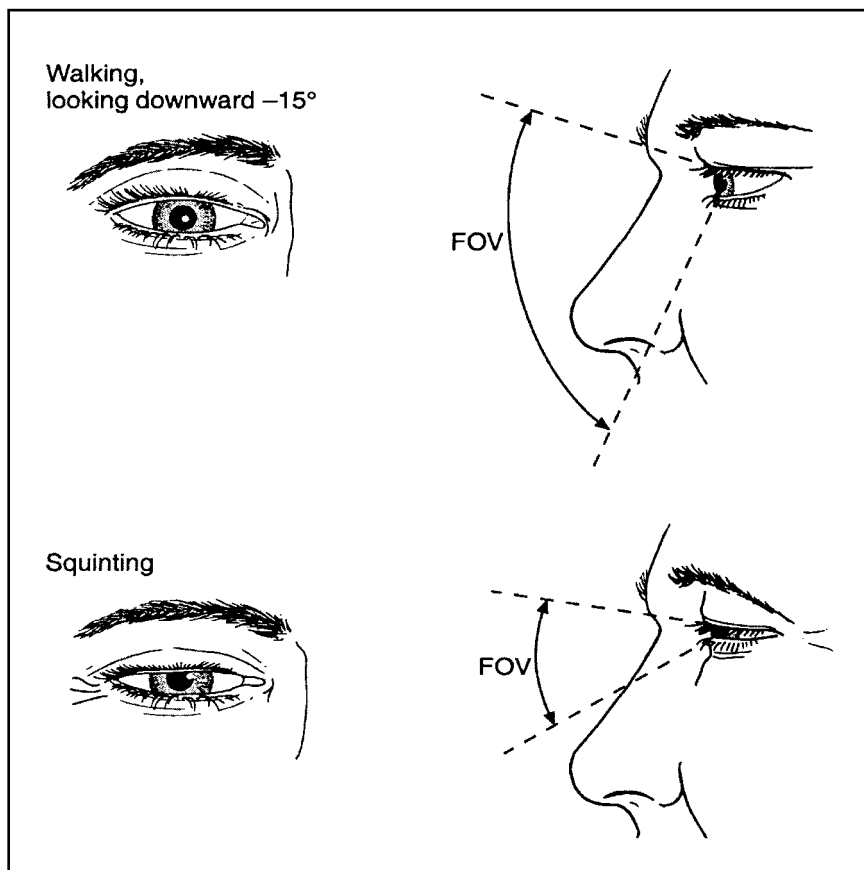


FIGURE 6.4 Geometric factors reduce ocular exposure to UVR. 'Squinting' narrows the field of view (FOV) and strongly limits ocular exposure to UVR from sky scatter. The upper lid blocks most of the skylight and covers the upper limbus (from Slaney, 1995b)



- 12** It can be seen from this background that individual exposure may vary 100-fold by reason of a difference in reflectance from different terrains, by a factor of four to five with variation in yearly overhead UVR with latitude and by a factor of two with variation of altitude, with UVR being highest at greater altitude. Behavioural factors may further modify exposure (Sloney, 1995a).

Personal dosimetry and facial geometry

- 13** As has been noted, 'squinting' reduces the UVR dose to the ocular surface and consequently to the lens and retina (Figure 6.4). Narrowing the palpebral aperture may cause a 20-fold reduction in lens exposure. The upper lid is said to provide over 1000-fold protection to the retina from solar radiation. A brimmed hat may virtually eliminate direct exposure to the eye. However, as with the wearing of sunglasses, such shading may result in greater lid opening and a larger pupil so that the eye may encounter a greater fraction of the incident radiation, particularly from below. A brimmed hat will not exclude ground reflection as a source of ocular UVR and in the same way, sunglasses do not exclude indirect, reflected and scattered radiation from sources lateral to the eyes. If sunglasses are simply dark and designed only to filter out the visible wavelengths but fail to absorb UVR, then such glasses will lead to an increase in UVR exposure, both to the surface of the eye and to intraocular structures. The wearer no longer narrows the lids for protection and does not direct gaze away from the sun sector of the sky; the larger pupil may further amplify irradiance of the lens and retina.

Modelling ocular exposure

- 14** Based on dosimetric studies and considerations of lid position ('squinting') and other behavioural factors, Sloney (1995a) calculated the total ocular exposure to solar radiation as follows:

$$H_O = H_S + H_H$$

where H_O is the total ocular exposure, H_H is the ocular exposure from the ground, and H_S is the skylight component, determined by the duration of exposure (t). Now, L_S is the UVR sky irradiance and Ω_U is the field of view above the horizontal (the solid angle in steradians; affected by upper lid position). Thus

$$H_S = \Omega_U L_S t$$

- 15** H_H is determined by the solid angle, Ω_D , of exposure over the lower hemisphere and by the ground UVR radiance, L_G :

$$H_H = \Omega_D L_G t$$

- 16** The ground radiance is the incident global UVR, E_{GL} , multiplied by the ground reflectance (which varies according to the type of surface), divided by π , the effective solid angle for diffuse lambertian reflection.

- 17** A similar approach was taken for the Chesapeake Bay Waterman Study, which was the first study in which an attempt was made to develop a detailed model of personal ocular exposure (Taylor *et al.* 1988). Field studies were used to determine the ratio of ocular UVB to ambient levels and to establish the modifiers of ocular exposure to UVB,

using questionnaires addressing the time spent out of doors while working, and the use of spectacles and hats since the age of 16 years.

- 18** The methods used for the waterman study, which examined white males working in an unusual solar environment, were further developed for application to a general population of males and females, including both whites and African Americans, living in the district of Maryland (the Salisbury Eye Evaluation project: SEE project) (Duncan *et al.* 1995, 1997a,b). This model was as follows:

$$H = R_{\text{oa}} \left[\sum F_i(t_i) H_a(t_i) \right] T_{\text{hat}} T_{\text{eye}} G$$

where H = personal ocular exposure,

R_{oa} = ocular/ambient exposure ratio or OAER (variable with season: between 10% and 19%; diminished by hat wear by about 30%; published data used for the reduction with glasses: Rosenthal, 1986; 1988a),

$F_i(t_i)$ = fraction of time spent out of doors in the i th period of the day,

$H_a(t_i)$ = global ambient exposure during this day,

T_{hat} = reflectance reduced by hat wear (= 30%),

T_{eye} = reduced exposure conferred by eyewear (for UVB: 96% for plastic and 80% for glass),

G = a correction factor which relates the total yearly ambient exposure in Maryland to that seen elsewhere in the world, using satellite data from the total ozone mapping spectrometer, to measure the total ozone column and the Nimbus satellite data for cloud cover. This was used to obtain the biologically weighted yearly radiation dose for any point on the globe excluding the polar regions.

- 19** Cumulative exposure was calculated in Maryland Sun Years (MSY), with each MSY taken to be 75.94 J cm^{-2} effective integrated energy density (erythemal spectral weighting), or alternatively 3616 minimum erythemal doses. In the SEE population, the cumulative ocular exposure varied from 0 to 5.3 MSY, with a median of 1.474 MSY (Duncan *et al.* 1997a). Exposure each month was summed over the months and then over each year of life since the age of 30 years.
- 20** An important component of this model is the ocular/ambient exposure ratio or OAER. This was initially estimated in a group of subjects who were instrumented to measure UVB radiation in the plane of the face, while information was collected about time out of doors, spectacle and hat use, eye colour and photophobia. Ambient radiation was measured simultaneously. The OAER was found to be unaffected by job category, but was highly sensitive to the reflectivity of the work surface. The model also includes a geographical correction factor for location, including reflectivity.
- 21** These studies showed that OAERs in the UVB range are generally higher than in the visible wavelengths (13% versus 6%), display no significant variation with job category, and show a seasonal effect [highest in the winter-spring months (18%), lowest in the summer months (10%) and an intermediate value in autumn (14%)] (Duncan *et al.* 1997b). For UVB, they were reduced 34% by the use of hats, a lower value than that reported by Rosenthal *et al.* (1991) for groundkeepers (57%) but similar to that estimated

for watermen (39%). The differences may relate to differences in the surface reflectance between the different studies.

- 22** The low summer OAER for UVB may be due to the low reflectivity of grass and green leaves in the summer. For white light, the OAERs were the reverse of those found for UVB, ie highest in the summer and lowest in the winter. The higher reflectivity of grass for white light was thought to be one of the factors explaining this reversal. For the visible wavelengths, OAERs showed a weak, non-significant effect with job category and were not affected by the use of hats. This difference may be because it is unusual for an individual to look directly towards the light of the sun. Neither eye colour nor reported photophobia affected the OAERs.
- 23** Using this model Duncan *et al* (1997a) found the average annual ocular exposure in Salisbury, Maryland, to range from 0 to 0.109 MSY with a median of 0.011 MSY. The SEE population had a median value of less than half that of the watermen population. Thus 50% of the watermen had an average annual ocular UVB exposure above 0.022 MSY, whereas less than 25% of the SEE people had exposures above this value. However, the groups were not precisely comparable. Vacation time was not assessed in the waterman study; in addition, this study made assessments from the age of 16 years rather than 30 years.
- 24** In this study it was possible to identify several factors modifying UVB exposure. Females had substantially lower exposure levels than males and there was also lower exposure in those who had received five or more years of education (Figure 6.5).
- 25** Average annual exposures declined with age and exposure was less in those who claimed to suffer from photophobia, suggesting an aversive behavioural response. There was no significant difference in exposure as between whites and African Americans.

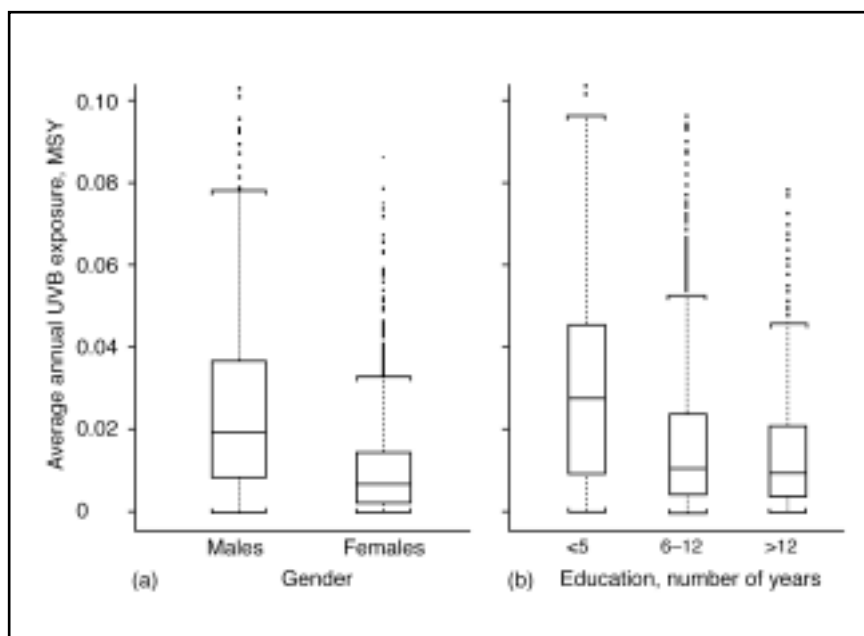


FIGURE 6.5
 (a) average UVB exposure of men and women from the SEE project (from West, 1999).
 (b) average annual ocular UVB exposure according to educational status (from Duncan *et al*, 1997a)

- 26** In considering the value of this model, it should be noted that:
- (a) it does not address acute exposure,
 - (b) it makes estimates of exposure in the plane of the face, rather than the interior of the eye,
 - (c) it depends on recall over extended periods of time,
 - (d) it uses no estimates of brow shading or squinting, although the effects of such parameters could be reflected in the decreased exposure identified in those reporting photophobia.

Coroneo effect

- 27** A further factor influencing personal dosimetry is the optical path taken by radiation striking the temporal edge of the cornea from a direct or indirect source lateral to the eye. The lateral part of the eye is unprotected from light incident on the eye at a shallow angle. Radiation incident from other sectors is shielded by the cheeks, nose, brow and lids. Coroneo *et al* have demonstrated that radiation impinging on the cornea in this way is focused, by a fibre-optic mechanism, on the region of the nasal limbus, and the nasal side of the lens (Coroneo, 1990, 1993; Coroneo *et al*, 1991) (Figure 6.6). It is envisaged that such rays are focused on the limbal area, where the stem cells of the corneal epithelium are located and those passing through the pupil (about 1% of the total) may reach the equatorial lens directly, or be reflected from the posterior capsule into this critical region, where the germ cells of the lens reside. This effect has been invoked to explain the preference of pterygium for the nasal limbus and the preferential occurrence of cortical spoke cataracts inferonasally (Klein *et al*, 1992).

Ocular transmission of UVR

- 28** The effects of UVR on the eye have been reviewed by Wittenberg (1986), Andley (1987) and Zigman (1995). Tissues at risk include the skin of the lids, the exposed parts of the conjunctiva and the transparent structures of the eye.
- 29** Most incident UVR reaching the eye, is absorbed by the cornea and lens. Both the cornea and conjunctiva absorb strongly at wavelengths shorter than 300 nm. UVC radiation (absent from solar sources) is absorbed by the superficial layers of the cornea and UVB radiation is absorbed by the cornea and lens. There is a small decrease in optical transmission by the cornea with age, chiefly in the range 300–400 nm (Marshall, 1985) (Figure 6.7).
- 30** Mitchell and Cenedella (1995) measured the relative contributions of different components of the bovine cornea to its overall absorptive capacity. Between 240 and 280 nm the insoluble fraction (mainly collagen) accounted for 40%–50% of the UVR absorbance, while in the physiologically important range of 290–300 nm, the water-soluble plus lipid-soluble fraction accounted for 65% of the total absorption, with water-soluble proteins alone accounting for 45% of the total. The latter, tryptophan-containing proteins, include aldehyde dehydrogenase, the major soluble protein of the cornea (20%–40% of its total soluble protein) which is found particularly in the epithelium (Abedinia *et al*, 1990; Alexander *et al*, 1981). Aldehyde dehydrogenase is involved in the metabolism of peroxidic aldehydes generated by UVR exposure (Uma *et al*, 1996). Studies by Downes *et al* (1994) have shown that mice expressing a low activity variant of corneal aldehyde dehydrogenase are more susceptible to the damaging

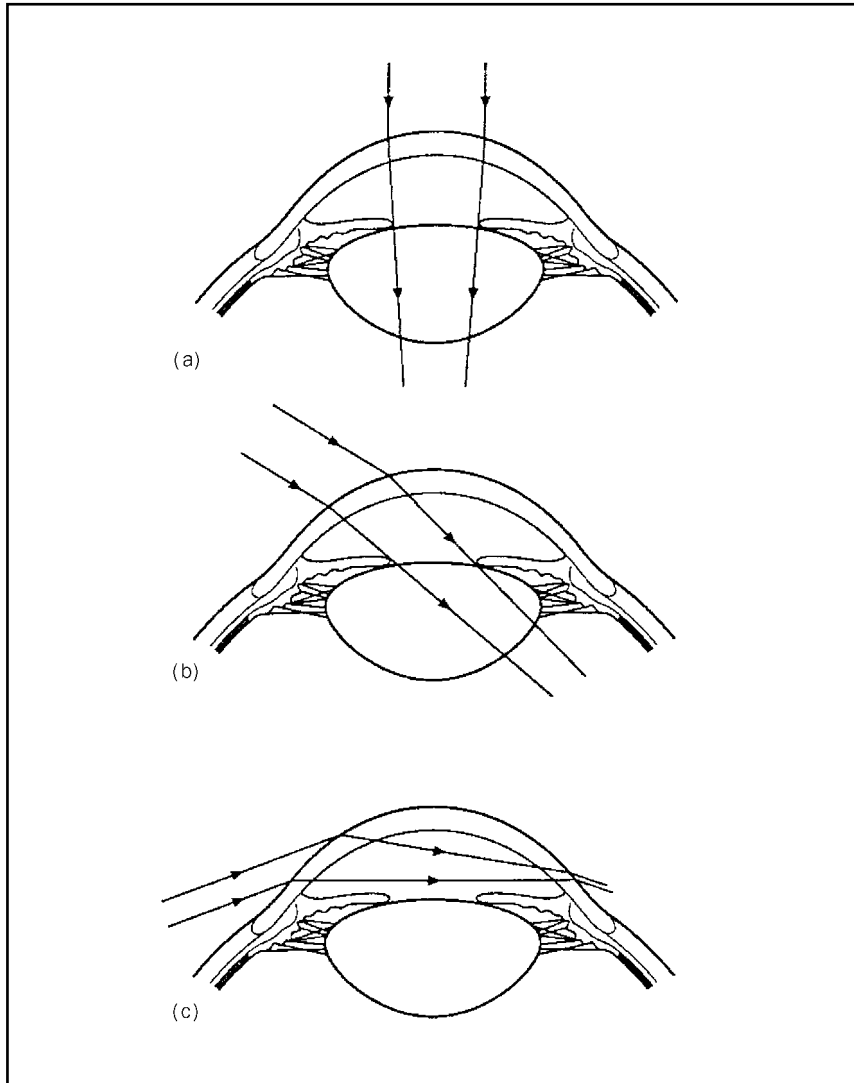
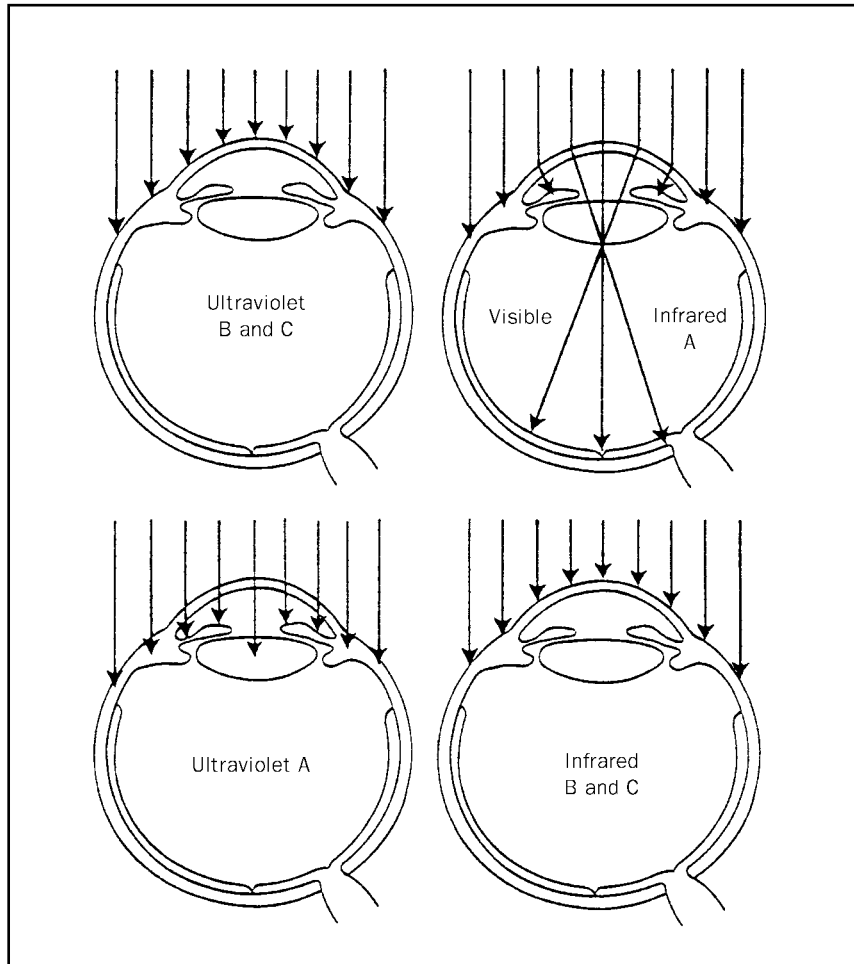


FIGURE 6.6
Pathways taken by optical radiation after refraction by the cornea: (a) frontal source, (b) slightly oblique source, and (c) highly oblique source from the temporal side. Here, incident radiation is focused towards the region of the nasal limbus and adjacent conjunctiva (from Coroneo, 1990)

effects of UVB exposure on the cornea, than normal mice. Genetic variation in key enzymes such as aldehyde dehydrogenase could contribute to differences in susceptibility of individuals to solar radiation damage.

- 31** Ascorbic acid is secreted into the aqueous humour by the ciliary body and in diurnal animals aqueous levels are up to 20 times higher than in the plasma. High levels are also encountered in the cornea and lens and retina. Ringvold (1998) has suggested that corneal epithelial ascorbic acid (about 70 mg per 100 mg of tissue) makes an important contribution to the UVB absorptive capacity of the cornea. Ringvold (1980, 1996, 1998) has estimated that absorption by the corneal epithelium over the range 280–310 nm is due to the presence of ascorbate, protein and nucleic acid, acting in roughly equal

FIGURE 6.7
Absorption of optical radiation: the wavebands are: UVB and UVC, 200 to 315 nm; UVA, 315 to 400 nm; visible and infrared A (IRA), 400 to 1400 nm; IRB and IRC, 1400 to 10 000 nm. A narrow waveband in the UVB, 295 to 315 nm, will pass through the cornea and may be a hazard to the lens (from Marshall, 1985)



proportions. Ascorbate, in cooperation with other compounds such as vitamin E, glutathione and superoxide dismutase acts as a potent antioxidant in the eye (Koskala *et al*, 1989). The protective role of ascorbate in the eye is supported by the study of Reddy *et al* (1998), who showed an inverse correlation between lens epithelial DNA strand breaks and aqueous ascorbate levels in animals exposed to UVB radiation. DNA damage was highest in ascorbate-deficient guinea pigs and lowest in rats receiving supplemental ascorbate by intra-peritoneal injection.

- 32** In various structures of the eye, some of the energy of UVB absorbed by the tissue is dissipated into wavelengths of lower energy, by means of fluorescence at longer wavelengths. The induction of fluorescent stray light results in some functional visual loss due to a loss of low contrast acuity. This effect increases with age over the range 21–80 years (Elliott *et al* 1993).
- 33** Absorption in the far UVR (260–190 nm) is of interest in relation to tissue ablation in laser photorefractive keratoplasty. Human corneal stroma shows a weak absorption

between 260 and 240 nm, a steep increase over the range between 240 and 220 nm, and a further, more gradual increase, below 220 nm. Therapeutically, with respect to photo-refractive surgery for refractive error, there is an 'ablation window' between 190 and 220 nm (Lembares *et al.*, 1997).

- 34** The lens of the eye absorbs strongly in the range 305–400 nm (Wittenberg, 1986) and opacities (cataracts) have been induced experimentally by wavelengths within this range. Absorption by human lenses is due to the presence of yellow chromophores which attenuate transmission in the waveband 300–400 nm, accumulate with age and lead to a steady decrease in transmission of UVA and blue light (Lerman, 1983) (Figure 6.8).
- 35** The lenses of diurnal primates and a few other diurnal species also possess yellow pigments which absorb UVA, but these are absent from the lenses of most common laboratory animals, so that study of such animals may not fully reflect the human situation. In the primate eye, there is a small peak in transmittance in the UVA (under 1% of the total), at 320 nm, with a bandwidth of 40 nm and between 375 and 400 nm (Figure 6.9).

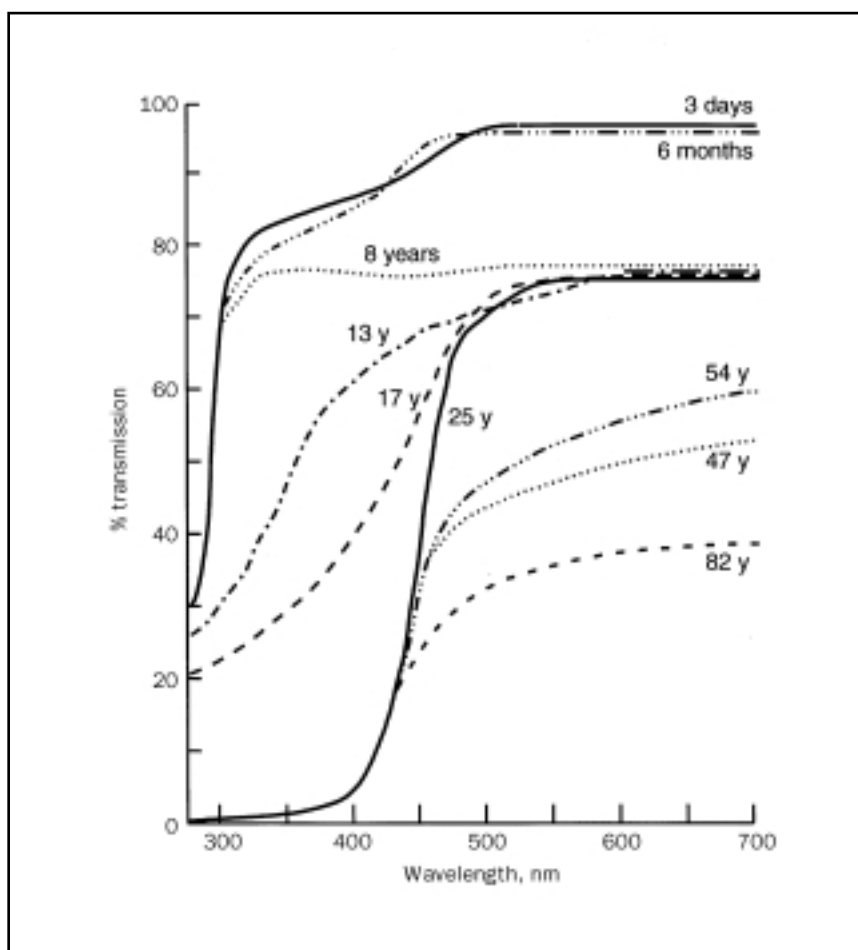
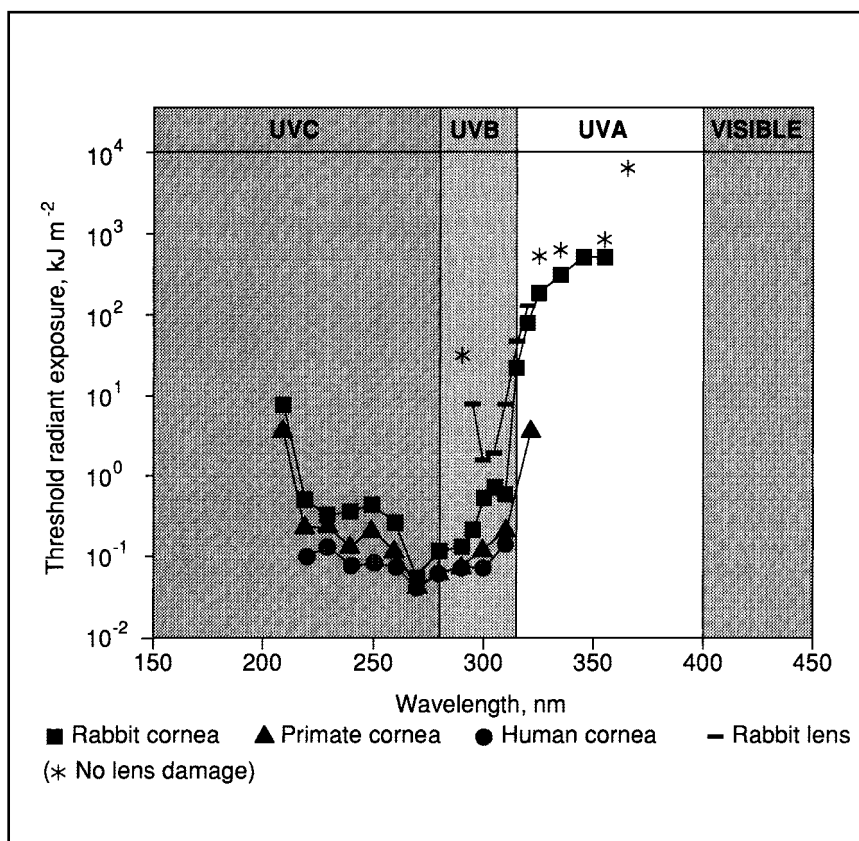


FIGURE 6.8
Transmittance of
optical radiation by
the human lens at
various ages (from
Lerman, 1983)

FIGURE 6.9
Comparison of the
rabbit corneal and
lens thresholds with
those of the primate
(from Pitts *et al.*
1977b)



- 36** Consequently, there is almost as much UVR reaching the retina at 320 nm as at 400 nm. A similar increase in transmission at 320 nm has been reported in human lenses, decreasing rapidly with increasing age. Dillon *et al* (1999) noted that only a small amount of UVB reaches the surface of the lens after filtering by the cornea and that 60 times more UVA and 114 times more visible light is transmitted by the young human lens than by older human lenses. Since the young lens transmits virtually all visible light (ie greater than 400 nm), ageing considerably decreases the transmission of visible light by the lens.
- 37** In the young human lens, at the ages of 6 months to 8 years there is 75%–90% transmission in the waveband 300–400 nm. This falls to about 20% from the age of 25 years onwards due to the accumulation of yellow chromophores, chiefly in the lens nucleus (Lerman and Borkman, 1976; Lerman, 1983) (Figure 6.8).
- 38** Transmittance to the retina in the visible spectrum exceeds 90% at the age of 6 months, but falls with age, particularly in the waveband 400–500 nm.
- 39** The absorption of optical radiation by the lens rises exponentially with age (Said and Weale, 1959; Weale, 1988; van Best *et al* 1985; Zeimer and Noth, 1984) inversely more for all wavelengths of the visible spectrum and in the ultraviolet. The rise in absorption is highest for wavelengths at the blue end of the spectrum, around 460–470 nm

and, as noted, this has been attributed to the postnatal accumulation of yellow chromophores (Dillon and Atherton, 1990). Another fluorescent chromophore found in clear lenses emits a blue fluorescence (at 420 nm) in response to radiation at 340 nm (Jacobs and Krohn, 1981; Satoh, 1972; van Best *et al.* 1985). Various proposals have been made as to how these UVR filters can interact with and modify lens proteins and lead to cataract formation (Bando *et al.* 1985; Ellozy *et al.* 1994; Malina and Martin, 1996; Stutchbury and Truscott, 1993; Truscott *et al.* 1994).

- 40** The lens possesses three major tryptophan-derived fluorophores, or UVR filter compounds, 3-hydroxykynurenine glucoside (3-OHKG) (van Heyningen, 1971), 4-(2-amino-3-hydroxyphenyl)-4-oxobutanoic acid)-O-glucoside (AHBG) (Truscott *et al.* 1994), and a recently discovered compound, which is the adduct of glutathione (GSH) with a deaminated form of 3-OHKG (termed GSH-3-OHKG) (Garner *et al.* 1999). In contrast to the first two compounds, whose concentrations either decline or remain constant during adult life (Bando *et al.* 1985; Wood and Truscott, 1993, 1994), this latter compound increases with age and is probably the major contributor to fluorescence in the ageing lens. Increasing yellowing of the lens and absorption of wavelengths at the blue end of the spectrum plays a protective role against the effects of optical radiation on the macula.

- 41** In the retina, damaging radiation at the blue end of the visible spectrum is partly filtered out by yellow, carotenoid retinal pigments (lutein and zeaxanthin), which are concentrated at the macula (Bone and Landrum, 1992). These probably also serve an antioxidant role (Khachik *et al.* 1997). A fraction of the photons falling on the retina is absorbed by the photopigments of the photoreceptors (rods and cones) and generates nerve impulses, which pass to the visual cortex. Optimum image formation is aided by the retinal pigment epithelium (outside the rods and cones), which absorbs light and reduces light scatter. Pigment in the overlying choroid also serves this function.

TARGETS FOR UVR DAMAGE

Cornea and conjunctiva

- 42** There is evidence for both acute and chronic UVR injury to the conjunctiva and cornea in animals and human subjects.

Acute injury

- 43** Action spectra for corneal damage (photokeratitis) have been determined for rabbits and primates (Pitts and Tredici, 1971; Pitts *et al.* 1977b). Thresholds are at a minimum value of 50 and 40 J m⁻², respectively, at 270 nm, and rise rapidly at shorter and longer wavelengths (Figure 6.9)
- 44** The threshold dose for corneal damage (Cullen, 1980; Pitts *et al.* 1977b) in pigmented rabbits was 200 J m⁻², at 295 nm. Exposure of rabbit eyes to wavelengths between 290 and 305 nm at levels above the corneal damage threshold induced severe uveitis. Inflammation of the iris may in part be due to the release of neural inflammatory mediators. In anaesthetised macaque monkeys damage to all cell layers of the cornea occurred following exposure to 800 J m⁻² at a wavelength of 300 nm (Pitts *et al.* 1987), with more severe damage after exposure at 6 kJ m⁻². This was followed by a return to normal function within 8 days, although some morphological changes persisted. Podskoschy *et al.* (2000) demonstrated apoptosis to be the manner of cell death in

rabbit corneas exposed to UVR. Radiation in the region of 280 nm caused epithelial and superficial keratocytic death, while a wavelength of 310 nm caused damage to cells throughout the corneal thickness.

- 45** Inflammation and cellular damage following UVR exposure also occur in the conjunctiva (Cullen and Perera, 1990, 1992). Inflammation in humans starts within 4 hours of exposure and peaks within 6–8 hours. The action spectrum for photoconjunctivitis is similar to that for photokeratitis, with a maximum response at 270 nm but with lower thresholds up to 310 nm (eg 30 J m^{-2} at 270 nm), possibly due to backscatter from the underlying sclera (Cullen, 1994). Irradiance levels were of the same order of magnitude as solar UVB and these results suggest that subclinical damage could be produced within minutes of direct exposure to sunlight.
- 46** The long-term consequences of UVR exposure have not been extensively investigated. Although permanent stromal corneal damage can be caused by high irradiance at 300 nm (Doughty and Cullen, 1987), even severe epithelial damage can readily be repaired within 2–7 days. Doughty and Cullen (1990) reported that a single exposure of albino rabbit eyes to 1.25 kJ m^{-2} UVB caused persistent corneal swelling for up to 112 days, possibly due to damage to the corneal endothelial cells, which maintain corneal transparency. Suprathreshold exposures of around 10 kJ m^{-2} resulted in endothelial damage lasting longer than 6 months.

Photophthalmia

- 47** When the eyes are open, acute UVR exposure in human subjects may cause both corneal and conjunctival damage. The major signs and symptoms relate to the corneal injury (photokeratitis) since the cornea is more richly innervated than the conjunctiva. Photophthalmia may follow exposure to the arc welder's flash ('arc eye') or occur as a result of exposure to UVR reflected from snow, as 'snow blindness'.
- 48** Photokeratitis in human beings is accompanied by pain, light sensitivity and tearing, with a latency as short as 30 minutes or as long as 24 hours, depending on the intensity of exposure. Typically it is 6–12 hours, with acute pain lasting 6–24 hours. Discomfort usually disappears within 48 hours. A photokeratitis action spectrum has been determined in volunteers whose eyes were exposed to UVR at narrowband wavelengths between 220 and 310 nm (Pitts, 1973, 1974), and that for the conjunctiva is similar. Thresholds were determined according to several factors, including reduced visual acuity and the presence of epithelial change. The minimum threshold of 40 J m^{-2} was observed at 270 nm. Symptoms appeared much earlier and returned to normal more quickly following UVR exposure at wavelengths shorter than 250 nm.
- 49** In contrast to the skin, the cornea becomes more sensitive with repeated exposures. UVR at wavelengths shorter than 310 nm can still penetrate the cornea after the onset of photokeratitis, whilst the transmission in the visible spectrum decreases (Schive *et al*, 1984).

Chronic injury

- 50** Chronic injury occurring over many years is considered to be due chiefly to radiation scattered from environmental surfaces.
- 51** *Pterygium* arises as a wing-shaped overgrowth of the conjunctiva, which spreads on to the nasal cornea, advancing towards its centre. In extreme cases it may obstruct vision (Figure 6.10).

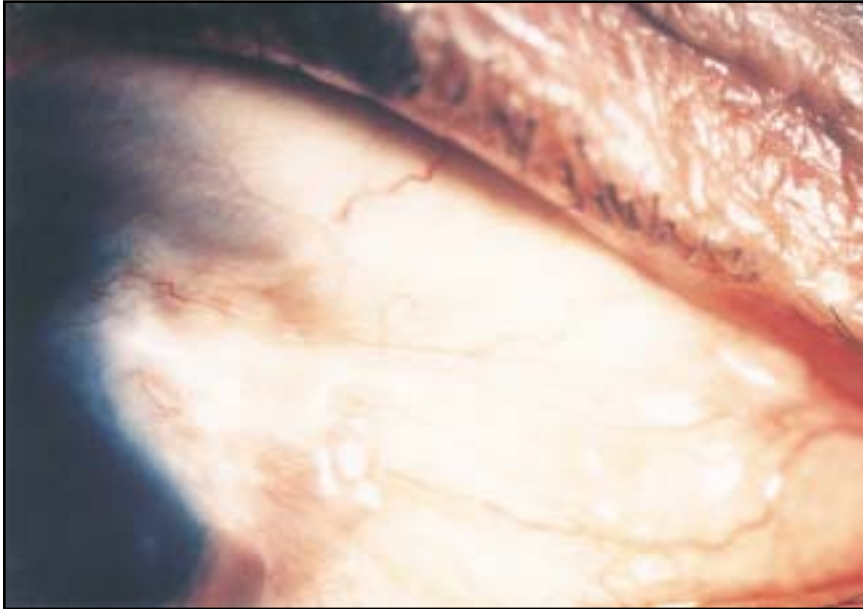


FIGURE 6.10
Pterygium: an
overgrowth of
conjunctival
spreading on to
the cornea

- 52** Large studies in Australia, the Pacific islands, the USA and South America have implicated direct and indirect exposure to UVB as a causal factor in pterygium (Cameron, 1965; Darrell and Bacharach, 1963; Elliot, 1966; Kerkenezov, 1956; Moran and Hollows, 1984; Rojas and Malaga, 1986; Taylor, 1980; Wharton and Yolton, 1986). The relationship of its global pattern to latitude is attributed to UVR exposure (Cameron, 1965; Taylor, 1981). Moran and Hollows (1984) demonstrated a strongly positive correlation between climatic UVR exposure and pterygium prevalence in the Aborigines of rural Australia, with an overall prevalence of 3.4% in the Aborigines population, and 1.1% in non-Aborigines. There was no difference in prevalence between Aboriginal men and women, who share a similar outdoor life, whereas the prevalence in non-Aboriginal women (0.65%) was about half that in non-Aboriginal men (1.5%), reflecting their lower climatic exposure. In this study it was not possible to exclude confounding factors related to differences in living conditions between racial groups. In a case-control study of 278 patients undergoing primary surgery for pterygium, in Brisbane, Australia, the risk of pterygium was increased in those patients who, in their third decade of life, worked out of doors in an environment with high reflectivity for UVR. Risk was increased several-hundred-fold among those who worked on sand and 20-fold for those who worked over concrete, compared with those who worked indoors. Spending the majority of time out of doors in early life was associated with a 20-fold increase in the risk of developing pterygium (Mackenzie *et al* 1992).
- 53** In a population-based study of individuals of 40 years and older, in the state of Victoria, Australia, pterygium was present in 6.7% of rural residents, 1.2% of Melbourne residents and 1.7% of nursing home residents. Risk factors were found to be age, male sex, rural residence (OR = 5.28; 95% CI = 3.56, 7.84), and lifetime ocular sun exposure (OR = 1.63, 95% CI = 1.18, 2.25). The attributable risk of sunlight for pterygium was 43%

(95% CI = 42.7, 44.6). Substituting UVB exposure for broadband sun exposure in the model did not influence the result. It was concluded that in this population, pterygium occurred primarily as a result of sun exposure and was a significant public health problem in rural areas (McCarty *et al.* 2000).

- 54** *Pingueculae* are small, bilateral, fleshy elevations of the nasal and temporal, interpalpebral conjunctiva, accompanied by elastotic degeneration. They have no effect on vision. An association with UVR exposure has been reported in several studies, although the relationship is less convincing than for pterygium. It is not explained why pingueculae invariably affect both the nasal and temporal conjunctiva, while pterygium usually affects only the nasal conjunctiva. It may imply a lower sensitivity of the conjunctiva to UVB in the production of pinguecula than pterygium. Dushku *et al.* have indicated that different tissue elements are activated in these conditions (Dushku and Reid, 1997; Dushku *et al.* 1999). They have also demonstrated that nuclear p53 expression (lacking in normal conjunctiva) is up-regulated in pingueculae, pterygia and in certain limbal tumours, in the absence of increased apoptosis and they have advanced the view that mutations in the *p53* gene may be of aetiological significance.
- 55** *Climatic droplet keratopathy* (CDK) consists of a bilateral accumulation of yellow/brown deposits in the exposed part of the conjunctiva and cornea, possibly due to the denaturation of subepithelial plasma proteins (Figure 6.11) (Johnson, 1981, 1982). Corneal clouding may cause considerable visual loss.
- 56** CDK is more common in men, increases in severity with age and is found in those latitudes where the solar UVR levels are high. The condition has been reported in Labrador and Newfoundland (Freedman, 1965), North Cameroon (Anderson and Fugelsang, 1976), Australia (Fraunfelder *et al.* 1972; Fraunfelder and Hanna, 1973; McGuinness *et al.*

FIGURE 6.11
Climatic droplet degeneration of the cornea: there is a yellow, proteinaceous deposit in the exposed region of the superficial cornea (reproduced by courtesy of Dr J D C Anderson, International Centre for Health, London)



1972; Taylor, 1981), India (Prasadrao, 1961; Singh and Singh, 1995), the Seychelles (Pilley, 1976), in New Guinea (English, 1975) and in the Dahlak islands of the Red Sea (Bietti *et al.* 1955; Rodger, 1973). Rodger (1973) demonstrated that in the Dahlak islands there was a three- to eight-fold greater amount of UVR reflected from the white coral sands than at a comparable site in England. In North Cameroon it affects over 50% of the population (Anderson and Fugelsang, 1976), and in the Dahlak islands it accounts for 57% of all cases of blindness (Rodger, 1973).

- 57** UVR exposure is generally accepted as the aetiological agent for CDK. It is more severe in men than in women, particularly those spending their working lives out of doors (Gray *et al.* 1992). In temperate zones the severity of the condition is positively correlated with episodes of snow blindness. Squint, ptosis or prolonged voluntary lid closure give some protection. There is an association between this condition and basal cell carcinoma of the lid whose occurrence is also known to be related to UVR exposure (Klintworth, 1972). In Labrador, Johnson *et al.* (1983) identified the peak prevalence of CDK as occurring between 55° and 56° latitude. This corresponds almost exactly with the distribution of the peak total flux of UVR across Labrador. Taylor (1981) found a significant association between broadband UVR exposure (290–400 nm) and CDK, but this relationship could not be confirmed in studies of UVR distribution in Australia.
- 58** Chronic injury to the cornea may give rise to endothelial damage. A study of welders exposed to UVR suggested that chronic, subthreshold exposure accelerates endothelial ageing (Good and Schoessler, 1988).

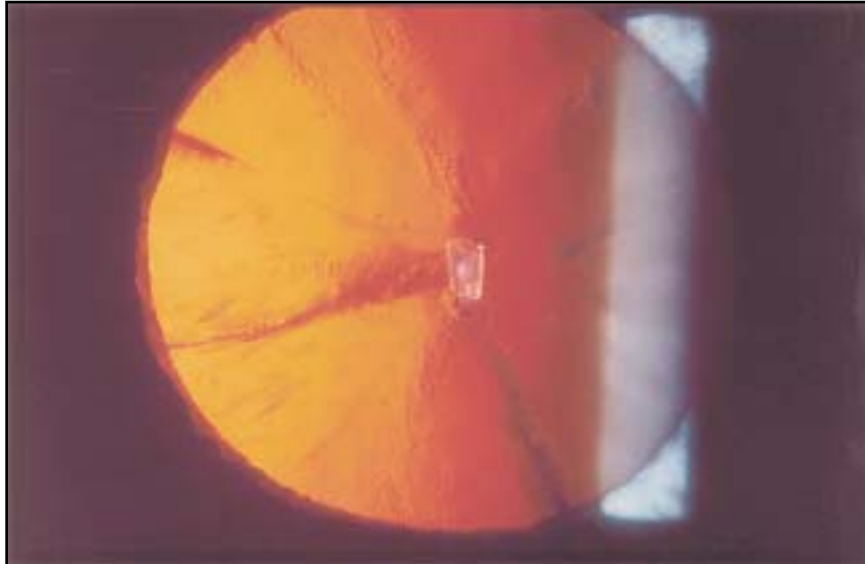
Lens and cataract

- 59** Despite advances in cataract surgery, cataract remains the leading cause of visual loss in the world due to a deficiency of adequate services (Thylefors, 1997). Cataracts are opacities of the lens of the eye, described as cortical, nuclear, or subcapsular, depending on their location (Figure 6.12). They are due to a loss of optical homogeneity caused by intracellular or intercellular swelling and cell disruption and, in the lens nucleus particularly, by increased scattering of light by aggregated proteins (Brown and Bron, 1996; Harding, 1991).
- 60** UVR in the wavelength range 305–400 nm penetrates the cornea and is strongly absorbed by the lens. Experimentally it may cause damage to lens proteins and cells. It is thus biologically plausible that UVR may contribute to the cause of human cataract and this is supported by epidemiological evidence.

Experimental studies

- 61** Experimentally, cataract has been induced by acute or chronic exposure to UVR, usually to UVB, rather than UVA.
- 62** In pigmented rabbits exposed to wavelengths below 300 nm for up to 8 hours, severe corneal changes occurred before lens opacities were observed (Pitts *et al.* 1977b) (Figure 6.9). Corneal damage also preceded lens changes following exposure to UVR at wavelengths between 295 and 320 nm. At wavelengths above 324 nm, transient alterations to the anterior suture and capsule were seen, but no lens opacities. Such studies are confounded by the risk that secondary inflammatory changes may have contributed to cataract formation.

FIGURE 6.12
Cortical cataract
showing typical
spoke-like opacities,
silhouetted by light
reflected from the
internal eye



- 63** Chronic studies have also shown a preferential ability of UVB to cause lens opacities in mice and rabbits. Albino mice developed anterior lens opacities after daily exposure for 1–2 months to a combined UVB/UVA source (290–400 nm), but not if the source was filtered to remove UVB (Jose and Pitts, 1985). Anterior subcapsular cataracts have been produced in the eyes of pigmented rabbits by exposure to UVB radiation, at levels exceeding the photokeratitis threshold (Pitts *et al.* 1977b). However, anterior subcapsular cataracts have also been induced in young albino mice, 60 weeks after irradiation with a source emitting predominantly UVA, with some UVB (Zigman and Vaughan, 1974; Zigman *et al.* 1974; Jose, 1986).
- 64** In primates, lens opacities were not induced following acute (less than 8 hours) exposure to suprathreshold levels for photokeratitis (100 J m^{-2} at 300 nm), although the induction of granules in the anterior epithelium and an increased prominence of the anterior sutures were noted (Pitts *et al.* 1977b) following exposure to 120 J m^{-2} . Prolonged (3 years) irradiation of rhesus monkeys with UVA at 10 W m^{-2} did not result in detectable opacities (Ham and Mueller, 1989). In contrast, Zigman *et al.* (1991) reported the appearance of anterior cortical opacities in the lenses of grey squirrels chronically exposed (for 400 days) to predominantly UVA radiation ($350 \pm 35 \text{ nm}$) at 60 W m^{-2} . Histology revealed damage to the epithelial cells and underlying fibres in the central, anterior region of the lens.

Role of UVR in human cataract

- 65** Early research into the association between cataract and solar radiation used an ecological approach, linking place of residence to sunlight or UVB exposure. Past studies have been summarised by West (1999) (Table 6.2).
- 66** A national survey by Hollows and Moran (1981) showed increasing cataract prevalence according to ambient exposure to UVB, in five regions of Australia. In Nepal,

a national blindness survey showed that cataract was four times higher in regions where sunlight hours were maximal, compared with sites where exposure was 7 hours or less (Brilliant *et al.* 1983). This study took account of the shading action of mountains, which reduced UVB exposure at high altitude (solar UVB irradiance normally increases with increase of altitude). However, it should be noted that an earlier study from North India also found fewer cataract at higher altitudes (Chaterjee, 1973). In the USA, the National Health and Nutrition Survey (NHANES) conducted over 35 geographical regions, demonstrated an increased risk of cortical cataract at sites with more sunshine (Hiller *et al.* 1977, 1983). Another study, carried out in a white population in Wisconsin, found an increased risk of cortical cataract with UVB exposure in males (Cruickshanks *et al.* 1992). A lack of contrasting exposure rates in females at the low doses encountered may have explained the inability to show an effect in females.

67 Such studies used place of residence as a surrogate for cumulative ocular exposure. Other studies have taken into account the need to estimate the influence of personal behaviour on both ambient solar exposure and ocular exposure, according to time spent out of doors, the use of spectacles, sunglasses and hats, and the effects of migration over the lifetime of an individual (Collman *et al.* 1988; Dolezal *et al.* 1989; Leske *et al.* 1991; the Italian American Study Group, 1991; Wong *et al.* 1993). The

| Population | Assessment of cataract | Exposure variable | Results | Author |
|---|------------------------------|------------------------------------|---------------------------------|-------------------------------------|
| 838 fisherman | Clinical, by type | Personal exposure | Risk cortical | Taylor <i>et al.</i> (1988) |
| 2520 population, ages 65–84 years | Photo, by type | Personal exposure | Risk cortical | West <i>et al.</i> (1989) |
| 771 population, age 40+ years | Photo, by type | hx of residency | Risk cortical for males | Cruickshanks <i>et al.</i> (1992) |
| NHANES 1971–1972, 2225 population | Clinical, multiple examiners | hx of residency, ambient UVB | Risk cortical | Hiller <i>et al.</i> (1986) |
| 160 matched cataract surgery cases and controls, mostly nuclear | Chart review | Residency plus time spent outdoors | No association | Dolezal <i>et al.</i> (1989) |
| 113 cases, 161 controls | Chart review | Residency plus time spent outdoors | Risk cortical, PSC (but NS) | Collman <i>et al.</i> (1988) |
| 63 798 Aborigines | Clinical – all | UVB zones of Australia | Prevalence of cataract, UVB | Hollows and Moran (1981) |
| 27 785 residents of Nepal | Clinical – all | Average daily sunlight hours | prevalence of cataract sunlight | Brilliant <i>et al.</i> (1983) |
| 435 controls, 1380 cataract cases | Photo, by type | Questions on working in sunlight | No association | Leske <i>et al.</i> (1991) |
| 1008 cataract cases, 469 controls | Photo, by type | Activities in sunlight, hat use | Risk cortical with time in sun | Italian American Study Group (1991) |
| 367 (54%) ages 55–74 years in fishing village | Clinical | 'Lifetime exposure to sunlight' | Risk cortical exposure to sun | Wong <i>et al.</i> (1993) |

TABLE 6.2
Relationship of UVR exposure to cataract in epidemiological studies (from West, 1999)

Chesapeake Bay Waterman Study was the first to compare a detailed model of personal ocular exposure with the prevalence of cataract, assessed using a standardised system for classifying and quantifying cataract (Taylor *et al.* 1988). In the fishermen studied, the influence of time spent out of doors, job history since the age of 16 years and use of powerful modifiers, such as spectacle wear and hats, was estimated. An increased risk of cortical opacity was found with increasing average annual ocular UVB exposure with no increase for nuclear opacity. The increased risk of cortical cataract was found in all age groups. The methods used in the waterman study were refined for application to a wider population in the SEE study, using a more generalised model of personal ocular exposure (Duncan *et al.* 1995, 1997a,b). In that study, a risk for cortical opacity was found with increasing UVB exposure in both men and women, which showed no threshold dose and was the same among African Americans and Caucasians. An increase of 0.01 MSY was associated with a 10% increase in the risk of cortical opacity. West (1999) has stated that there is now conclusive evidence for an association between cortical opacity and chronic ocular UVB exposure, even with the low exposures likely to be encountered by a general population living in a temperate climate. There is less certainty as to a role for UVA, either on its own or interacting with UVB, or of the influence of UVR exposure in childhood.

- 68** Perkins (1985) proposed that if UVR had a role in the development of cataract then cataract should occur more frequently in patients with pingueculae. However, he found no such association. In the waterman study, too, no relation between pterygium and cataract was shown, despite the strong dose-relationship between UVR and pterygium (Taylor *et al.* 1989). A lack of association between pterygium and cataract had been noted previously by other authors (Franken and Mehta, 1968; Peckar, 1972) and other reports have failed to find a relationship between cataract and climatic droplet keratopathy, for which solar radiation is accepted as a major aetiological factor (Freedman, 1973; Johnson *et al.* 1989; Rodger, 1973). Contrasting with these findings, in the Blue Mountains Eye Study, in Australia, involving a population of 3654 individuals (aged 49-97 years), an association between pinguecula and cortical cataract was found with an OR of 1.40 after multivariate adjustment. Similarly, after multivariate adjustment, pterygium was associated with subcapsular cataract, with an OR of 1.90 (CI = 1.19, 3.04). The degree of association was small (Lim *et al.* 1998) and it is of interest that the association of pterygium was with posterior subcapsular, not cortical cataract.
- 69** Caution must be exercised before dismissing these conflicting observations. Although pterygia and pingueculae may reasonably be regarded as surrogates for ocular surface exposure to UVR, factors influencing the relative doses to lens and ocular surface and differences in tissue biology with respect to UVR may determine the susceptibility of each tissue.
- 70** Considering the biochemical events in human cataract in relation to UVR exposure, Harding (1991) has pointed out that loss of tryptophan from the lens would be expected to be an early and demonstrable sign of UVR-induced protein damage, expected to precede the occurrence of yellowing, increased fluorescence and cross-linking encountered as a feature of cataract (Buckingham and Pirie, 1972). No loss of tryptophan has been reported in human cataract, even in the most advanced, brunescient nuclear cataracts (Dilley and Pirie, 1974), although a change in the tryptophan indole ring angle has been noted by Raman spectroscopy (Duindam *et al.* 1998). Hightower (1995),

however, has suggested that UVR might damage tryptophan in key epithelial proteins responsible for maintaining ion-water balance in the lens. A similar argument may be advanced in relation to proteins in the superficial lens cortex, which are metabolically active and engage in protein turnover. Such a view could explain the occurrence of damage in the absence of a measured fall in protein tryptophan.

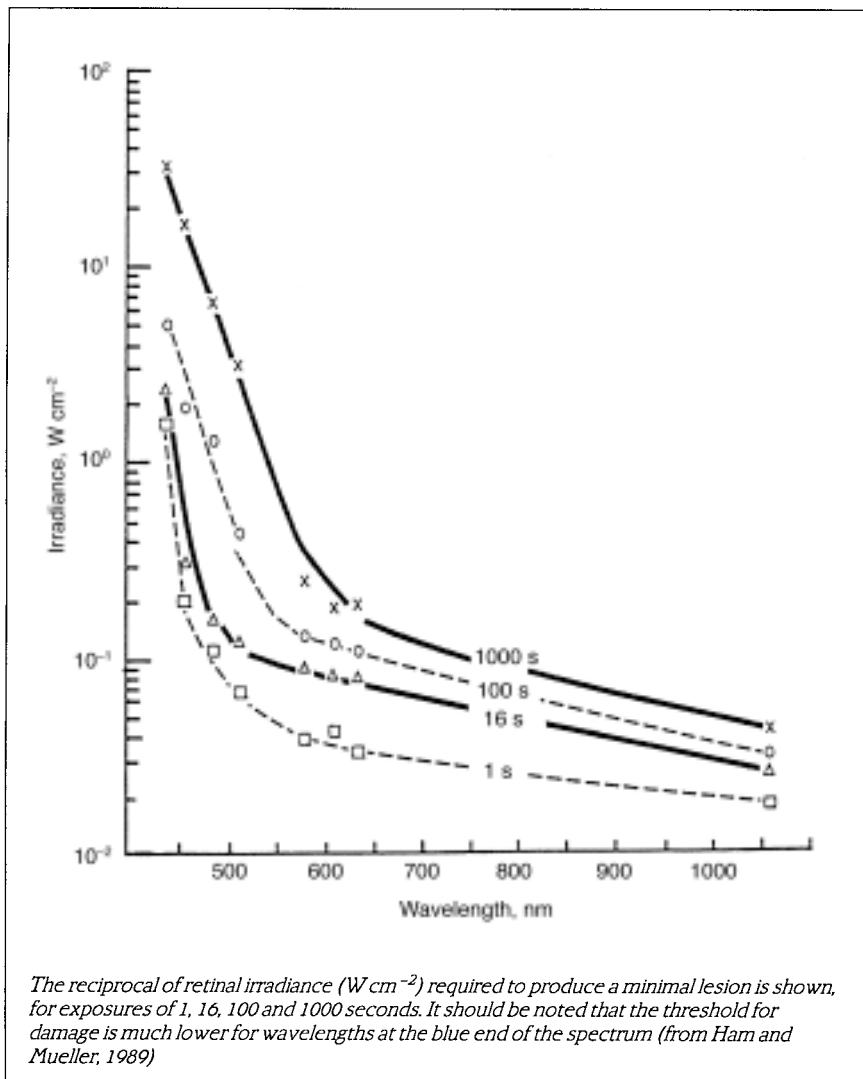
Vitreous

- 71** The posterior part of the eye comprises the gel-like vitreous humour and the retina. Irradiation of calf vitreous humour *in vitro* with visible radiation in the presence of photosensitisers produced partial liquefaction, possibly through the release of activated oxygen species.

Retina

- 72** The retina is unique among body tissues in that optical radiation is focused continuously on a group of cells that are highly oxygenated and potentially susceptible to UVA and blue-light-induced damage, via activated oxygen species. The effects of long wavelength UVA and visible radiation on the retina have been widely investigated (Cronley-Dillon *et al.* 1986; Marshall, 1985; Waxler and Hitchins, 1986; Young *et al.* 1993).
- 73** In the past it had been considered that UVR does not reach the retina in harmful amounts (Duke-Elder and MacFaul, 1972; Wald, 1952). This is not in fact the case. Transmission occurs between 310 and 340 nm and again between 375 and 400 nm. UVR shows a small peak of transmission to the retina at around 320 nm in the intact eye and over a greater part of the UVA range in the lens-free (or aphakic) eye (Lerman and Borkman, 1976). Maximum transmittance at 320 nm is essentially the same as that at 400 nm. The neuroretina is, however, more sensitive at 320 nm than at 400 nm or in the visible range. The pigment epithelium absorbs UVA strongly from 375 to 400 nm.
- 74** Thermal injury to the retina results from exposure times ranging from approximately microseconds to extended durations (more than 1 second) provided that the retinal irradiance is high enough to produce an appreciable elevation of temperature (more than 10 °C) in the retina. Histological examination 1 or 2 days after exposure reveals structural damage to the pigment epithelium. The damage is maximal in the centre of the lesion tapering off towards the periphery. This is in sharp contrast to minimal photochemical lesions, where damage is uniform across the lesion with a definite border between injured and uninjured pigment epithelial cells. Thermal injury merges into thermoacoustical damage as exposure durations become extremely short and retinal irradiance become very high.
- 75** Photochemical rather than thermal damage to the retina can occur following extended exposures to very bright light sources, particularly blue light, at retinal irradiances too low to produce appreciable heating. Several different damage mechanisms exist, resulting from light absorption by different chromophores within the retina. These include the pigment melanin of the pigment epithelium and the visual pigments within the photoreceptors.
- 76** One important type of lesion to the macular or paramacular region of the retina results from damage to the pigment epithelium following the absorption of short wavelength (blue) light (400–500 nm). In aphakic animals (whose lenses have been surgically removed), the action spectrum increases exponentially with decreasing wavelength (Figure 6.13), following roughly the absorption spectrum for melanin, and

FIGURE 6.13 Action spectrum showing the sensitivity of the rhesus monkey retina to photic damage from laser radiation, between 441 and 1064 nm



extending into the UVA region (325–400 nm). The lesion, sometimes called the blue-light lesion, closely resembles that of solar retinitis in patients, following prolonged gazing at the sun.

- 77** Other forms of photochemical damage to the retina result from absorption by the visual pigments, ie rhodopsin, the rod photopigment, which has a maximum absorption peak in the blue-green at about 500 nm and another much lower absorption maximum at about 350 nm in the UVA. The blue, green and red cone pigments have absorption maxima in the visible region at about 440, 535 and 570 nm, respectively. The cone pigments also show high absorption in the UVA region.

Experimental studies

- 78** The retinal damage caused by optical radiation in rats has been summarised by Noell (1980). Exposure of rats to constant visible radiation in the wavelength range 490–580 nm, for between 12 and 26 hours, resulted in a depletion of the photoreceptors and retinal pigment epithelium. Action spectra suggested that the effect was mediated by the rod photopigment rhodopsin. Factors that increased retinal damage following light exposure included raised body temperature, absence of ocular melanin and dark adaptation prior to exposure (Noell *et al.* 1966; Noell, 1980; Rapp and Williams, 1980).
- 79** In contrast to the findings in rats (which have entirely rod retinas), rod cells in the primate monkey retina are less susceptible to light-induced damage than cone cells. Localised loss of rod cells and pigment epithelium occurs only in regions where extensive destruction of cone cells and inner retinal layers has occurred (Lawwill, 1982), suggesting that the rhodopsin-mediated damage to rod photoreceptors seen in rats (and other nocturnal animals) was much less effective in predominantly diurnal primates. The principal type of light-induced damage to the primate retina is to cells throughout the retina, increasing in severity as the wavelength decreases towards the blue region (the blue-light hazard). Superimposed on this, is a wavelength-specific effect on the three types of cone cells (namely, blue-light sensitive, green-light sensitive and red-light sensitive) mediated by the three cone pigments.
- 80** The action spectrum for blue-light mediated retinal damage follows the absorption spectrum of melanin, increasing exponentially in the UVA region (Ham *et al.* 1986), and suggesting that the initial site of damage is in the retinal pigment epithelium. Increasing the oxygen concentration *in vivo* increases the level of damage, suggesting the involvement of an active species of oxygen. Studies in aphakic monkeys show an increased susceptibility to shorter wavelengths of light in the UVA region of the spectrum, in keeping with the removal of filtering by lens chromophores (Ham *et al.* 1982). A similar picture was seen in the retinas of aphakic American grey squirrels, whose retinas are similar to primate retinas (Collier *et al.* 1989). Ham *et al.* (1987) have shown a cumulative effect on the retina of daily, subthreshold exposures to short wavelength light (10%–30% of the acute exposure threshold), at 440, 475 and 533 nm, in the macaque monkey.
- 81** Selective functional loss following exposure to monochromatic or narrowband visible radiation can be correlated with wavelength-specific damage to cones in the non-human primate retina (Harwerth and Sperling, 1971; Sperling *et al.* 1980). In this case, the visual detriment was seen as a loss of spectral sensitivity, rather than a change in visual acuity. For measurements made at background intensities sufficiently high to suppress rod function, a complex spectral sensitivity function was obtained that had prominent peaks at 460, 550 and 620 nm, corresponding to the absorption spectra of the three cone photopigments in the rhesus monkey. Multiple intermittent exposures over 4 to 5 days of intense 460 nm light (1 W m^{-2}) produced a permanent loss in short wavelength spectral sensitivity. Reversible alterations in increment threshold spectral sensitivity were obtained with exposure to 520 nm light, so that spectral sensitivity curves returned to their pre-exposure shape within 4 weeks of exposure. Exposures to intense red light produced only short-term losses in long wavelength spectral sensitivity. Thus, blue cones were more susceptible to permanent damage than green or red cones.

82 In rhesus monkeys, susceptibility of the retina to damage was found to increase steadily as a function of decreasing wavelength from 650 down to 400 nm (Ham *et al.* 1976), below which light was not readily transmitted through the lens. In particular, exposure to blue light (441 nm) at about 350 kJ m^{-2} over a 1000-second period resulted in disruption of the pigment epithelium 2 days after exposure, with photoreceptor damage becoming apparent 5 to 6 days after exposure (Ham *et al.* 1978). The degree of damage declined over the following 10 to 30 days, and the retina resumed an almost normal appearance at 60 days following exposure. Many of the photoreceptors, as well as the cellular structure of the retinal pigment epithelium, are irreversibly damaged within 1 or 2 days following exposure (Ham, 1983). Usually, by 20 to 30 days post-exposure, the photochemical lesion has healed, leaving only hypopigmentation and macrophages in the subretinal space. By 90 days post-exposure, the macrophages have disappeared but a slight granular and depigmented area remains in the pigment epithelium that has been likened to the appearance of atrophic senile macular degeneration (Ham, 1983). Exposure at 600 J m^{-2} was sufficient to result in a transient loss of normal visual acuity and exposure at 900 J m^{-2} resulted in permanently impaired vision (Moon *et al.* 1978).

UVR damage to the human retina

83 Certain groups are more at risk of retinal damage from optical radiation. Neonates and infants are more at risk of photic retinal damage because their eyes transmit more radiation in the UVA and blue end of the spectrum. They may be exposed to high, blue-light irradiances in neonatal intensive care units. Also, adult patients undergoing ophthalmic examination with the slit-lamp microscope or indirect ophthalmoscope are exposed to high irradiances of visible radiation, and exposure is increased where examination is performed under anaesthesia and the eye is immobile. Retinal damage has been produced in anaesthetised and immobilised monkeys by 15-minute exposures to the indirect ophthalmoscope at irradiances about one-third that of the slit lamp (Friedman and Kuwabara, 1968; Tso *et al.* 1972). In clinical practice these extremes of exposure are probably avoided by the lack of a focused image and by constant movement of the source, but these observations underscore the need for awareness of the risks, especially in anaesthetised patients whose eyes are immobilised.

84 After cataract surgery, the protection to the retina provided by the crystalline lens is removed. Replacement by a polymethyl methacrylate (PMMA) lens implant does not restore this protection (Mainster, 1978a,b, 1986; West *et al.* 1989) and it is necessary to incorporate appropriate filters (Figure 6.14). A UVR filter alone is not sufficient since it does not exclude the blue-light hazard. Many UVR-protected intraocular lenses transmit well in the blue, showing an 80%–90% transmission between 400 and 450 nm, compared to 5%–45% for a normal human lens of 53 years (Mainster, 1986) or 0%–15% at 75 years. Even in the young human lens, transmission does not reach 90%, below a wavelength of 450 nm (Boettner and Wolter, 1962). Mäntyjärvi *et al.* (1997) reported a shift in colour sensitivity towards the blue end of the spectrum in patients who had undergone cataract surgery with the implantation of UVR-protected lenses and it would appear that such patients would not be protected from the risks of blue-light toxicity. However, modern lens implants, including foldable, silicone lenses, protect against both forms of radiation (Yang *et al.* 1997). A foveomacular retinitis can occur in response to repeated

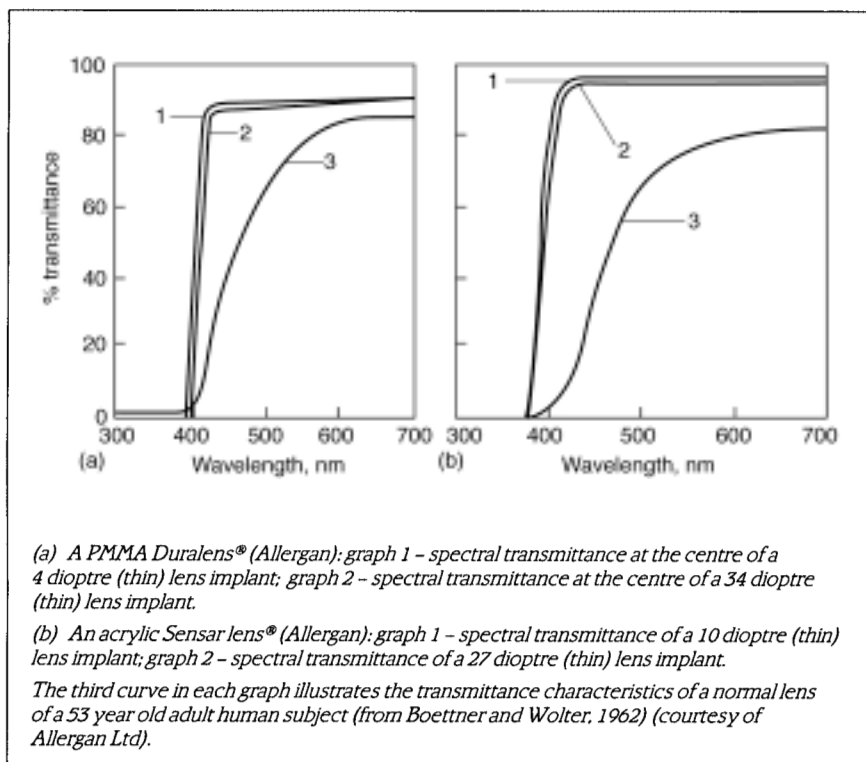


FIGURE 6.14
Transmittance characteristics of two sorts of intraocular lens, a PMMA and an acrylic lens, containing spectral filters absorbing particularly in the UVR and to a lesser extent in the blue region of the spectrum

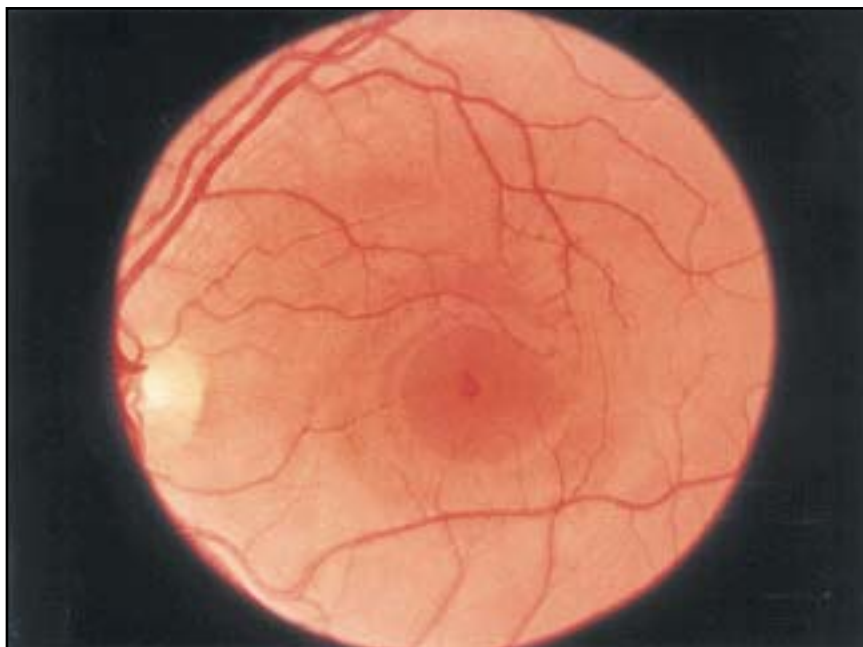
exposure to the flash of a welder's arc (Terrien, 1902; Romanchuk *et al*, 1978; Uniat *et al*, 1986). Damage is due chiefly to wavelengths in the UVB and UVA and is more likely in the young. Injury may be sufficiently severe to cause a hole in the macula (Wurde mann, 1936).

- 85** Individuals working with high power lasers may receive accidental injury, often during alignment procedures or, alternatively, as a result of reflections from neighbouring surfaces (Boldrey *et al*, 1981; Rathkey, 1965; Sliney and Wolbarsht, 1980). Bystanders observing laser ocular surgery may suffer injury as a result of reflections from contact lenses used to direct radiation into the patient's eyes (James *et al*, 1988; Sliney and Wolbarsht, 1980). Subtle defects in colour contrast may be demonstrated in laser users exposed to the blue, argon, aiming beam (Frennesson and Bergen, 1998).

Solar retinitis

- 86** Prolonged viewing of the sun may cause solar retinal burns in the form of solar or foveomacular retinitis (Figure 6.15). This was experienced by anti-aircraft gunners and plane spotters during World War II, who gazed directly at the sun (Flynn, 1942; Smith, 1944). It is experienced by those who look directly at the sun with incomplete, or no protection, during an eclipse. Injury is mainly photochemical, possibly with some thermal enhancement. Gazing directly at the sun (in religious rituals or under the influence of hallucinogens) for periods of more than 90 seconds, even with a constricted

FIGURE 6.15 The dark circular patch in the centre of the retina, seen through an ophthalmoscope, is an acute retinal burn, caused by looking at a bright light such as the sun (reproduced by courtesy of Mr T J Ffytch, St Thomas' Hospital, London)



pupil, exceeds the threshold for photochemical retinal damage (Sloney *et al*, 1980). The risk of damage is increased by the use of poorly designed sunglasses, which screen out the visible, long-wave radiation but transmit UVA and blue light. This promotes pupil dilation and therefore increases the retinal irradiation at harmful wavelengths (Mainster and Kahn, 1994). The risk of damage is higher in the young because of the higher UVR transmittance of the young lens (Boettner and Wolter, 1962; Sloney, 1986). Solar retinitis is also recorded without direct solar observation (Gladstone and Tasman, 1978; Jacobs *et al*, 1985; Kuming, 1986; Yanuzzi *et al*, 1987).

- 87** A degree of recovery can occur from an eclipse burn and depends on the length and intensity of exposure. Preservation of the pigment epithelium and the retinal photoreceptor cell body appears to be necessary for recovery to take place. Retinal burn thresholds in man have been calculated to be 10.9 J cm^{-2} . In one report, solar retinitis in three sunbathers was attributed to an increase of solar radiation resulting from reduction of the ozone layer by 15%–23%. A drop in visual acuity occurred which recovered over the following 3–9 months (Yanuzzi *et al*, 1987). Since loss of the ozone layer results in an increase of radiation below 340 nm, it is assumed that the damage was photochemical, perhaps enhanced by the rise in temperature created by the visible and infrared radiations reaching the retina; the degree of retinal warming is increased by increased pupil size (Mainster and Kahn, 1994).

Age-related macular maculopathy

- 88** The macula is the cone-rich, central part of the retina, responsible for high acuity and colour vision. Age-related maculopathy (ARM) is a condition of the macula leading to progressive loss of visual acuity (Figure 6.16). It is the major cause of blindness in the



FIGURE 6.16
Picture of the retina
to illustrate age-
related maculopathy
(ARM) in an adult
patient

developed world. It is a multifactorial condition in which both age and genetic factors play a part. Early ARM and late macular degeneration (late AMD) are recognised forms. Retinal drusen, which are degenerative changes in the basal laminae lying at the interface of the retina and the choroid, are common, age-related features which often present as a component of ARM.

- 89** It has been suggested that optical radiation, probably at the UVA and blue end of the spectrum, contributes to macular degeneration (Mainster, 1978a,b; Young, 1981) but the evidence overall is not convincing. The prevalence of AMD is reduced in the presence of cataracts, particularly nuclear cataracts, which would be expected to screen out those wavelengths known to be capable of causing photic retinitis (van der Hoeve, 1920; Sperduto *et al*, 1981). In the waterman study an association was found between blue-light exposure and AMD over the 20 year period prior to assessment, but not with UVA or UVB exposure (Taylor *et al*, 1992; West *et al*, 1989).
- 90** In the population-based, Beaver Dam Study, from Wisconsin, USA, an association between macular pigmentation and time spent out of doors in summer, was found in men after adjusting for age, but not in women (OR 1.44; 95% CI = 1.01, 2.04), (Cruikshanks *et al*, 1993). Women received lower exposures than men, but this may not have fully explained the difference. Wearing spectacles was inversely associated with an increase in retinal pigmentation (OR 0.75; CI = 0.58, 0.97) and the wearing of hats or sunglasses was inversely associated with soft retinal drusen. Both these results suggested a protective effect of reducing exposure to solar radiation. The risk for advanced macular changes was assessed in men and women as a combined group, and it was found that the amount of leisure time spent out of doors in the summer was associated with exudative macular degeneration (OR 2.26; CI = 1.06, 4.81) and with late AMD (OR 2.19; CI = 1.12, 4.25). There was no association between maculopathy and the calculated

annual exposure to UVB, although it should be noted that estimates of UVB exposure were crude, being based on residential history alone. In another population study, conducted in the Blue Mountain region of Australia, a blue iris colour was associated with an increase in late AMD (OR 1.69; CI = 1.0, 2.85) and early ARM (OR 1.45; CI = 1.09, 1.92), while either a high or low sensitivity of the skin to sunburn was associated with an increased risk of late AMD (Mitchell *et al.* 1998). The number of severe episodes of sunburn, history of skin cancers and signs of sun damage to the skin were not associated with ARM.

- 91** A number of other studies have reported an increased risk of late AMD in people with blue or light-coloured irises (Hyman *et al.* 1983; Holz *et al.* 1994; Sandberg *et al.* 1994; Weiter *et al.* 1985) but the reason for such an association is not understood. The blue iris is deficient in stromal pigment, but still possesses a double layer of pigmented epithelial cells, whose ability to screen out UVR has not been assessed. Genetic factors have been proposed and it has also been suggested that if iris colour were a surrogate for retinal and choroidal pigmentation, the association might reflect a lack of protective melanin in these structures in those with blue irises. However, it should be noted that other studies have found no association with iris colour (Blumenkranz *et al.* 1986; Gibson *et al.* 1986; the Eye Disease Case Control Study Group, 1992; Vinding, 1990; West *et al.* 1989).
- 92** In contrast with these findings, in a case-control study from Newcastle, Australia, those with AMD showed significantly less tanning ability, were more sensitive to glare (OR 2.5; CI = 1.8, 2.5) and received a lower annual sun exposure, than controls, in a population showing a wide variation in sun exposure, estimated by questionnaire (Darzins *et al.* 1997). The authors concluded that sensitivity to glare and a poor tanning ability were markers for AMD but the inference was that members of this group were more likely to avoid sun exposure than the non-AMD controls.
- 93** It must be concluded from these studies that at the present time the evidence for a relationship between age-related macular degeneration and sun exposure is conflicting and that the demonstration of risk is complicated by the unquantified influence of sun avoidance and other behavioural factors. A small adverse risk from blue-light exposure cannot be ruled out (Seddon, 2000).

Ocular neoplasia

Carcinoma of the eyelids

- 94** UVR is an important aetiological factor in the development of basal cell carcinoma (BCC), the commonest form of skin cancer among Caucasians (see Chapter 7). Most tumours are situated on the sun-exposed regions of the body, particularly the face. BCCs account for 80%–90% of all malignant tumours of the eyelids. Lindgren *et al.* (1998) studied the relationship between UVR exposure and eyelid tumours, using polysulphone dosimeters and an evaluation of BCCs on the lids of patients in Gothenborg, Sweden. They found that the distribution of tumours contrasted with the apparent distribution of solar radiation (mainly UVB). Of the tumours, 68% (225/329) occurred on the lower eyelid, and 26% at the medial canthus. UVR exposure assessed on mannequins and in two human subjects showed that, in mannequins, the upper eyelids received slightly more UVR than the lower, in both the upright and recumbent position, while the medial canthi and lateral areas of the upper and lower eyelids showed low values. In human

subjects, however, the medial canthi and the medial part of the lids received the lowest dose, while the lateral parts of the lids received the highest. The difference between mannequins and human subjects was attributed to behavioural factors. The authors concluded that UVR exposure only partially explained the aetiology of periorbital BCC.

- 95 The evidence for a role for UVR in the aetiology of squamous cell carcinoma (SCC) is more straightforward than that for BCC (see Chapter 7), but does not appear to have been explored specifically in relation to lid tumours.

Uveal melanoma

- 96 Uveal melanoma is the most common primary intraocular malignancy and is fatal in more than half the cases (Jensen and Prause, 1983). The evidence for solar radiation as a risk factor for ocular melanoma is less conclusive than for skin melanoma (Seddon *et al.* 1990).

- 97 The cornea transmits little radiation below 300 nm and about 50% of the radiation at 315 nm. The iris is therefore exposed to a fraction of the UVB, and much of the UVA from solar radiation. In adults most UVB and some UVA is absorbed by the cornea and lens before reaching the retina, while a greater fraction is transmitted in children whose lenses lack the yellow chromophores. However, there is limited transmission of UVR through the retina to the uveal tract, because of the high absorptive capacity of the retinal pigment epithelium, which intervenes between the retina and choroid.

Epidemiology

- 98 In white and Japanese men, eye cancer rates are on average slightly greater in rural than in urban areas, but in women urban and rural rates are on average almost the same (Doll, 1991). In contrast to cutaneous melanoma, there has been no increase in the incidence of ocular melanoma over time (Scotto *et al.* 1976; Strickland and Lee, 1981), or any gradient of incidence with latitude.

- 99 Registry-based studies of ocular melanoma in non-Hispanic whites in the USA by state of birth have not found a significantly increased risk for those born in more southerly states. A raised risk for birth in a southern state was found in one case-control study in the USA (Tucker *et al.* 1985), but there was no relation to number of years spent in southern states after adjusting for the state of birth. Another case-control study in the USA found virtually the opposite: a reduced risk for those born in southern states, and a raised risk for those living several years in the south after adjusting for state of birth (Seddon *et al.* 1990). In this study, conducted in New England, the relative risk (RR) was increased with ancestry from more northern latitudes, with a substantially elevated risk for Northern European ancestry (RR, 6.5%; CI = 1.9, 22.4) and more than a two-fold risk for British ancestry (RR, 2.4; CI = 1.5, 4.9), compared to the risk with southern European or Mediterranean heritage. Use of sunlamps was a determinant of risk for both random-digit-dialled controls (RR, 3.4; CI = 1.1, 10.3) and sibling controls (RR, 2.3; CI = 1.2, 4.3). Tucker *et al.* (1985) reported an association between uveal melanoma and participation in snow sports and a lack of shading by sunglasses. The UVR-filtering effect of sunglasses is, however, difficult to ascertain retrospectively. It may be relevant that there is about a 58-fold excess risk of choroidal melanoma in patients with xeroderma pigmentosum, a condition exhibiting a defective DNA repair mechanism following UVB damage (Kraemer *et al.* 1987).

100 Studies of risks of second cancer, using cancer registry data, have found no association between non-melanoma skin cancer and ocular melanoma risk in the same individual (Swerdlow *et al*, 1995).

101 In case-control studies, a raised risk of ocular melanoma has been found for individuals with blue, green and hazel eyes, fair or red hair, light skin, cutaneous freckling, many cutaneous naevi, iris freckles and iris naevi, and inconsistently for those with a tendency for their skin to burn and not tan in the sun (Gallagher *et al*, 1985; Holly *et al*, 1990; Horn *et al*, 1994; Seddon *et al*, 1990; Tucker *et al*, 1985). Iris and skin freckles have been found to be stronger risk factors for iris melanoma than for choroidal and ciliary body melanomas, which would be consistent with a solar UVR aetiology since the choroid and ciliary body, but not the iris, are protected by the lens, and pigmented epithelia, from most UVR.

Anatomical location and sun exposure

102 According to Horn *et al* (1994), the anatomical locations of choroidal and iris melanomas were mainly in more sun-exposed areas, which was also in favour of a solar UVR aetiology. However, Schwartz *et al* (1997) found no preferential location of choroidal melanomas in relation to estimated UVR. In other studies, risk estimates of intermittent or cumulative sun exposure have also been inconsistent and in those studies with positive results, dose-response relationships were generally not present (Gallagher *et al*, 1985; Holly *et al*, 1990; Seddon *et al*, 1990; Tucker *et al*, 1985).

Influence of eye protection

103 Tucker *et al* (1985) found a reduced risk of ocular melanoma overall, for people who 'almost always' used sunglasses, hats or visors when out of doors, but found no gradient of risk, related to frequency of use. When iris melanomas were analysed separately, however, there was a stronger effect and a gradient of risk was demonstrated. Another study found no significant relation of ocular melanoma risk to the use of sunglasses, visors, eye glasses or contact lenses (Seddon *et al*, 1990), and a third study found no relation to the wearing of glasses or contact lenses (Holly *et al*, 1990). The extent to which glasses protect against UVR, however, varies greatly depending on the material from which the lenses are made, their size, and wearing position.

Artificial sources of UVR

104 A significantly increased risk of ocular melanoma in relation to welding has been found in one study (Tucker *et al*, 1985) but not in another (Seddon *et al*, 1990), while a third found a significantly raised risk for a history of a physician-diagnosed ocular welding burn, or snow blindness (Holly *et al*, 1990). These three studies all found a raised risk of ocular melanoma in relation to UVR lamp exposure: Tucker *et al* (1985) found a non-significant trend ($p = 0.10$) of increasing risk with increasing frequency of use of sunlamps; Holly *et al* (1990) found a significantly raised risk for exposure to artificial UVR or 'black light' with a trend in risk in relation to duration of exposure. Seddon *et al* (1990) found a significantly raised risk for frequent or occasional use compared to rare or no use of sunlamps. The last authors found a raised risk also in relation to exposure to fluorescent lighting for 40 or more hours per week, significant in comparison with one control group but not another.

Genetic interactions

- 105** Five cases of ocular melanoma have been reported in patients with xeroderma pigmentosum (Kraemer *et al.* 1987), suggesting that the risk of this malignancy may be raised in patients with this rare condition in which there is a defect of DNA repair.
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SUMMARY AND CONCLUSIONS

- 106** Ultraviolet radiation is a cause of acute photophthalmia, due either to UVR exposure from arc welding or as a feature of snow blindness. Chronic UVR exposure is a major contributor to corneal and conjunctival disorders such as climatic droplet degeneration, pterygium and, probably, pinguecula. Risk is increased where solar UVR reflectance from work surfaces is high and where the level of protection is low. In geographical regions of high solar exposure and to a lesser extent in regions with lower exposure rates, UVR contributes to the occurrence of cortical cataract. Its role in the causation of other forms of cataract is less clear. The UVB component of UVR is thought to be the main causative factor in the above conditions, but UVA may also play a part. Protective behaviour, including avoidance of direct exposure to solar radiation, the wearing of hats and of UVR-absorptive sunglasses, appears to reduce risk.
- 107** Direct viewing of the sun may cause irreversible visual loss through the mechanism of solar retinitis. Retinopathy may also occur occasionally through laser injury or as a response to arc welding, in unprotected individuals. The longer UVA wavelengths and wavelengths at the blue end of the visible spectrum, contribute to this damage. There is limited evidence to support sunlight exposure as a contributor to age-related macular degeneration.
- 108** There is no good evidence to suggest a relationship between solar UVR exposure and choroidal melanoma, although a weak relationship may exist for iris melanoma. Studies have supported a relationship between choroidal melanoma and exposure to sunlamps and arc welding sources.
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7 The Skin

INTRODUCTION

- 1 This chapter reviews studies of dermatological conditions that have been associated with exposure to ultraviolet radiation (UVR) from both natural and artificial sources. The previous report on UVR by the Advisory Group discussed in detail the epidemiological evidence on UVR and cancer then available, and rather than re-iterate that material, the present review summarises features from the earlier literature, references for which can be found in NRPB (1995), and gives greater detail on the evidence published since then. Detail is also given on photoageing, a subject less extensively covered before.
- 2 Both UVA and UVB are potentially hazardous to the skin. UVA penetrates deeper into the skin than UVB and has the capacity to cause greater dermal damage. The availability of high output sources emitting predominantly UVA for use in tanning has necessitated the examination of possible clinical hazards from cumulative exposures to UVA as well as those from UVB. High-UVA-emitting devices are also used therapeutically, most commonly in conjunction with a systemically administered photosensitising agent, a psoralen, in the management of certain skin diseases such as recalcitrant psoriasis, cutaneous lymphoma and selected cases of eczema. The combination is referred to as photochemotherapy or PUVA (psoralen plus UVA irradiation), and there have recently been important studies published on the effect of this on risk of malignancy, which are summarised below.
- 3 An additional development, stimulating the need for greater research into the separate and combined effects of UVA and UVB on the skin, is the use of topical sunscreens that block a high proportion of UVB but a lesser proportion of UVA. Thus, there is now the opportunity for greater exposures to UVA than previously, when this might have been prevented or restricted by UVB-induced erythema.
- 4 There are also theoretical reasons for concern about the effect of cutaneous UVR exposure on the immune system in man, which are supported, for example, by the recurrence of herpes simplex or cold sores on the lips after exposure to natural or artificial UVR. These immunological aspects are discussed in Chapter 5 rather than here.

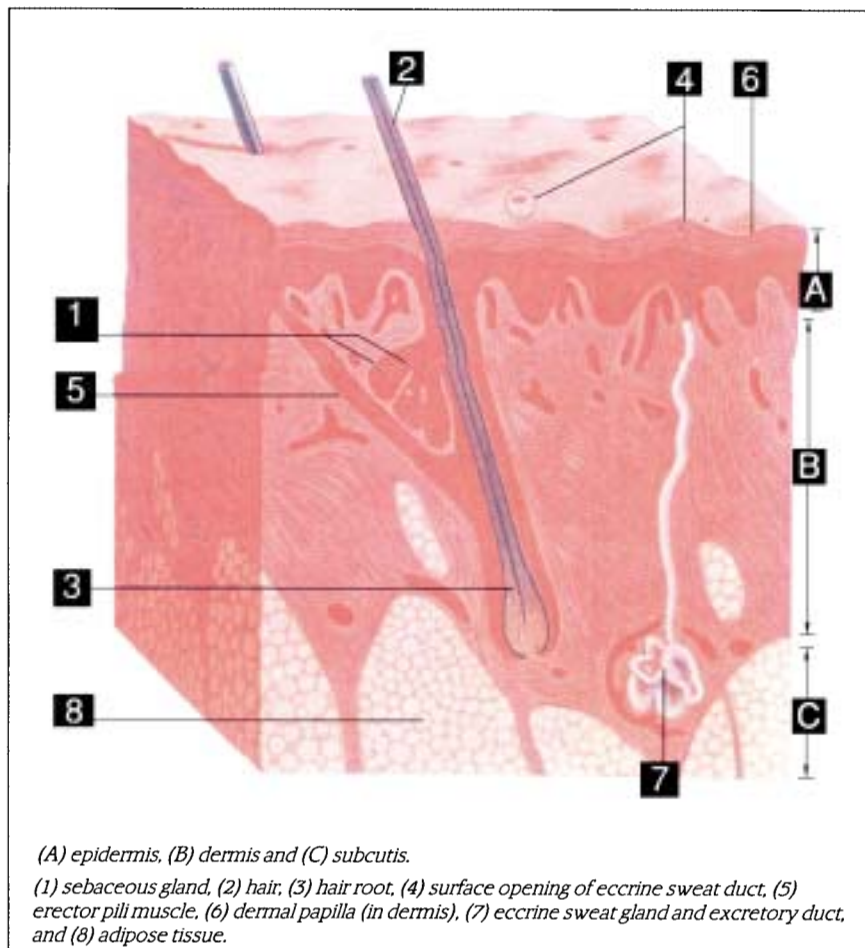
Anatomy and physiology of normal skin

- 5 A diagrammatic representation of normal skin is shown in Figure 7.1. The three horizontal layers are the epidermis, the dermis and the subcutis. These three layers are traversed vertically by the skin appendages.
- 6 The epidermis is further subdivided into (from the external surface inwards) the stratum corneum, the granular layer, the keratinocyte or prickle cell layer, and the basal layer. Within the epidermis, the main cell is the keratinocyte, a cell committed to terminal differentiation which matures as it rises through the epidermis and is sloughed off at the skin surface. The basal layer is the source of keratinocyte renewal in the epidermis. The basal keratinocytes divide intermittently giving rise to one daughter cell that remains in the basal layer and one daughter cell that enters the terminal differentiation process and migrates upwards through the epidermis. There is also a postulated population of

longer-lived stem cells either in this basal layer or in the keratinocytes in the skin appendages. In addition to epidermal keratinocytes, there is a population of melanocytes mainly at the dermo-epidermal junction, and a population of Langerhans cells situated in the mid-epidermis. Keratinocytes give rise to the malignancies basal and squamous cell carcinomas, and melanocytes to malignant melanoma.

- 7 In the dermis the main component is collagen fibres. A population of fibroblasts and elastic tissue are interspersed throughout the collagen. In addition, there is a vascular supply, a nerve supply, and small strips of smooth muscle. UVR-induced actinic damage to dermal collagen can be easily seen under the microscope. The dermal collagen stains grey, and the fibres have a thickened, swollen appearance.
- 8 The skin appendages develop in fetal life as a result of interaction between epidermal and dermal components. These appendages are the pilosebaceous follicle, the eccrine sweat glands and the apocrine sweat glands. The pilosebaceous follicle is further divided into the hair follicle, the sebaceous gland and the arrector pili smooth muscle. Skin appendages are rarely affected by UVR damage.

FIGURE 7.1
Section of skin
showing three
different layers



Skin types in relation to reaction to sun exposure

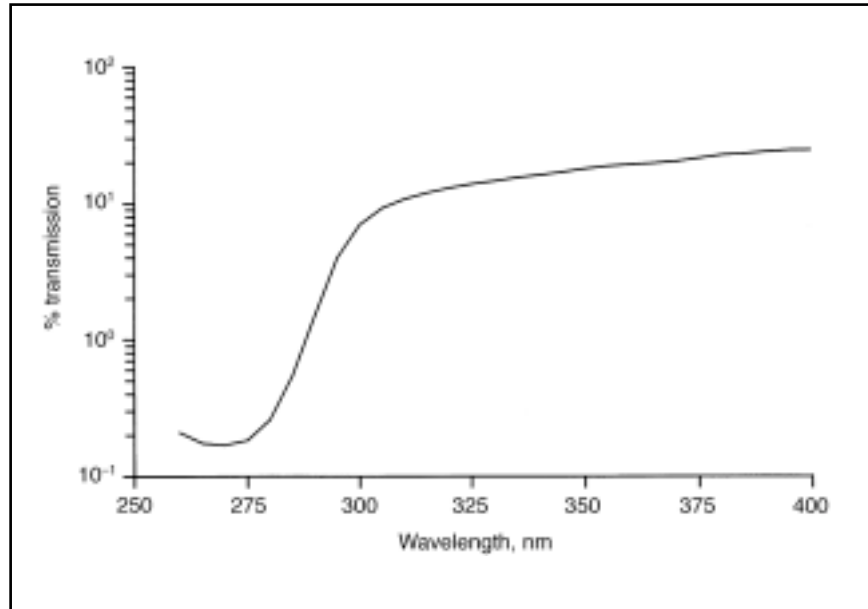
- 9 Human skin varies greatly in response to exposure to UVR. In general, there is a more damaging response in individuals who have very fair, genetically non-pigmented skin with relatively little ability to synthesise melanin after exposure to the sun. Tanning ability and burning after sun exposure are inversely correlated. Table 7.1 shows the six skin phototypes. Fair skinned Caucasians who burn easily and never tan have type I skin, type II individuals burn easily and tan with difficulty, type III individuals tan easily and burn rarely, and type IV skin is found often in individuals with a southern Mediterranean ancestry. These individuals tan very easily and virtually never burn. Type V skin is characteristic of Asians, but within this skin colour there is considerable variation in propensity to burn. Type VI is black or Afro-Caribbean skin. These individuals do not burn but can develop skin dryness after excess sun exposure.

| Skin type | Unexposed skin colour | Commonest racial groups | UVR sensitivity | History of sunburn | History of tanning ability |
|-----------|-----------------------|--|----------------------------|---|--|
| I | White | Caucasian | Extremely sensitive | Always burns on minimal sun | Never tans |
| II | White | Caucasian | Very sensitive | Burns very readily | Tans slowly and with difficulty, freckles common |
| III | White | Caucasian | Moderately sensitive | May burn on regular sun exposure with no protection | Tans relatively slowly |
| IV | Light brown | Caucasian, often of Mediterranean extraction | Relatively tolerant of UVR | Burns rarely | Tans rapidly on exposure to minimal UVR |
| V | Brown | Asian or Middle Eastern | Very variable | Despite pigmentation may burn surprisingly easily on sun exposure | Difficult to assess because of presence of genetically determined pigmentation |
| VI | Black | Afro-Caribbean | Relatively insensitive | Rarely burns (Note: sunburn is difficult to detect on heavily pigmented skin) | Again difficult to detect on heavily pigmented skin |

TABLE 7.1 Skin type and reaction to UVR exposure

- 10 Over the last five years extensive studies have been carried out on Melanocortin 1 receptor variants looking at both mutations and polymorphisms in subjects with red hair and skin cancer (Valverde *et al* 1996). Although it was initially suggested that a specific variant of the MC1R receptor (ASP84GLU) was associated with melanoma, further more extensive studies have shown extensive polymorphisms in the MC1R gene which are associated with red hair and loosely with an increased risk of all types of skin cancer (Smith *et al* 1998). This observation has recently been confirmed in an Australian population by Palmer *et al* (2000), who also report that the effect of MC1R variants on melanoma risk is largely related to pigmentation phenotype.

FIGURE 7.2
UVR penetration
of the skin



Beneficial effects of UVR on the skin

- 11 Exposure of the skin to small amounts of natural sunlight or to an alternative source of short-wave UVR is necessary to convert 7-dehydrocholesterol (pro-vitamin D), which is ingested in the diet and stored in the skin, to pre-vitamin D, which then isomerises to form vitamin D₃. Vitamin D is essential for bone health throughout life. (This is discussed in Chapter 10.)
- 12 In addition, artificial sources of both UVB and UVA are used therapeutically by dermatologists as part of the treatment plan for selected patients with severe psoriasis, dermatitis and a number of rarer skin conditions. The mechanism of action of UVR in this situation is at least in part immunologically mediated.

NON-MALIGNANT CUTANEOUS DISORDERS

- 13 Excessive UVR exposure has several effects on the skin. In the epidermis, the keratinocyte, melanocyte and Langerhans cell systems are all affected. The keratinocytes release a number of cytokines which in turn may have a local immunosuppressive effect, and Langerhans cells are temporarily reduced both in numbers and function, also giving rise to temporary immunosuppression. Melanocytes are stimulated to synthesise melanin protein which is located as a supranuclear cap above the melanocyte nucleus.

Acute UVR exposure

- 14 Acute UVR exposure leads to sunburn, recognised as erythema and blistering. This is mainly caused by the UVB component of the solar spectrum and is maximal at 8–24 hours after exposure. This then gradually subsides over a period of 3–4 days with

subsequent dryness and peeling of the skin. Solar lentigines, or sunburn freckles, can be stimulated by only one or two episodes of acute burning UVR exposure. This is seen most often on the shoulder area, particularly in men.

Chronic UVR-induced cutaneous changes – photoageing

- 15** Photoageing is the term reserved for the clinical and histological features of chronically sun-exposed skin (Taylor *et al* 1990). The word, although synonymous and thus interchangeable with photodamage, does not appertain to sun-induced skin cancer. Inevitably, photoageing is a mixture of those features consistent with chronic sun exposure and those associated with intrinsic or chronological skin ageing. In most cases the features of photoageing far outweigh the more subtle changes of intrinsic ageing.
- 16** Animal models used for study of pathomechanisms of, and putative repair agents for, photoageing include the micro-pig and the hairless (skh-1 and skh-2) mouse (Bissett *et al* 1987; Kligman *et al* 1985a). Although pig skin is probably a more faithful model of photoageing in human skin, in that its histological features are very similar to the human condition, most work has been performed using mice – particularly as the artificial photoageing process in pigs takes at least one year.
- 17** Work on the skh hairless mouse, mainly by Lorraine Kligman (Kligman *et al* 1985a), has characterised the action spectra responsible for photoageing in this model and the characteristic clinical and histological features associated with them. Using Westinghouse FS tubes and solar-simulated radiation this model has proven useful for studying sunscreen products (Bissett *et al* 1987, Kligman *et al* 1982) and potential repair agents such as topical retinoids (Kligman *et al* 1984). UVB produces the predominant changes – more so than solar-simulated radiation (UVA and UVB) and qualitatively different from UVA. The physical skin wrinkles seen in the photoaged hairless mouse are not a structural counterpart to photoageing-related wrinkles in human skin but are a useful outcome for sunscreen and repair agent studies (Bissett *et al* 1991; Kligman *et al* 1982, 1984). Histological changes in this mouse model of photoageing are as follows:
- (a) elastic fibres are hyperplastic, dermal collagen is quantifiably reduced late in the process – mainly a reflection of changes in collagen I and the aminopropeptide of procollagen III (Schwartz *et al* 1989),
 - (b) glycosaminoglycans (GAG) are increased – mostly heparin and heparin sulphate,
 - (c) the basement membrane of the dermo-epidermal junction is duplicated.
- UVA produces similar but less apparent effects than UVB on elastin and collagen, GAGs are deposited at the dermo-epidermal junction rather than throughout the dermis and the vascular basement membrane is duplicated. Physical differences between the different UVR spectra are that UVB-induced wrinkles are transverse, whereas UVA produces longitudinal wrinkles and skin yellowing.
- 18** The salient clinical features of photoaged human skin are seen on those anatomical sites most frequently exposed to sunlight – such as face, neck and dorsa of hands, although any site, if chronically sun exposed, will demonstrate similar features. This was first recognised in farmers and sailors in the nineteenth century, ‘farmer’s neck’ (Unna, 1894) refers to the heavily wrinkled appearance of the nape of the neck – cutis rhomboidalis nuchae (Figure 7.3) – seen in outdoor workers and sportsmen such as golfers. The characteristic clinical features of photoaged skin include wrinkles (Figure 7.4), both

FIGURE 7.3 *Cutis rhomboidalis nuchae*
- 'farmer's neck':
note that the skin
protected by the
collar is smoother as
it is sun protected



FIGURE 7.4
Characteristic
wrinkles associated
with photoageing





FIGURE 7.5 Actinic lentigines or 'age spots' occur most commonly on the dorsum of the hand

coarse and fine, actinic lentigines or 'age spots' (Figure 7.5), mottled hyperpigmentation (which includes freckles), a yellow appearance - elastosis, leatheriness - the skin is thickened, with surface roughness, telangiectasia and actinic keratoses. In contrast, non-sun-exposed or purely intrinsically aged skin is pale, smooth and relatively unwrinkled (Kligman and Lavker, 1988).

- 19** Overall the presence of wrinkling on the face and hands is related to the risk of basal cell and squamous cell carcinomas (Green and Battistutta, 1990; Holman *et al*, 1984). Solar elastosis of the nape of the neck appears to be a predictor of risk of either of these skin cancers. Cutaneous microtopographs of grades 4-6 (severe) carry with them an odds ratio of three for non-melanoma skin cancer (see Appendix A). Holman *et al* (1986) demonstrated that increasing severity in microtopograph grade is strongly associated with a past history of non-melanoma skin cancer. Overall this is probably a useful technique but it should be borne in mind that facial (as opposed to hand) wrinkling does not necessarily correlate with presence of basal cell carcinoma (Brooke *et al*, 2001; Kricker *et al*, 1999); indeed the two may be inversely related. To take this further it would seem that microtopography is not an absolute index of UVR exposure unless weighted for skin type and anatomical site.
- 20** Different skin types exhibit different forms of photoageing. For example, wrinkles are not always a feature of photoaged white skin in that some chronically sun-exposed individuals have atrophic, smooth (unwrinkled), telangiectatic skin. Far-east Asians may develop many actinic lentigines as a consequence of photoageing (Goh, 1990), whereas black skin may not wrinkle even after many years of intense sun exposure. Anatomical site can also dictate clinical features of photoageing; for instance, actinic lentigines are commoner on the dorsa of the hands than on the face, and coarse wrinkles are more prevalent on the nape of the neck. Bateman's or 'senile' purpura is most commonly

seen on the extensor forearm and is produced by photoageing-related rigid, thick-walled dermal blood vessels being less flexible and less protected as a consequence of loss of surrounding collagen and thus more susceptible to trauma. This form of purpura is a feature of sun exposure and not necessarily age.

21 Although wrinkles are one of the most recognisable of dermatological conditions, relatively little is known about their underlying pathomechanisms and biology (Kligman *et al.* 1985b). The key discriminatory features of photoageing and intrinsic ageing are given in Tables 7.2 and 7.3. Early photoageing is an inflammatory event – heliodermatitis – in which mast cells, monocytes and neutrophils, infiltrate the dermis (Lavker *et al.* 1988). This may be the histological correlate of ‘red neck’. The characteristic histological feature of photoaged skin is an increase in dermal elastin (Sams and Smith, 1961), although the elastotic material is not laid down in an ordered fashion but is grossly abnormal, and amorphous with severely truncated fibres. GAGs, mainly hyaluronate and dermatan sulphate, are deposited within the dermis in amounts similar to those present in fetal skin. Photoaged epidermis is initially hyperplastic but with time becomes atrophic and individual epidermal keratinocytes are irregular and at times dysplastic. Melanin content in the epidermis is variable ranging from the usual increase to areas of loss, the histological correlate of hypopigmented macules. The dermal vasculature is reduced and individual vessels are telangiectatic with a thickened, duplicated basement membrane making them less flexible and more liable to damage from trauma.

22 Collagens I and III are significantly reduced in photoaged skin (Talwar *et al.* 1995) (Figure 7.6), particularly within the papillary dermis, and this loss is accompanied by a near absence of fibrillin (Watson *et al.* 1999) (Figure 7.7) within the same zone. Collagen VII (Craven *et al.* 1997) – the key constituent of anchoring fibrils – is also significantly reduced. Pertinent to these observations is that as fibrillin and collagen VII are produced mainly by epidermal keratinocytes, they are consequently more likely to be the extracellular matrix molecules most severely affected by sun exposure.

TABLE 7.2 Clinical features of photoaged and intrinsically aged human skin

| Photoageing | Intrinsic ageing |
|--|---------------------|
| Rough | Smooth |
| Dyspigmentation: actinic lentigines and freckles | Pale |
| Flat, pigmented seborrhoeic keratoses | Few wrinkles (fine) |
| Wrinkles, coarse and fine | |
| Elastosis | |
| ‘Leathery’, thickened | |
| Purpura | |

TABLE 7.3 Histological features of photoaged and intrinsically aged human skin

| | Photoageing | Intrinsic ageing |
|------------------------------------|----------------------|------------------|
| Skin thickness | Increased | Decreased |
| Fibroblasts | Active | Inactive |
| Mast cells, monocytes, neutrophils | Infiltrate initially | None |
| Collagen | Decreased | Decreased |
| Elastin | Increased | Decreased |
| Glycosaminoglycans | Increased | Decreased |

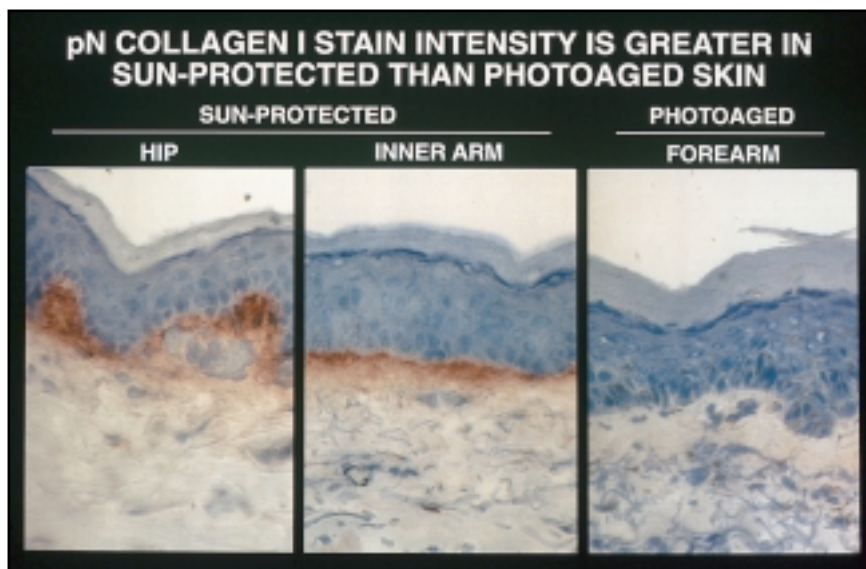


FIGURE 7.6 Loss of collagen I (stained orange) in dermis photoaged as compared to sun-protected skin

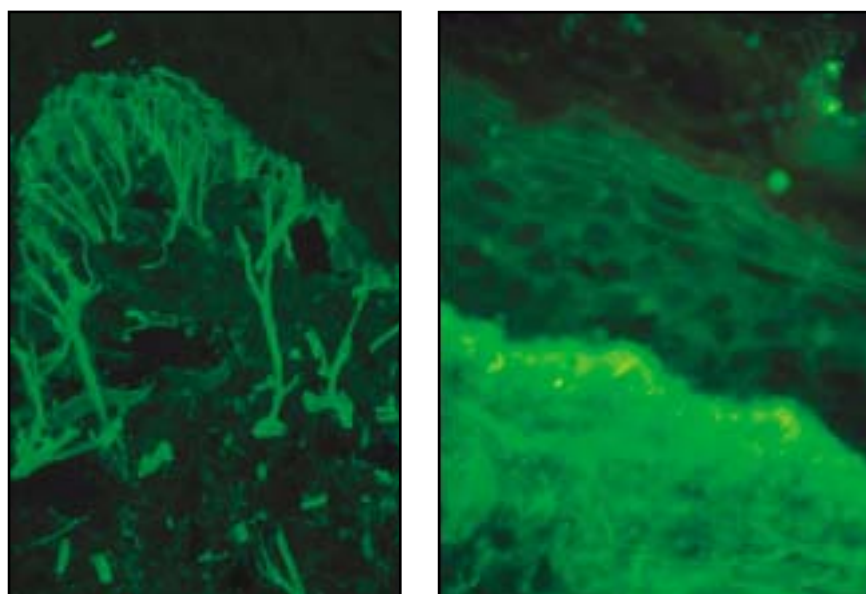


FIGURE 7.7 (a) sun-protected skin showing fibrillin fibres (stained pale green) in candelabra pattern in papillary dermis, immediately below epidermis and (b) photoaged skin - complete loss of fibrillin

(a)

(b)

- 23** Wrinkling is most probably the clinical consequence of loss of collagens within the papillary dermis. It appears that this collagen loss is a product of UVR-induced increases in epidermal and dermal production of metalloproteinases such as collagenases, stromelysin and gelatinase accompanied by inhibition of collagen synthesis (Fisher *et al*, 1997). Exposure to UVR leads to collagen breakdown and repair on each occasion; however, the repair process is not quite 100% - repeated exposure thereby leading to a net loss of collagen and consequent wrinkle formation. Loss of collagen-VII-containing anchoring fibrils leaves the epidermis less securely anchored to the underlying dermis, ie the skin is more fragile. This may be the reason for sunbed-induced blistering.
- 24** Actinic or solar lentigines are usually multiple, circumscribed macules 1-50 mm in diameter induced by UVR from exposure to both the sun and artificial sources, eg PUVA and sunbeds (Rhodes *et al*, 1983). Confusion arises over the other names for actinic lentigines which included 'age spots' or 'coffin spots', connoting senility. Actinic lentigines are commoner in later life only because of cumulative sun exposure. Histologically an actinic lentigo shows elongated, club-shaped epidermal rete-ridges containing increased numbers of dopa-positive, dendritic melanocytes indicative of increased reactivity (Rhodes *et al*, 1991).
- 25** Ephelides are sun-induced freckles or pigmented macules occurring in childhood. In contrast to actinic lentigines, ephelides are transient, tending to fade or disappear when the skin is no longer sun-exposed. Ephelides are commoner in children with red hair and are associated with a susceptibility to sunburn (Azizi *et al*, 1988). The histology of ephelides is very similar to that of actinic lentigo, although biopsies from very young children are scarce.
- 26** Although most investigative work has been performed on photoaged sun-exposed skin, it would appear logical that similar changes would be seen in people habitually using sunbeds.

Pre-malignant UVR-induced cutaneous damage

- 27** Chronic UVR exposure is also associated with the development of actinic keratoses (Figure 7.8). These are small scaly, erythematous lesions which are seen on sites of habitual sun exposure, such as the face and back of the hands, and are usually multiple. They tend to persist and may bleed easily after the minor trauma of washing or shaving. Although studies from Australia have suggested that some actinic keratoses may regress if the skin is protected from further UVR exposure, they are regarded as pre-malignant lesions and have the potential to progress to squamous cell carcinoma (SCC). However, there is controversy about the frequency with which they do so. An Australian study (Marks *et al*, 1986) suggests that less than 1% of such lesions progress to invasive SCC per year and that some may regress if appropriate sun avoidance is taken. However, since many people have 20 or more solar keratoses, which may be present for over 20 years, the probability that a patient with multiple actinic keratoses will develop SCC over time is substantial.
- 28** Other less common conditions associated with chronic excessive UVR exposure include Bowen's disease, actinic porokeratosis and actinic granuloma.
- 29** *Bowen's disease* is sometimes referred to as intraepidermal carcinoma *in situ* and is seen on the skin as a red scaling patch clinically indistinguishable from actinic keratosis.



FIGURE 7.8 Actinic keratosis: note the marked pigmentary change and damage on the hand and light-exposed skin of the face of this individual who has had an outdoor job all his life

- 30** *Actinic porokeratosis* is most frequently found on the lower legs and is seen as a circular raised lesion with a very characteristic raised border. This also is an epidermal UVR-induced condition.
- 31** UVA penetrates more deeply into the dermis than UVB but the precise contributions of each of the wavelengths of UVR to dermal damage are not yet established.
- 32** In the dermis, solar 'elastosis' may result from degeneration of the dermal collagen.
- 33** *Actinic granuloma* is a dermal problem thought to arise as a result of dermal collagen degeneration. These lesions present as deep seated round or oval elevations on the skin with a raised palisaded outer margin.

Sunbed or sunlamp exposure and non-malignant cutaneous effects

- 34** Non-malignant adverse cutaneous effects of sunbed use are well recorded.
- 35** They include skin dryness, irregular pigmentation and, in time, excess wrinkling and sagging of the skin due to the fact that UVA penetrates much deeper into the skin than UVB and therefore causes a proportionately greater degree of dermal damage.
- 36** A few sunbed users develop large blisters, a condition known as pseudoporphyria, which is thought to be due to UVA-induced weakening of the normally strong links between the epidermis and the underlying dermis.
- 37** Many fair skinned sunbed users develop so-called sunbed lentigines, similar to PUVA freckles. These are large, unsightly irregular macular areas of pigmentation which may be heavily pigmented and are permanent. On biopsy, these lesions are seen to arise as a result of overproduction of melanin pigment rather than as a result of naevus cell or melanocyte proliferation.

MALIGNANCY

- 38** The three main types of cutaneous malignancy associated with excessive UVR exposure are squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma. BCCs and SCCs arise from keratinocytes, the main cell population in the epidermis, while malignant melanomas arise from the pigment producing cells of the epidermis, the melanocytes.
-

NON-MELANOMA SKIN CANCER

Clinical features of non-melanoma skin cancer

Squamous cell carcinoma

- 39** Squamous cell carcinomas appear as persistent, red crusted lesions on the exposed skin, most commonly on the face and scalp (Figure 7.9). SCCs also occur on the head, neck and hands, all areas of the body surface that are prone to excessive UVR exposure. Normally, the incidence of SCC is considerably less than that of BCC (about a quarter of the rate), with the exception of organ transplant recipients who are therapeutically immunosuppressed. SCC metastasises more commonly than BCC and is occasionally fatal.
- 40** The evidence that cumulative lifetime sun exposure is the main risk factor for SCC is strong, with the highest incidence being reported in Caucasians in countries such as Australia and South Africa; this evidence is detailed below under 'epidemiology' (paragraphs 55–74).

Basal cell carcinoma

- 41** Basal cell carcinoma or rodent ulcer is the commonest type of skin malignancy – the numbers of cases are rising steadily in ageing white populations in developed countries.
- 42** The typical BCC (Figure 7.10) is a raised translucent nodule which develops slowly over a period of months or even years on the face, often around the eye. The central panel of the face is the commonest site, but there is an increasing incidence of non-facial BCCs which may cause diagnostic confusion as they lack the typical clinical features seen in facial lesions. BCCs on any site have the capacity for relentless local spread and destruction. Thus, if not treated, they can destroy large areas of skin and cartilage and even bone. They rarely metastasise and cause death but multiple lesions are common, making them a significant cause of morbidity and a large burden on the health care system for an ageing population.
- 43** BCCs are cured by simple surgery or radiotherapy. Local recurrence and metastases are both very rare, but patients who have had one BCC are at a substantially increased risk of a second primary BCC.
- 44** The evidence for UVR being a substantial cause of BCC is clear in epidemiological studies of populations, but less obvious clinically in individuals. The epidemiological evidence is considered in detail below (paragraphs 55–79).

Causes of skin cancer

- 45** Before discussing in detail the epidemiological evidence on non-melanoma skin cancer and UVR, the following paragraphs outline briefly other known causes of these tumours – immunosuppression, viruses, ionising radiation, and certain chemicals.

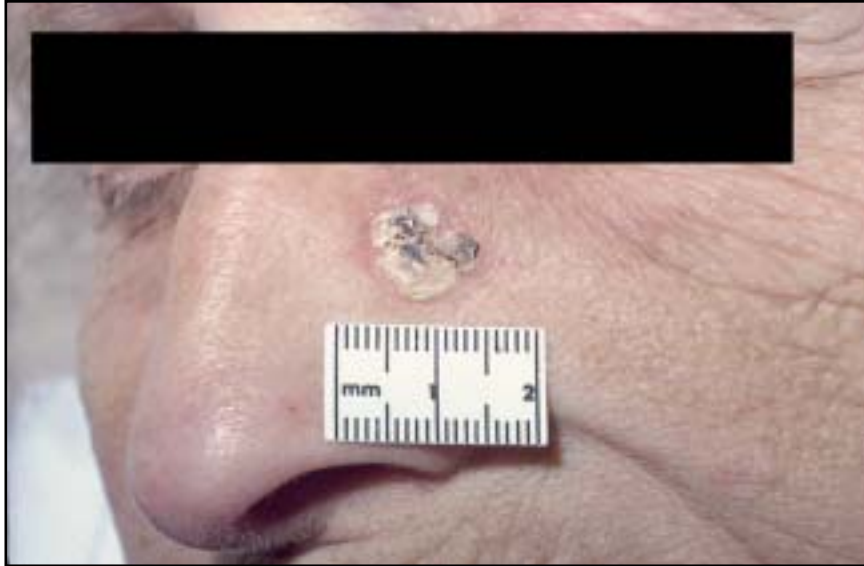


FIGURE 7.9
Squamous cell carcinoma: this is a large ulcerated SCC on the chronically light-exposed skin of an elderly male



FIGURE 7.10
Basal cell carcinoma: note the raised rolled edge with a rather pearly appearance and the central ulceration

Immunosuppression, UVR and SCC

- 46** Patients who are therapeutically immunosuppressed after an organ transplant, most commonly of a kidney, are at a significantly increased risk of cutaneous malignancy, the greatest risk being for SCC. The risk of BCC is also increased and there is probably a moderately increased risk of malignant melanoma. The malignancy risk is higher in parts of the world closer to the equator such as Australia and South Africa than in temperate countries, even after taking into account the higher incidence of all types of skin cancer in non-immunosuppressed individuals living in such regions. Furthermore, almost all the SCCs occur in sun-exposed areas of the body, particularly the face and back of the hands. For example, in one study carried out in the Netherlands, 97% of SCCs in a group of 39 renal allograft recipients occurred in such sites (Hartevelt *et al*, 1990).
- 47** Current studies report that 40%–70% of long-term survivors after organ transplantation may develop SCC and also that their carcinomas have a more aggressive biological behaviour pattern than that in immunocompetent individuals (Euvrard *et al*, 1997; Jensen *et al*, 1999; Veness *et al*, 1999).
- 48** A report from Norway found that cardiac transplant recipients have a 2.9 times higher risk of SCC than renal transplant recipients, and that adding cyclosporin to the immunosuppressive regime of prednisolone and azathioprine increases the risk by 2.8 times (Jensen *et al*, 1999).
- 49** A second group of immunosuppressed individuals consists of those people with the rare inherited disease, epidermodysplasia verruciformis (EV), in which there is an underlying defect in cell-mediated immunity. Characteristic multiple flat warts and macular lesions develop and, in approximately one-third of cases, some of the lesions – most frequently on sun-exposed areas of the body – progress to SCC, often when the patients are in their third decade of life.

Possible contribution of virus infection to development of SCC

- 50** It is well established since the work of Spencer and Andersen (1970) that immunosuppressed individuals have an increased incidence of viral warts caused by human papillomavirus (HPV) infection, compared with the general population, and that the number of those affected rises substantially with longer duration of graft survival, as does the cumulative risk of developing cutaneous malignancies. For example, in one study in the south-east of Scotland, 20% of renal allograft recipients had HPV infections and 2% had skin cancers 5 years after transplantation, whereas 77% had HPV and 13% had skin cancers between 5 and 22 years following transplantation (Barr *et al*, 1989). Most cancers were SCCs and they outnumbered the BCCs by 15 to 1, a reversal of the predominance of BCC found in immunocompetent subjects. The SCCs are often preceded by actinic or verrucous keratoses. Histologically, viral warts and keratotic lesions in renal allograft recipients often display varying degrees of epidermal dysplasia. Similarly, many SCCs retain histological features characteristic of viral warts.
- 51** The role of HPVs in the development of cutaneous and mucosal malignancy is an area of active investigation. The HPVs most clearly associated with oncogenic potential are types 16 and 18, found in the majority of genital carcinomas. These are not generally detected in the skin, but a range of HPV types have been identified in cutaneous tumours from renal transplant patients, some of which are not found in normal people. The predominant types are 5 and 8. They are not thought to have the same

transformation strategy as types 16 and 18: for example, HPV-8 E6 does not form a complex with p53 and HPV-8 E7 does not bind to the cellular retinoblastoma protein (Pfister, 1992). There may be a permissive situation in immunosuppressed individuals which, together with local UVR exposure, allows HPVs that are not normally pathogenic to contribute to the development of malignancy.

- 52** The skin lesions in subjects with epidermodyplasia verruciformis are induced by at least 20 HPV types, of which 5 and 8 are found most frequently in the cutaneous carcinomas. In this case host specificity may be related to genotype. (See Chapter 5 for further detail on immunological aspects of HPV infection.)

Ionising radiation

- 53** Exposure to ionising radiation was found to cause skin cancer within a few years of the discovery of x-rays in 1895. Observations on the survivors of the atomic bombings of Hiroshima and Nagasaki and other exposed groups have shown that ionising radiation can induce NMSC, due almost entirely to a strong association with BCC (UNSCEAR, 2000). However, the risk from the doses normally encountered, even from radiotherapy, is small in absolute terms, and ionising radiation causes only a small fraction of the total number of cases of the disease. The possible interaction between UVR exposure and exposure to ionising radiation is unresolved. Studies of groups exposed to ionising radiation for medical reasons indicate that the relative risk of NMSC from ionising radiation is higher on skin exposed to UVR than on UVR-shielded skin (ICRP, 1991; NRPB, 1997). However, the most recent data for the Japanese atomic bomb survivors show that the relative risk is not larger for UVR-exposed parts of the body than for shielded parts (Ron *et al* 1998).

Chemical exposure and cutaneous malignancy

- 54** Historically, carcinogenic hydrocarbons found in soot were a recognised occupational cause of scrotal cancer in chimney sweeps. Tar, mineral oil, and other agents that include polycyclic aromatic hydrocarbons cause SCC of the skin, and inorganic arsenic compounds cause both SCC and BCC of the skin (IARC, 1980), but modern health and safety regulations have ensured that chemically induced cutaneous malignancy in man is virtually non-existent. Chemical carcinogens are still used by scientists in animal models of cutaneous malignancy, but the relevance of these experiments to cutaneous malignancy in man must be considered with care.

Epidemiological studies of non-melanoma skin cancer

- 55** Non-melanoma skin cancer accounted for 14% of registered malignancies in England and Wales in the most recently published data, for 1993 (ONS, 1999), and 20% in Scotland in 1997 (ISD Scotland, personal communication), but since there is substantial under-registration (Ko *et al*, 1994; Lloyd Roberts, 1990; Lucke *et al*, 1997), the true percentage must be appreciably higher. Despite this, NMSC accounts for less than 0.5% of cancer deaths in Britain.
- 56** About three-quarters of the cases of NMSC are BCCs and nearly all of the rest are SCCs. For both of these histological types, solar UVR appears to be the main causal factor. An important advance in understanding in recent years, however, has been a realisation that the pattern of exposure responsible differs: for SCC the data suggest that the risk increases with increasing cumulative lifetime dose of UVR, whereas for BCC the

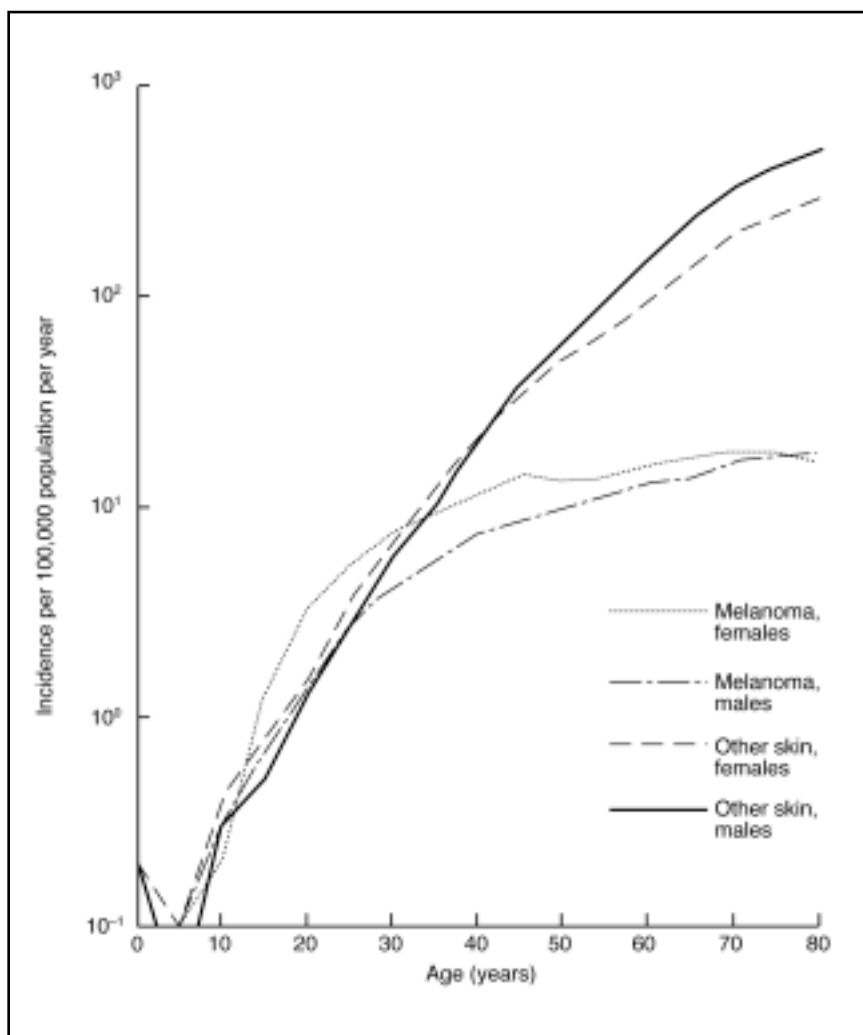
relation to UVR is less simple, and there is evidence, reviewed below, that above a certain dose the risk does not rise, and that the degree of intermittency of exposure may be of importance.

Sex and age

57 In white populations NMSC is generally more common in men than in women (Figure 7.11). In most recent studies (Franceschi *et al*, 1996; Green *et al*, 1996; Karagas *et al*, 1999; Staples *et al*, 1998; Zanetti *et al*, 1996), but not all (English *et al*, 1997), the male : female ratio has been greater for SCC than for BCC.

58 The incidence of SCC increases steeply with age, but in several studies the increase in the incidence of BCC with age has been less steep or, for women in parts of Australia, has reached a plateau by middle age (Buettner and Raasch, 1998; English *et al*, 1997; Franceschi *et al*, 1996; Karagas *et al*, 1999; Staples *et al*, 1998).

FIGURE 7.11
Incidence rates of cutaneous melanoma and non-melanoma skin cancer (excluding Kaposi's sarcoma) at ages 0–84 years, by sex and age, England and Wales 1988–90 (data from Parkin *et al*, 1997). (The greater rate at ages 0–4 than 5–9 is based on small numbers and is not of importance.)



Geographical distribution

- 59** The risk of NMSC in white populations of similar ethnicity generally increases with decreasing latitude – across locations of comparable data quality – both within and between countries, in accord with UVR aetiology, and positive correlations have been shown between NMSC incidence/mortality and estimates or measures of UVR dose at the same locations, with a steeper gradient for SCC than for BCC. The highest recorded incidence rates have been in Australia. In Western Australia in 1987–92, incidence rates of BCC were 7.1 per 100 per year in men and 3.4 per 100 in women aged 40–64 years, while rates of SCC at these ages were 0.8 and 0.5 per 100, respectively, and more than half of subjects with a skin cancer in 1987 had developed another by 1992 (English *et al.* 1997). In Queensland, annual incidence rates of BCC in 1985–92 at ages 18–69 years were 2.1 per 100 in men and 1.6 per 100 in women, and rates of SCC were 1.0 and 0.5 per 100, respectively (Green *et al.* 1996), and in Northern Queensland in 1996–97, incidence rates of each of BCC and SCC in men aged 80 years and above were, astonishingly, over 10% per year (Buettner and Raasch, 1998).
- 60** Rates of NMSC in British immigrants to Australia have been found to be about half of those in Australian natives, with the risk of BCC decreasing with increasing age at immigration, implying that early UVR exposure or cumulative exposure is important to risk.

Time trends

- 61** Complete registration of NMSC is notoriously difficult, mortality is low and death certificates coded to this cause are often incorrect. As a consequence, time trends are usually best assessed from special surveys rather than from routine cancer registration or mortality data. Recent studies continue to show increasing incidence of both SCC and BCC in white people in temperate countries and in places closer to the equator, with increases generally greater, in percentage terms, for SCC than for BCC, and for SCC in women than in men. In Norway, age-standardised incidence of SCC has more than trebled in men and more than quadrupled in women from 1966–70 to 1991–95 (Iversen and Tretli, 1999), while in Rochester, Minnesota, it doubled in women and increased by a half in men from 1984–86 to 1990–92 (Gray *et al.* 1997). In New Hampshire from 1979–80 to 1993–94, SCC incidence doubled in men and tripled in women (Karagas *et al.* 1999), with particularly large increases at older ages, and in Australia from 1985 to 1995 it doubled in men and increased by slightly less in women (Staples *et al.* 1998). Increases in BCC have generally been less marked: in New Hampshire from 1979–80 to 1993–94 there were increases of 80% in each sex (Karagas *et al.* 1999), and in Australia from 1985 to 1995 there were increases of 30% in men and 6% in women, with decreases in incidence at ages under 50 years (Staples *et al.* 1998). The latter decreases might reflect the success of preventive campaigns, which have been particularly intense in Australia, but also they could be an artefact of greater awareness leading to early detection of BCC in the early years of the study period.

Occupation

- 62** In some routine cancer registration and mortality data, NMSC has been more common in outdoor than in indoor workers, and this has sometimes, but not always, been true in data from special surveys and in case-control and cohort studies. A new meta-analysis of NMSC in farmers found a relative risk of 1.00 (Khuder, 1999); the comparison group was not made explicit, but was presumably either the general population or the working population. In a recent large case-control study in southern

Europe, cumulative hours of outdoor occupational sun exposure were significantly associated with the risk of SCC but not BCC (Rosso *et al.* 1996). In men in Alberta, however, no significant association of SCC was found with occupational sun exposure (Bajdik *et al.* 1998), and the same was true for SCC and BCC in Queensland (Green *et al.* 1996). The latter study provided an interesting insight into the possible reasons for the lack of a strong and consistent association with occupation. It was found that people with fair or medium complexions and a tendency to sunburn were under-represented among outdoor workers compared with other subjects, which suggested self-selection of sun-tolerant individuals (ie those at low risk of NMSC) to become and/or remain outdoor workers. The authors also found that outdoor workers were more likely than others to wear sunhats, ie that they modified their behaviour to protect themselves against the sun.

Skin site distribution

- 63** The anatomical distribution of both SCC and BCC on the skin accords with aetiology by sun exposure, and indeed by cumulative rather than intermittent exposure. In contrast to melanoma, the majority of cases of both histological types in almost all studies have occurred on the head and neck. The percentage on these sites in certain studies in Australia has been lower than elsewhere. Most recently, in a study in Western Australia only one-third of BCCs and around one-half of SCCs in each sex were on usually exposed parts of the head and neck (English *et al.* 1997). For both SCC and BCC, a much greater proportion of tumours are on the ear in men than in women, consistent with solar UVR aetiology.
- 64** In recent studies the percentage of tumours that have occurred on the trunk has consistently been greater for BCC than for SCC (Buettner and Raasch, 1998; English *et al.* 1997; Franceschi *et al.* 1996; Karagas *et al.* 1999; Zanetti *et al.* 1996). The detailed site distribution of SCC on the face parallels fairly exactly the extent of sun exposure, whereas for BCC this is not the case. The distal parts of the limbs (hand, forearm, lower leg and foot) are sites at which a greater proportion of SCCs than BCCs occur (Buettner and Raasch, 1998).

Ethnic distribution and host characteristics

- 65** NMSC is much more common in white than in non-white populations. Data from case-control and cohort studies within white populations have shown a raised risk in individuals with fair coloured eyes, pale skin, and red or blond hair (ie in those with least melanin protection from UVR), as well as in those who burn easily and do not tan in the sun. In general, recent case-control studies have confirmed this for BCC (Green *et al.* 1996; Lear *et al.* 1997; Zanetti *et al.* 1996) and SCC (Bajdik *et al.* 1998; Green *et al.* 1996; Zanetti *et al.* 1996). An exception was a Danish study of BCC, which did not find significant associations (Lock-Anderson *et al.* 1999), but the study was not large (145 cases) and heterogeneity of phenotype was low – 80% of controls had had blond hair at age 25 years and 70% had blue eyes.
- 66** Strongly raised risks of both SCC and BCC have been found in relation to various observable biological markers presumed to indicate long-term cutaneous sun damage – facial telangiectasia, elastosis of the neck, signs of skin damage in cutaneous microtopographs, and the presence of a large number of solar keratoses (Green *et al.* 1996). However, the direct evidence on the relation of these markers to phenotype and to UVR exposure, and for instance the different contributions of cumulative UVR dose and

intermittency of exposure, is weak. Raised risks of SCC and BCC have been found in relation to freckling – in the most recent data this was significant only for BCC (Green *et al*, 1996). New studies have found a raised risk of cutaneous melanoma and lip cancer in people who have had BCC (Frisch *et al*, 1996; Levi *et al*, 1998) or SCC (Levi *et al*, 1997a), as well as excesses of SCC after BCC (Levi *et al*, 1998) and vice versa (Levi *et al*, 1997a), and excesses of NMSC after melanoma (Levi *et al*, 1997b; Wassberg *et al*, 1996). These findings accord with the phenotypic risk factors in common and associations with UVR exposure in common of these different skin tumours.

Patients with albinism and xeroderma pigmentosum

- 7** Oculocutaneous albinism is an uncommon autosomal recessively inherited disorder of melanin synthesis characterised by the reduction or complete absence of melanin pigments in the skin, hair and eyes. The prevalence varies considerably around the world; in the UK, the prevalence is estimated at 5 per 100 000 population. Albino patients are particularly sensitive to the effects of UVR and show an increased frequency of sunburn, actinic damage and BCCs and SCCs compared with non-albino subjects.
- 68** Xeroderma pigmentosum (XP) is a rare autosomal recessive condition in which there is a DNA excision repair defect and both cellular and clinical hypersensitivity to UVR. Almost half of the published cases have had NMSC reported (Kraemer *et al*, 1987), and almost all of these tumours were on constantly exposed skin sites. In a British study 23 NMSCs were recorded in 48 patients with XP, although ascertainment of subjects was reliant upon reporting-in by clinicians, and therefore might have given rise to bias (Pippard *et al*, 1988). In another British study which may have overlapped with the above, 15 of a cohort of 32 patients ascertained systematically from case-notes at two hospitals were known to have developed NMSC during follow-up (English and Swerdlow, 1987). Despite potential selection of study subjects and the absence of data giving formal comparisons of observed and expected numbers of cancers, it is clear that patients with XP are at a greatly increased risk of NMSC.

Sun exposure

- 69** Obtaining more-direct information than the indications above about past sun-exposure history is not easy. Several case-control studies have taken histories of sun exposure and painful sunburns, although there must be uncertainty about the extent to which these are accurately recalled and whether recall bias might have occurred. Details of the studies can be found in IARC (1992) and Krickler *et al* (1994). The early studies generally found that the risk of NMSC increased with greater cumulative sun exposure (although with considerable uncertainties in interpretation in many instances), and for SCC this has been true in the two most recent analyses (Bajdik *et al*, 1998; Rosso *et al*, 1996). For BCC, however, a large recent case-control study in southern Europe found that a plateau of risk was reached at higher cumulative exposure levels, and indeed there was a slight downturn in risk for the highest exposure level (Rosso *et al*, 1996). This plateau and fall accord with previous results from a carefully conducted study of BCC in Western Australia (Krickler *et al*, 1995a). The lack of dose-response at high exposures also accords with a study of Maryland watermen (fishermen), in which a less subjective assessment of cumulative UVR exposure was made than in the purely questionnaire-based studies above, because the stable work patterns of the watermen enabled current UVR exposure measurements to be used to imply past occupational exposure levels (Strickland *et al*, 1989). The southern European study (Rosso *et al*,

1996), as the earlier Australian one (Krickler *et al.* 1995a), found the UVR dose-response curve for BCC differed by phenotype, between good tanners, for whom risk continued to rise with greater cumulative dose, and poor tanners, for whom it did not.

- 70** Given the evidence that SCC relates to cumulative UVR exposure, it might be expected that wearing a hat would diminish the risk of SCC of the head and neck. In a recent study, however, the opposite was found; a doubling of risk occurred for men who had worn a hat in childhood and adolescence or had worn a hat in adulthood (Bajdik *et al.* 1998). A similar result has been found previously for BCC (Krickler *et al.* 1995b), and analogous results for BCC in relation to sunscreen use in an American cohort study (Hunter *et al.* 1990). Although these studies adjusted for sun-sensitivity variables as currently measured, the most likely reason for the apparently paradoxical results is that people who burn easily will tend to respond to this by using sunhats and sunscreens more, and the sun-sensitivity measures variables used for adjustment in the analyses do not capture with sufficient precision the phenotypic variables that lead individuals to adopt protective behaviours but are also markers of intrinsic high risk.
- 71** Studies of NMSC risks in relation to leisure exposures to UVR have given inconsistent results. A case-control study in Western Australia in 1995 suggested a relation of risk of BCC to degree of intermittency of UVR exposure (Krickler *et al.* 1995b). Recent studies of SCC have found no significant relation of risk to leisure exposures (Bajdik *et al.* 1998; Green *et al.* 1996; Rosso *et al.* 1996), while for BCC there was a significant relation in one study (Rosso *et al.* 1996) but not another (Green *et al.* 1996).
- 72** Most studies, but not all, have found increased risks of NMSC in relation to past number of painful sunburns. In recently published case-control studies, Green *et al.* (1996) found significantly raised risks of both SCC and BCC with a history of repeated sunburns, whereas in the study by Zanetti *et al.* (1996) there was a significant relation for BCC but not SCC, and a significantly increased risk of BCC for a history of a first sunburn before age 15 years. Certain previous studies have also found raised risks of BCC in relation to sunburn at young ages (Gallagher *et al.* 1995; Krickler *et al.* 1995b). It should be noted, however, that sunburn is a reflection of phenotype as well as exposure, and that lifetime or early life histories of sunburn have great potential for recall error and specifically for bias.
- 73** In conclusion, therefore, the data on sun exposure are compatible with the view that the risk of SCC is related directly to cumulative dose of UVR, but that risk of BCC, as for melanoma, is affected by intermittent, intense UVR exposure of the type that occurs from sunbathing and outdoor recreational activities. The descriptive epidemiology of BCC and of melanoma differ appreciably, however, especially in skin site distribution, suggesting that the aetiology of the two tumours is not entirely the same, and that BCC may be related to cumulative as well as intermittent UVR, and may have an aetiology sharing aspects with both SCC and melanoma (Swerdlow, 2000).

Trial of prevention of NMSC by sunscreen application

- 74** One of the most important developments in NMSC epidemiology in the last few years has been the publication of randomised trials of whether sunscreen application can prevent NMSC or its precursors. In a community-based randomised trial, 1621 adult residents of Nambour, Queensland, were randomised between daily application of a

sun protection factor 15-plus sunscreen to the head, neck and hands and the individual's usual use of sunscreen (the study was of a 2 x 2 factorial design such that subjects were also randomised between beta-carotene supplementation and placebo tablets) (Green *et al*, 1999a). After 4.5 years of follow-up, 250 of 1383 participants with dermatological follow-up had developed 758 new skin cancers. There were no significant differences between the sunscreen and no-sunscreen groups in incidence of first new BCC, rate ratio 1.03 (95% CI 0.73, 1.46) or SCC, 0.88 (95% CI 0.50, 1.56), on the skin sites treated with sunscreen, nor in the total numbers of BCCs incident on these skin sites (and no significant effect of beta-carotene). There was, however, a significant reduction in the numbers of SCCs incident in the sunscreen group, 0.61 (CI 0.46, 0.81); a re-analysis restricted to histologically diagnosed SCCs also showed a significantly reduced risk. Although there does not seem to be any reason to believe that the number of tumours incident is a more valid outcome measure than the number of people in whom a tumour develops, it does provide larger numbers for analysis, and the persons analysis for SCC gave results in the same direction. Thus the study overall gives direct evidence for the first time that sunscreens, and hence presumptively a reduction in UVR dose, can prevent SCC, and that the levels of UVR exposure occurring as recently as the last five years may affect the risk of SCC. This adds to less-direct evidence from a previous Australian trial of 588 subjects (Thompson *et al*, 1993) and a smaller American study of 50 subjects (Naylor *et al*, 1995) in which a reduction in the incidence of actinic keratosis, a precursor of SCC, was shown with sunscreen use.

Artificial sources of UVR

Therapeutic UVR lamps

- 75** Psoriatic (and other dermatological) patients have been treated with oral 8-methoxypsoralen plus UVA irradiation (PUVA) since the mid-1970s. Several cohort studies have shown increased risks of NMSC in such patients, but this does not in itself indicate carcinogenicity of UVA, or even of UVA and psoralens in combination, because the patients often receive other treatments that might be carcinogenic, and because potentially psoriasis itself might be associated with skin cancer. However, as well as the overall raised risk of BCC and SCC in PUVA patients, cohort studies have found a strong dose-response relationship between cumulative PUVA dose and SCC risks which does not appear to be explicable by past exposure to other carcinogenic agents. Recent publications adding to the evidence of a raised risk of SCC have come from follow-up for up to 21 years of 4800 Swedish patients treated with PUVA (Lindelöf *et al*, 1999), and from a meta-analysis of eight studies with at least five years of follow-up after oral PUVA treatment (Stern and Lunder, 1998). The latter analysis found that the risk of SCC after high dose PUVA (more than 200 treatments or over 2000 J cm⁻²) was 14.0 times (95% CI 8.3, 24.1) that after low dose (less than 100 treatments or 1000 J cm⁻²). For BCC, a less strong dose-response relationship with PUVA, or none, has been found.
- 76** An almost 100-fold increased risk of male genital SCC has been found in patients with psoriasis treated with PUVA, with a dose-response relationship. In women given PUVA, however, for whom in contrast to men the genitalia are not exposed to the UVA treatment, the rate of genital malignancy has been far lower, despite a greater expected rate than in men (Stern *et al*, 1990). This suggests that direct UVA exposure was a causal factor for the high SCC risk in the men.

- 77 The literature therefore gives strong evidence that PUVA treatment causes SCC and a weaker suggestion that it might cause BCC. Since psoralen dose increases as UVR dose increases, it is not clear whether UVA alone is carcinogenic in these treatments or, indeed, with the exception of genital cancers, whether UVA contributes to carcinogenesis. The fact that the SCC distribution in PUVA-treated patients tends towards sites other than the head and neck more than is true for SCC in general, suggests that the therapeutic UVA (which would reach sites less exposed to solar UVR) might at least be contributory.
- 78 It is less clear whether dermatological treatments involving UVB are associated with a raised risk of NMSC; this was reviewed by the Advisory Group previously (NRPB, 1995) and there have been no substantial additional data in recent years to resolve it.

Sunlamps

- 79 In 1995, the Advisory Group noted that there have been few and inconsistent data on the relation of the risk of NMSC to sunlamp exposure (NRPB, 1995). This remains the case.
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CANCER OF THE LIP

- 80 SCC of the lip (vermilion border and adjacent mucous membrane, but excluding the skin of the lip) involves the lower lip almost exclusively. It is predominantly a male disease. An excess of dysplasia and malignancy of the lip (the latter based on only two cases) has also been shown in renal transplant patients, with the lesions occurring particularly among subjects with long-term sun exposure, smokers and men (King *et al.* 1995) (see also paragraphs 38–40). Cumulative UVR exposure appears to be important to risk, but some other factor is also involved as the geographical distribution does not in some instances follow ambient UVR – the greatest recorded incidence in men, for instance, has been in Newfoundland. The most important such factor is smoking tobacco, particularly in pipes, which acts synergistically with UVR to produce the disease.
- 81 Lip cancer is more common in white than in black populations, in outdoor than in indoor workers, and in those who have spent a lifetime in an area with high solar exposure. A recent meta-analysis found a significant relative risk of 2.0 for lip cancer in male farmers, and a non-significant relative risk of 1.3 in female farmers (Khuder, 1999) (the comparison group was not made explicit, but was presumably either the general population or the working population). The risk of lip cancer is raised in white people with light phenotypes and sun-sensitive skins. Fuller details can be found in NRPB (1995). A recent case-control study in women, as well as confirming relations to fair, sun-sensitive complexion and time spent outdoors, found some evidence, but not significant, of a protective effect of the use of lip covering (lipstick or other agents) among women with high outdoor UVR exposure (Pogoda and Preston-Martin, 1996).
- 82 The incidence rates of lip cancer are falling, especially in men, in many white populations. Recent studies have shown large declines in incidence in both sexes in Connecticut (Morse *et al.* 1999), and in incidence and mortality in England and Wales (Swerdlow *et al.* 2001).
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MALIGNANT MELANOMA

- 83** Melanoma melanoma is a relatively rare form of skin cancer but is responsible for 80% of skin-cancer-associated deaths. The risk of malignant melanoma is associated with excessive UVR exposure, but the relationship appears to be complex. Short, sharp episodes of intense exposure have been incriminated, but cumulative total lifetime sun exposure probably also contributes to risk.

Clinical features of malignant melanoma

- 84** The four main clinical pathological types of melanoma are:
- (a) superficial spreading,
 - (b) nodular,
 - (c) lentigo malignant melanoma,
 - (d) acral (or acral/lentiginous) melanomas, including subungual lesions.
- 85** Superficial spreading melanomas (Figure 7.12) are the most common type of melanoma. They are most often found on the leg in women and the trunk in men. They are small brown or black lesions characterised by an irregular lateral edge, and three or more central shades of brown, black, red blue and even white.
- 86** Nodular melanomas (Figure 7.13) may be seen on any site, but are commonest on the trunk. They are usually densely black raised nodules, frequently with a history of bleeding.
- 87** Lentigo maligna melanomas (Figure 7.14) are the melanomas of the sun-exposed skin of the elderly. They have a slow initial growth pattern over months or years, with initially a flat, irregular brown lesion which over time develops a central raised nodule.
- 88** Acral melanomas are found on the palms and soles and are usually brown or black, flat or raised lesions, with again an irregular outline and several colours in the central portion of the lesion (Figure 7.15).
- 89** Some recent studies have questioned the consistency with which these four subtypes of melanoma can be recognised on clinico-pathological examination, and they would not appear to have prognostic significance once controlled for tumour thickness. However, until the exact dose-response and UVR intensity relationship with melanoma is established, the sub-classification remains of possible value in considering the relationships of these clinically very different lesions to UVR exposure.
- 90** The likelihood of survival after surgical treatment of primary melanoma is directly related to the thickness of the tumour. This is measured by calculating in millimetres the thickest area of invasion of the primary tumour, measured from the granular layer in the epidermis to the deepest invasive melanoma cell in the underlying dermis. Thus, a tumour of thickness 1 mm or less at the time of primary surgical excision is associated with a 95% prospect of five year disease-free survival, but one 3 mm or thicker has a five year disease-free survival prospect of only 50%.

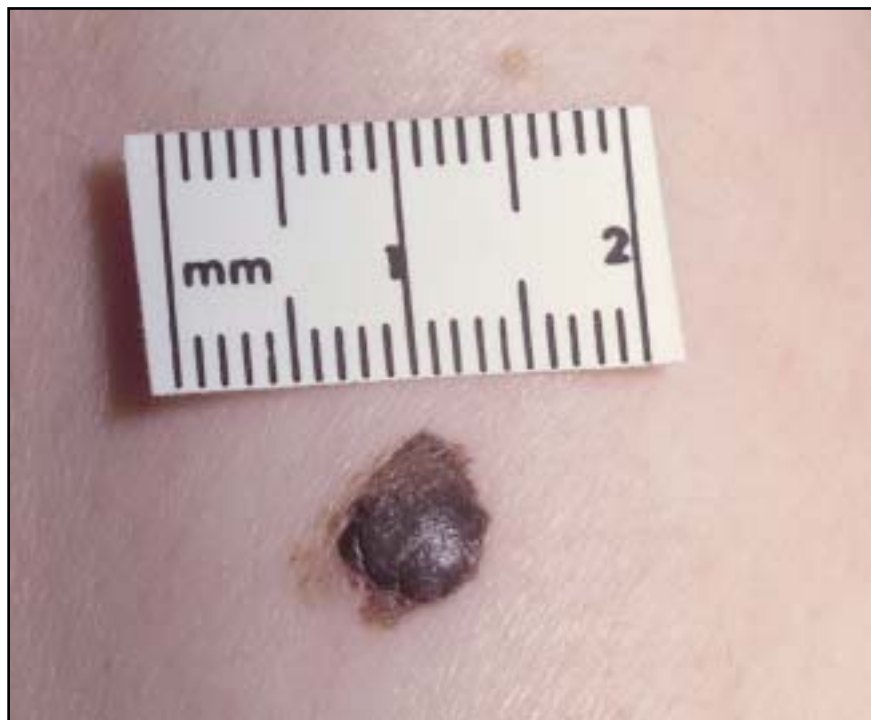
Naevi

- 91** The strongest risk factors yet found for melanoma risk in white populations are large numbers and atypicality of naevi ('moles') (Holly *et al*, 1987; Swerdlow *et al*, 1986). A recent study has found naevi to be a risk factor particularly for *p53*-negative melanoma (Whiteman *et al*, 1998). Based on histological examination, a proportion of malignant melanomas appears to arise from pre-existing benign melanocytic naevi. This proportion varies in different studies from 20% to 40%.

*FIGURE 7.12
Superficial spreading
malignant
melanoma: note the
irregular outer edge
and irregular colour
within the lesion*



*FIGURE 7.13
Nodular malignant
melanoma*





*FIGURE 7.14
Lentigo maligna
melanoma on the
cheek of an elderly
female. These
lesions tend to be
found on chronically
light-exposed skin
and have a rather
slower tempo of
growth than other
melanomas*



*FIGURE 7.15 Acral
melanoma: ulcerated
acral malignant
melanoma on the
sole of the foot. This
is the type of
melanoma for which
there is least
evidence for sun
exposure as a major
aetiological factor*

- 92** These associations have led logically to studies of factors pre-disposing to the development of melanocytic naevi. Early childhood sun exposure appears to be an important association, and recent studies have added to the evidence for this. In young white children in Queensland, Australia, where UVR levels are exceptionally high, naevus counts have been found greater than in other places with lower ambient UVR, and naevus densities have been found greatest on habitually sun-exposed sites and, for larger naevi, on the intermittently-exposed skin of the trunk (Harrison *et al.* 1999). In children in Germany, reported episodes of sunburn and the extent of intense sun exposure were positive risk factors for numbers of naevi gained between ages 7 and 12 years (Luther *et al.* 1996). In adults in Washington State, USA (Dennis *et al.* 1996), Germany (Breitbart *et al.* 1997), and the Netherlands (Crijns *et al.* 1997), the history of sunburn at young ages and, where examined, high cumulative UVR exposure in childhood, were risk factors for large numbers of naevi; in Curacao, however, there was no such relation for numbers of naevi, although there was for atypical naevi (Crijns *et al.* 1997). It should be noted that sunburn may be a consequence of phenotype as well as of the extent of UVR exposure.
- 93** An important newly-published study from Vancouver, British Columbia, takes the evidence a step further (Gallagher *et al.* 2000). A total of 378 white school children were randomised to receive a supply of broad-spectrum sunscreen for use when in the sun for 30 minutes or more, or to receive no sunscreen and no advice about sunscreen use. Among the 309 children for whom naevus counts were successfully conducted (blind to treatment status) at the start and end of the three year study period, a smaller number of new naevi developed in the treated than the control group ($p = 0.048$), despite similar reported histories of time spent outdoors. There was a significant interaction between freckling and the effect of sunscreens, such that the latter had a greater effect in freckled children. Case-control studies in Europe, however, have found naevus prevalence to be greater in children who used sunscreens more – perhaps because of confounding by phenotype, which would be avoided in a trial, and because of an association of sunscreen use with time spent outdoors, which appears not to have occurred in the trial (see paragraphs 130 and 131 for details).
- 94** The relation of naevi to a raised risk of melanoma might occur because naevi may be a more accurate marker of carcinogenic sun exposures than is given by questionnaire responses, or because naevi may be an intermediate step by which the solar radiation aetiology of melanoma operates.
- 95** Naevus numbers also appear to have a large genetic component, and it may be that their presence indicates that genetic factors predisposing to melanoma are present. The study of Easton *et al.* (1991) from the UK of 45 twin pairs (23 monozygotic, MZ, and 22 dizygotic, DZ) showed a highly significant correlation for MZ twins of naevus counts for naevi over 3 mm (0.83) but no such correlation for DZ twins (-0.24); the MZ findings suggest a high degree of heritability. This has recently been confirmed by Bataille *et al.* (2000), who showed in a separate population of UK twins a correlation of 0.83 for MZ twins and a correlation of 0.61 for DZ twins. In Queensland, Australia, Zhu *et al.* (1999) have studied 12 year old twin pairs and in that environment showed similar results, with a correlation of naevus counts of 0.94 for MZ and 0.60 for DZ twins.
- 96** The great majority of melanocytic naevi in man can be divided on pathological grounds into junctional, compound and intradermal naevi, depending on the exact site

of the naevus cells. A small proportion of melanocytic naevi are described as dysplastic because of pathological features suggesting that the naevus cells are not totally benign and may have the potential to progress to melanoma. The term atypical naevi describes melanocytic naevi that are greater than 5 mm in diameter with an irregular edge, irregular pigmentation, and sometimes also a degree of inflammation.

Epidemiological studies of malignant melanoma and UVR

- 97** Although malignant melanoma is far less common than NMSC, it accounts for the majority of skin cancer deaths, and hence is the most serious health consequence of excessive exposure to solar radiation in white populations. Furthermore, the incidence of melanoma has been rising over many decades. In England and Wales it now constitutes 9% of cancers incident at ages 20 to 39 years and 5% of cancer deaths at these ages, based on the most recent data published – 1993 for incidence and 1998 for mortality; the cumulative incidence to age 75 years, based on current age-specific registration rates, is 0.48% in men and 0.66% in women (Parkin *et al.* 1997). A wide range of evidence from both descriptive and individual-based, analytical epidemiological studies, indicates that solar radiation exposure is a major aetiological factor for cutaneous melanoma in white people. The only other factors, apart from genotype and phenotype, for which there is substantial evidence of an aetiological association are organ transplantation and previous Hodgkin's disease (van Leeuwen *et al.* 1999).

Sex and age

- 98** In most white populations melanoma incidence is greater in women than in men at ages under about 60 years, and is fairly similar between the sexes, or greater in men, at older ages. In England and Wales, the female excess is particularly marked and persists into old age (Figure 7.11). This sex ratio scarcely accords with the extent of occupational sun exposure in the two sexes, but might be compatible with the extent of intermittent recreational exposures.
- 99** Head and neck melanoma and lentigo malignant melanoma increase in incidence progressively with age, as would be expected if risk is related to cumulative solar radiation exposure. For melanoma of the trunk and limbs, however, incidence increases up to middle age and thereafter increases little or even falls. This age curve in cross-sectional data (ie data for one point in time) is partly the result of a birth cohort effect (ie that more recent generations have had greater incidence rates at each age through life than had earlier generations), but this is not the whole explanation, as a decrease in the rate of rise with increasing age has also been shown within birth cohorts. This age distribution would be compatible with aetiological factors that occur less at older ages than at younger (as is likely to be the case for sunbathing and other recreational UVR exposures), and/or with greater susceptibility to exposure at young than at older ages.

Geographical distribution

- 100** The incidence of cutaneous melanoma in white populations, internationally and also within countries, generally increases with decreasing latitude. The highest recorded incidence has been in Queensland, Australia, at 53.9 per 100 000 population per year in men and 41.1 per 100 000 in women in 1996, age-standardised to the 'World' Standard

Population (Queensland Cancer Registry, 1999). These rates are, respectively, twelve times the rate recently recorded in men in England and Wales and six times the rate recorded similarly in women. In certain countries greater rates have been found in coastal areas than inland, and in North America geographical correlations have been shown between melanoma rates in white populations and measured or estimated UVR levels. Across Europe, however, the opposite gradient applies - rates have been high in Scotland and Scandinavia and relatively low in Southern Europe. Possible explanations for this are the gradient of skin pigmentation across Europe and perhaps that in recent decades North Europeans have experienced particularly intermittent exposures to UVR by taking sun holidays further south.

Risk in migrants

- 101** The risk of melanoma in white migrants from less to more sunny areas - for instance, immigrants to Australia from Britain and to Israel from Europe - have been lower than in natives of the host areas, and in Israel and Australia rates have been found to increase with duration since migration and to be greater in individuals who migrated young than those who migrated at older ages. The effect of age at migration is considered further below when discussing UVR effects in relation to age.
- 102** There are fewer data on the risk in migrants in the opposite direction (ie from high to low irradiation areas), and these show greater risk in the migrants than in the natives of the host areas.

Time trends

- 103** Melanoma incidence rates have been increasing in white populations for many decades, and mortality rates too have been increasing, although at a less rapid pace than incidence. Recent data from Scotland have shown a doubling of incidence in males and almost a doubling in females from 1979 to the late 1980s, with an apparent stabilisation thereafter (MacKie *et al*, 1997), and an increase in mortality in men but not women over this period. An active public education campaign encouraging earlier diagnosis of melanoma had occurred in the mid-1980s. Over a longer period, from 1960-64 to 1985-90, incidence in Scotland quadrupled in each sex, while from 1953-54 to 1990-93 mortality in each sex more than doubled (Swerdlow *et al*, 1998). In England and Wales, melanoma incidence tripled in men and more than doubled in women from 1971-74 to 1990-92, while mortality tripled in men and more than doubled in women from 1960-64 to 1995-97 (Swerdlow *et al*, 2001). A Swedish study examining incidence at ages 12 to 19 years found that rates had more than doubled from 1973-82 to 1983-92, and a pathology review confirmed that this was not due to dilution in pathological criteria over time (Karlsson *et al*, 1998).
- 104** Across Western European countries from 1970-90, mortality from melanoma has increased more in southern than in northern countries (Balzi *et al*, 1997), and in the USA the gradient of mortality with latitude has been decreasing over recent decades (Lee, 1997). In many Western countries skin cancer death rates in adults aged under 65 years (which have largely been due to cutaneous melanoma), increased for the 30 years from 1955-85, but showed a lesser rate of increase, or even a decline, over the decade from 1985-95, especially at younger ages (La Vecchia *et al*, 1999). A recent study from Belgium, however, showed large increases in melanoma mortality in each sex from

1954–92, with no stabilisation of rates yet apparent (Bleyen *et al.* 1999). Mortality data from Australia show a steady increase from 1931–85, but from 1985–94 all-age rates stabilised in females and less clearly in males, and at young ages there were decreases (Giles *et al.* 1996). In Queensland, where there had been a large health education effort in the 1970s, rates in women peaked in the late 1970s (Giles *et al.* 1996).

- 105** The increases in melanoma incidence internationally have generally been greatest for tumours of the trunk in men and lower limb in women, while there have been small increases or none for melanomas of the head and neck and, where such data have been available separately, for melanomas of the foot. This pattern has been present also in recent British data. In Scotland (Swerdlow *et al.* 1998) there were more than seven-fold increases in incidence from 1960–64 to 1985–90 for trunk melanoma in men and upper limb melanoma in women, and in England and Wales there was a four-fold increase for trunk melanoma incidence in men and more than a two-and-a-half-fold increase for upper limb melanoma in women from 1971–74 to 1990–92 (Swerdlow *et al.* 2001).
- 106** The lesser increases for melanoma of the head and neck than of more intermittently-exposed sites would accord with the view that intermittent rather than cumulative exposure has been the cause of the increasing incidence in melanoma overall. Data are lacking, however, on the relative changes in intermittent exposure over time for different clothed sites (trunk, lower limbs and upper limbs) by sex, to judge whether the sex-specific changes in melanoma at these sites accord in detail with the degree of change in exposure.
- 107** Melanoma rates do not appear to be increasing in black populations. The difference between trends in white and black populations may accord with solar radiation aetiology.
- 108** The increase in melanoma rates in white populations has generally followed a birth cohort pattern, ie in each succeeding generation rates have been higher through life than were the rates in the preceding generation. This implies that either the major aetiological factors act at an early age to affect lifetime risk, or behaviours are acquired early in life that are perpetuated and hence affect continuing risk. In several white populations the rate of increase in mortality has slowed in recent cohorts, and in some the trend has actually reversed. Such data for the USA and Sweden were noted in the previous Advisory Group review (NRPB, 1995), and recent publications show this for further countries. In Scotland, cohort-based increases in mortality occurred in generations of men born up to 1930–34 and women born up to 1920–24, but there was no clear trend for cohorts born subsequently (Swerdlow *et al.* 1998). Increases in incidence occurred in women through to the most recent cohorts, but in men there was only a slight increase for those born after 1930–34. In England and Wales, there were large increases in incidence in cohorts born before 1920, and lesser increases in cohorts born subsequently, and increases in mortality for cohorts of men born up to the 1940s and women born up to the 1920s, with decreases in each sex for cohorts born since 1950 (Swerdlow *et al.* 2001). In Australia, mortality rates in men rose up to the cohort born in 1930, were stable for those born from 1930 to 1950, and then fell in more recent cohorts; a similar pattern was present for women, but with the inflexion points about five years earlier (Giles *et al.* 1996).
- 109** Although part of the increase in recorded incidence of melanoma in white populations may relate to increases in presentation and biopsy of suspicious lesions, and to more complete diagnosis of melanoma including borderline malignant lesions, it

is clear that, in addition, there has been a substantial real increase in incidence. In particular, the rising mortality rates over several decades provide evidence in favour of this. While data are not available on trends in cumulative UVR exposure in white populations, the prevalence of outdoor occupations has decreased and the available evidence does not suggest there has been any appreciable increase in ambient UVR flux (see Chapter 2). The most plausible explanation hypothesised for the rise in melanoma incidence has been that it is due to a rise in intermittent recreational exposure to the sun. Although there are insufficient data to know whether changes in such exposure can specifically account for the detailed changes in melanoma incidence by skin site, sex and age, there have certainly been large changes over time in the degree of skin exposure considered socially acceptable during recreation and in the social desirability of appearing tanned. Moreover, data, in the UK at least, show large increases in overseas 'sun holidays' and indoor work and, in recent years at least, in outdoor recreation (Swerdlow *et al.* 2001).

Seasonal variation

- 110** Seasonal variation in rates of melanoma incidence has been recorded, with greater rates in the summer than winter months in both the northern and southern hemispheres. This would be consistent with a rapid, short-term promotional effect of summer sun exposure on melanoma development, but it might also reflect more rapid detection of tumours in summer. Interpretation is therefore uncertain. A finding in an Australian study that seasonal variation occurs in the degree of junctional activity of naevi (Holman *et al.* 1983) would favour a biological explanation for the summer excess.

Occupation

- 111** In routinely collected data, the risk of melanoma overall has been found greater for people with indoor occupations than those with outdoor occupations (and for those in high social classes, who tend to be indoor workers, than in lower social classes, who more often work outdoors). The risk of head and neck melanoma, however, has been greater in outdoor than indoor workers. Analyses in past case-control studies of risks in outdoor versus indoor occupations and in relation to the extent of outdoor work have given less consistent results than the routine data, and this has been true also in recent publications. In Andalusia, Spain, an increased risk of melanoma was found with occupational sun exposure (Rodenas *et al.* 1996), while in another Spanish study, farm work was found to be significantly protective (after adjusting for phenotype) but construction work was found to give a significantly increased risk (Arranz *et al.* 1999). In a meta-analysis of studies of farmers, melanoma risk was non-significantly decreased (Khuder, 1999) (the comparison group was not made explicit, but was presumably either the general population or the working population). In Sweden, outdoor occupation was associated with a decreased risk of melanoma of the extremities (Måsbäck *et al.* 1999) and in the USA with a decreased risk of melanoma of the extremities and head and neck (Chen *et al.* 1996), while in Italy and Austria there was no relation of risk of melanoma to occupational sun exposure (Rosso *et al.* 1998; Wolf *et al.* 1998). It should be noted that the exposure implications of outdoor work are likely to vary considerably between countries because of differences in the ambient UVR levels experienced, the clothing normally worn, the degree to which the general population has a year-round tan, and the degree of pigmentation of the population concerned.

Skin site distribution and patterns of clothing

- 112** In most white populations the most common site of melanoma incidence in men is the trunk and in women is the lower limbs, but there is a considerable incidence also on all other major parts of the body (upper and lower limbs, trunk, head and neck). Lentigo maligno melanoma tends to occur primarily on the head and neck. When assessed per unit of body area, the incidence of cutaneous melanoma overall is greater on usually-exposed parts of the body, such as the face, and intermittently-exposed areas, such as the back, than on unexposed areas, such as the genitalia and buttocks. The large proportion of melanomas occurring on intermittently-exposed skin sites has been taken as evidence for the intermittent exposure theory of aetiology. The greater UVR dose received by the trunk and limbs when lying (eg sunbathing or swimming) than when standing (eg when working) also accords with the intermittent recreational exposure hypothesis. It is possible, however, that solar radiation exposure could affect melanoma risk on less exposed sites systemically, by a 'solar circulating factor'. In support of this, it has been found experimentally that UVR exposure in man can cause melanocyte proliferation in shielded as well as exposed skin. The high incidence of melanoma in proportion to skin area on the face might indicate the importance of cumulative solar radiation exposure to aetiology.
- 113** There is a greater incidence of melanoma on the back in men than in women, and on the lower limb in women than in men. The lower limb difference, at least, might correspond with differences in everyday dress. Stronger evidence for sun-exposure aetiology comes from the far greater male to female incidence ratio of melanoma on the scalp and the ears than on the face, and the far greater female to male ratio for the lower leg than for the thigh and foot. The protective effects of clothing and sun avoidance are illustrated by findings in Israel of lower incidence of melanoma in Jews living in Orthodox than non-Orthodox neighbourhoods (Vardi *et al*, 1993); adult Orthodox Jews wear heavy clothes that cover virtually all of their body.
- 114** In an Australian case-control study (Holman *et al*, 1986) the risk of melanoma on the trunk was greater in women who had worn a two-piece bathing costume or bathed nude than those who had worn a one-piece costume, but more recent studies have not found an effect of type of swimsuit (Chen *et al*, 1996).

Ethnic distribution

- 115** Melanoma incidence rates are much greater in white than non-white populations living in the same geographical area (Parkin *et al*, 1997). Within white people, incidence rates are greater in non-Hispanic than Hispanic populations in the USA. In case-control studies in Canada and Australia, risks have been greater in white people of North European than those of South or East European origin, and sometimes have been greater in those of Celtic origin than in other whites.

Host characteristics in white people

- 116** A high risk of melanoma in people with light skin (melanin absorbs UVR), red or blond hair, blue eyes, and a tendency to burn and not tan on sun exposure has been shown in numerous past studies (NRPB, 1995), and recent data (Arranz *et al*, 1999; Austin and Reynolds, 1997; Chen *et al*, 1996; Lock-Anderson *et al*, 1999; Rodenas *et al*, 1996; Rosso *et al*, 1998; Wolf *et al*, 1998; Whiteman and Green, 1998), including a study of melanoma in children in Australia (Whiteman *et al*, 1997), have generally shown these relations too. In the literature overall, relative risks for blond or red hair compared

with dark hair and for blue compared with brown eyes have been around two or three. A study examining risk factors separately for *p53*-negative and -positive melanomas found that a tendency to burn and not tan in the sun was associated specifically with the latter (Whiteman *et al.* 1998). A study of acral melanoma (mainly of the soles of the feet) found that sun-sensitive complexion was a risk factor for these tumours too (Green *et al.* 1999b). Experimental studies have shown a lower minimum erythral dose, and more prolonged erythema persistence, in melanoma patients than in controls.

- 117** As patients with albinism have reduced or absent melanin pigmentation but a normal number of melanocytes, they might be expected to be at increased risk of melanoma. Although several cases of melanoma in albino patients have been reported, it is not known whether the risk is raised; no epidemiological studies of this question appear to have been published.
- 118** Based on case reports, there appears to be a considerably raised risk of cutaneous melanoma in patients with xeroderma pigmentosum, who have a genetic defect in repair of UVR-induced DNA damage. Studies in Britain also suggest a greatly raised risk. Three melanomas were known to have been incident in 48 patients in a study that ascertained XP patients from reports to the investigators by clinicians (Pippard *et al.* 1988) and 3 of 32 patients in a cohort of XP patients ascertained at two British hospitals were known to have developed melanoma (English and Swerdlow, 1987). There was one death from melanoma (less than 0.01 expected) in the former study and none (0.001 expected) in the latter. There may have been some overlap between the subjects in the two studies.
- 119** The risk of melanoma is also raised in individuals who have a tendency to freckle, and, as noted earlier, those with large numbers of naevi, and with atypical/dysplastic naevi - associations that have been shown in numerous past studies (NRPB, 1995) and confirmed in several recent ones (Austin and Reynolds 1997; Chen *et al.* 1996; Green *et al.* 1999b; Kelly *et al.* 1997; Måsbäck *et al.* 1999; Rodenas *et al.* 1996, 1997; Tucker *et al.* 1997; Whiteman *et al.* 1997; Whiteman and Green, 1998; Wolf *et al.* 1998). A recent Australian study suggests that these factors are associated particularly with *p53*-negative melanoma (Whiteman *et al.* 1998).

Sun exposure

- 120** The above characteristics of melanoma epidemiology give strong reason to believe that solar radiation exposure is a major risk factor for cutaneous melanoma, and the findings cannot be explained by any other hypothesis currently available. Solar radiation aetiology of melanoma is also plausible because melanocytes are situated in the epidermis and exposed to solar radiation, and such radiation is known to be carcinogenic in man. The findings do not show clearly, however, what pattern of sun exposure, or age at exposure, is important, and evidence on these issues is much less conclusive.
- 121** Various aspects of melanoma epidemiology, for instance its sex, age, and anatomical site distribution, militate against a simple linear relationship of melanoma risk to cumulative dose of sun exposure, except perhaps for head and neck melanoma and lentigo maligna melanoma*. These aspects of the epidemiology indicate that it may be the pattern rather than the total dose of solar radiation exposure that is most important to melanoma risk, and have led to a hypothesis that the critical aetiological

* Also, for melanoma of rarely exposed skin sites there is insufficient evidence to assess the relation of risk to sun exposure, but any effect would presumably have to be largely or entirely systemic - a recent report of an association of acral, mainly plantar, melanoma with extensive lifetime sun exposure (Green *et al.* 1999b) is intriguing in this respect.

exposure is intermittent (generally recreational), intense solar radiation exposure of untanned skin. Under this hypothesis, tanning (and skin thickening consequent on prolonged outdoor exposure) would give protection against the carcinogenic effects of solar radiation on melanocytes, and hence a relatively low risk would be associated with chronic, continuous sun exposure. Although most of the epidemiological evidence below fits best with this interpretation, there is some evidence that fits better with cumulative dose as an aetiological factor. It may well be that both are aetiological, with intermittent, intense exposure being more important for intermittently-exposed skin sites, superficial spreading melanoma and nodular melanoma, and being responsible for the increasing rates in white populations, and cumulative exposure being the predominant aetiological factor for 'permanently' exposed sites and lentigo maligna melanoma.

122 Over 30 case-control studies have now published data on the relationship of sun-exposure histories, obtained by interview, and the risk of melanoma. Details of the design and results of the earlier studies can be found in IARC (1992) and Elwood and Jopson (1997), and more recent studies are referenced below. These studies have incorporated questions in varying degrees of detail on time spent outdoors in work, recreation and vacations, history of sunburn, and type of clothing and use of sunscreens. There is considerable potential, however, for misclassification in lifetime recall of these factors. To the extent that this misclassification is not biased, it will tend to diminish the apparent strength of any real relationship of melanoma risk with solar radiation exposure. There is also the potential for recall bias, however, particularly in more recent studies as the sun-exposure aetiology hypothesis has become widely known.

123 For melanoma risk in relation to history of *cumulative exposure* to the sun over a lifetime or over long periods, studies have not shown consistent results. In several instances they have found no significant relationship; where significant relationships have been found they have not been in a consistent direction (Austin and Reynolds, 1997; NRPB, 1995; Rodenas *et al.* 1996; Rosso *et al.* 1998; Whiteman *et al.* 1997). A systematic overview of studies published before 1997 found a small, marginally significant, raised risk in relation to greater total exposure (Elwood and Jopson, 1997). However, case-control studies examining the relationship of cutaneous melanoma risk to biological indicators of cumulative sun exposure (actinic skin damage on cutaneous microtopography, and history or presence of actinic keratoses or NMSCs) have generally found substantial significant positive relationships (Austin and Reynolds, 1997; NRPB, 1995; Rodenas *et al.* 1996), suggesting that cumulative sun exposure does have a role in aetiology. A recent study found the relation to past NMSC was specifically for *p53*-positive melanoma (Whiteman *et al.* 1998). As the biological markers should not suffer from the extent of misclassification likely in recall histories of sun exposure, they might give more reliable evidence on the relation of melanoma to cumulative sun exposure than do the history data. This is uncertain, however, because the biological markers will in part depend on phenotype, and also they may be affected by intermittent acute as well as cumulative chronic UVR exposures: for instance, a report has described an apparent link between sunbed use and the incidence of actinic keratoses (Speight *et al.* 1994).

124 Case-control studies of the relation of reported *intermittent sun exposure* to melanoma have generally shown positive associations with the extent of activities such as sunbathing, boating, and holidays in sunny places, or with recreational exposures overall, although the magnitude of the effect has not usually been large. In recent investigations, positive associations with outdoor recreational exposure have been

found in studies in Spain (Arranz *et al.* 1999; Rodenas *et al.* 1996), Italy (Rosso *et al.* 1998) and the USA (Chen *et al.* 1996), and a case-control study in Belgium, Germany and France found a positive relationship to sun holidays (Autier *et al.* 1998a). However, a case-control study in children in Australia found no relation to sunbathing or vacations on the beach (Whiteman *et al.* 1997) and an Austrian case-control study found a significant decrease in risk with greater leisure exposure (Wolf *et al.* 1998). There are several reasons why relative risks might vary between the studies and why apparently small elevations in relative risk could be compatible with substantial real effects:

- (a) there is likely to be appreciable misclassification in the recall of exposures (see above),
- (b) individuals who are sensitive to solar radiation may alter their behaviour in order to reduce exposure (because they burn easily),
- (c) repeated recreational sun exposure will lead to tanning, which is hypothesised to protect against melanoma,
- (d) the UVR dose received from outdoor recreations will vary greatly according to latitude, climatic conditions, and season.

125 It is also possible that the effect of UVR may differ by phenotype, and therefore be less apparent in analyses in which all phenotypes are combined. For instance, in an American study of trunk melanoma in women, the risk in relation to frequent wearing of swimsuits when outdoors at ages 15–20 years was significantly six-fold raised in women of sun-sensitive phenotype, but there was a borderline significant protective effect for the same variable in sun-resistant phenotypes (Weinstock *et al.* 1991); the interaction was highly significant. Further complicating interpretation of the literature on melanoma in relation to the type of sun exposure, it should be noted that while recreational sun exposure is likely generally to be more intermittent than is occupational exposure, this difference may vary by latitude, and an increase in recreational exposure will contribute to an increase in cumulative as well as intermittent exposure dose.

126 There is evidence of two main types suggesting that the *age at solar UVR exposure* may be important to melanoma risk. First, there have been the results of studies asking about sun exposure and/or sunburn at different ages. Second, there have been studies of risk in migrants between areas of low and high insolation, or vice versa, at different ages of migration. The studies of sun exposure and sunburn histories have generally, but not always, found greater risk in relation to childhood than adult exposures (IARC, 1992; NRPB, 1995), but these findings are based on recall that has great potential for misclassification, and bias. A recent such study from Belgium, France and Germany (Autier *et al.* 1997, 1998a) found an increased risk in relation to the lack of sun protection on holidays, and that childhood exposures had an effect within strata of adult exposure levels. An Italian study showed effects of both childhood and adult beach holidays (Rosso *et al.* 1998), while an Australian study of childhood melanoma found no relation of risk to sunbathing or vacations on the beach (Whiteman *et al.* 1997).

127 With less potential for misclassification, an American investigation found a greater risk of melanoma in servicemen who had served in the tropics than in those who had served in the American or European theatres of the Second World War, implying that a period of high exposure in early adult life can have a long-term effect on melanoma risk (Brown *et al.* 1984). In men in Queensland, Australia, however, no increase in risk was

found for military service in the tropics, perhaps because background UVR exposure in Queensland is very high (Whiteman and Green, 1998). A cohort study of college graduates in the USA (Paffenbarger *et al* 1978), the design of which should have ensured that recall bias was not a problem, found a significantly increased risk of melanoma for graduates who had outdoor work (presumably short-term) before college, although no information was available on subsequent exposures.

128 Another source of data on childhood exposures has been studies of the risk of melanoma in relation to migrant status. A case-control study in Western Australia (Holman and Armstrong, 1984) showed a substantially lower risk of melanoma in immigrants after age 15 years than in native-born Australians, but risks at or above native rates for those migrating earlier than age 10 years, implying that early exposures may be critical to risk. An analogous risk differential was seen in New Zealand, where migrants from Britain before age 30 years had melanoma mortality rates similar to native non-Maori New Zealanders, whereas migrants at later ages had a much lower risk (Cooke and Fraser, 1985). Similar results have been found also for American migrants from low UVR areas to Los Angeles (Mack and Floderus, 1991), and a raised risk for childhood residence in areas of high insolation has been shown in Europe (Autier *et al* 1997, 1998a). In a nested case-control study of nurses in the USA (Weinstock *et al* 1989), residence at low latitudes at ages 15–20 years was significantly associated with a raised risk of melanoma, but latitude of residence after age 30 years was not. Recall bias is not a plausible explanation for these findings, which indicate that some aspect of residence at low latitudes in youth, most plausibly solar radiation exposure, is related to risk. This does not necessarily mean that childhood exposure is intrinsically more hazardous than later exposure, however. It might be that children act less cautiously and/or spend more time outdoors, and hence obtain more exposure than adults, or that the induction period of effect of UVR is long and hence childhood exposures are those relevant to young adult melanoma incidence, or that childhood exposures matter because they increase cumulative exposure (Swerdlow, 2000). Whichever the reason, however, it would seem wise for preventive campaigns to emphasise childhood sun protection.

129 Several case-control studies have investigated melanoma risk in relation to *history of sunburn*. Interpretation is not easy because the likelihood of sunburn depends on both skin sensitivity and sun-exposure behaviour, and it is difficult to distinguish the separate effects of these. Even if there is a relation to sunburn rather than to the skin type susceptible to sunburn, it would remain an open question whether this represented an aetiological effect of the sunburn itself or whether the burn was simply a marker of intense, intermittent exposure. Furthermore there is considerable potential for recall bias in histories of sunburn, particularly when the histories relate to childhood episodes occurring several decades before the interview.

130 In most instances studies have shown positive associations of risk with sunburn history, generally with relative risks around two to three in the highest sunburn group analysed (Chen *et al* 1996; Måsbäck *et al* 1999; NRPB, 1995; Rodenas *et al* 1996; Rosso *et al* 1998; Wolf *et al* 1998). In analyses adjusting for skin sensitivity or pigmentation type, some studies have found the sunburn relationship to reflect mainly these host factors, while others have shown a substantial residual effect of sunburn (NRPB, 1995). Certain studies have shown greater relative risks in relation to sunburn at young ages

than at older ages (NRPB, 1995; Rodenas *et al.* 1996; Rosso *et al.* 1998), although in others there was little or no such effect (NRPB, 1995), and a systematic overview found similarly raised relative risks for sunburn in adult life, adolescence, and childhood (Elwood and Jopson, 1997). A recent study found that a history of sunburn at specific anatomical sites related more closely to the risk of melanoma at the same site than at other sites (Chen *et al.* 1996); this is the pattern, however, that might be expected from recall bias, as well as the pattern that would accord with aetiology, and an earlier study found no specific association between site of sunburn and of melanoma (Green *et al.* 1986).

Sunscreens and melanoma risk

131 Several case-control studies have found a raised risk of melanoma in relation to reported use of sunscreens (Autier *et al.* 1995; Westerdahl *et al.* 1995; Wolf *et al.* 1998), even after adjustment for several phenotypic and sun-exposure variables. In one study the risk was particularly large for self-reported use of psoralen-containing sunscreens* by individuals with a poor ability to tan (Autier *et al.* 1995). A study in Queensland found a raised risk of childhood melanoma, after adjustment for phenotypic variables, in relation to sunscreen use on holiday but not sunscreen use at school (Whiteman *et al.* 1997). Other studies, however, in adults in the USA (Holly *et al.* 1995) and Spain (Arranz *et al.* 1999), have found a significantly decreased risk of melanoma associated with sunscreen use, after adjustment for phenotype and sunburn or sun exposure. In data from Canada the risk was similar in heavy users of sunscreen to those with the lowest use, after adjustment for sun exposure and phenotype, but was raised in those who used sunscreens only for the first few hours of exposure (Elwood and Gallagher, 1999). Recent studies of naevus counts in European children have found the highest counts (Autier *et al.* 1998b) and greatest increases in counts with age (Luther *et al.* 1996) associated with high levels of reported sunscreen use, although it should be noted that in the trial of sunscreen use in children described earlier (see paragraph 93) a protective effect was found.

132 Interpretation of results on sunscreens and the risk of melanoma is difficult because there is a potential for bias in the recall of sunscreen use and there is also a great potential for confounding. The latter pertains because propensity to use sunscreens is likely to be closely related to sun-response phenotype (notably whether the individual burns easily) and to type of sun exposure (for instance, whether the exposure is undertaken to gain a tan, and how hot the weather is) and these potential confounders are measured only very crudely by the variables used to conduct adjustment in the published studies†. Furthermore, the use of sunscreens may well induce a (false) sense of security and encourage individuals to spend longer exposed to the sun than they would without the sunscreen available. Thus even if the sunscreen is used properly (see Chapter 12, paragraphs 27–30), the total dose of UVR received might be raised in sunscreen users because of changes in exposure behaviour. Also it is unclear to what extent individuals know and can remember over long periods their extent and type of

* Such sunscreens have not been available in the UK since 1978.

† The contrast between the observational and trial results on the effects of sunscreen use in children on naevus numbers is highly suggestive of such confounding, which would not apply in the randomised groups in the trial.

sunscreen use, particularly if they change brands frequently. Overall, the relation of sunscreen use to melanoma is inconsistent in the epidemiological literature, and interpretation is further made difficult by potential confounding and uncertainty on UVR exposures.

Artificial sources of UVR

- 133** The wavelength spectra of different artificial UVR sources vary, and hence analyses of risk in relation to type of artificial source exposure have the potential to clarify the wavelengths aetiological for skin cancers, as well as having importance in relation to potential prevention of these malignancies.

Fluorescent lights

- 134** Fluorescent lights were at one time suggested as a potential cause of melanoma (Beral *et al*, 1982), but the subsequent literature has not supported this (NRPB, 1995).

Sunlamps and sunbeds

- 135** UVR lamps and beds are used for cosmetic purposes, to gain a tan ('sunlamps' and sunbeds), and also therapeutically for psoriasis and other skin diseases, as well as in the past for the treatment of tuberculosis and before about 1980 as non-specific 'health lamps', which emitted short-wave UVB. The latter lamps were withdrawn, and throughout the 1980s and 1990s the main source of recreational artificial UVR was beds or upright cabins fitted with lamps emitting almost exclusively in the UVA range. At the time of writing, however, there is a move to increase the relative quantity of UVB output in these appliances to make the output more similar to that of natural sunlight. The current outputs of sunbeds in the West of Scotland are described by McGinley *et al* (1998) (see Chapter 2, paragraph 21).

- 136** More than 20 case-control studies have now reported on history of sunlamp use in relation to melanoma risk (Arranz *et al* 1999; Chen *et al* 1998; Swerdlow and Weinstock, 1998; Westerdahl *et al* 2000; Wolf *et al* 1998). Although eight of these studies have found a significant relation for some aspect of sunlamp use (Chen *et al* 1998; Swerdlow and Weinstock, 1998; Westerdahl *et al* 2000), in certain instances with dose or duration-response relations (Swerdlow and Weinstock, 1998; Westerdahl *et al* 2000) or raised risk for exposure at young ages (Chen *et al* 1998; Swerdlow and Weinstock, 1998; Westerdahl *et al* 2000), the literature overall has been inconsistent, and methodological weaknesses of the studies leave the relation uncertain. For instance, the studies give no information on the intensity and spectral outputs of the lamps, which can vary considerably and might lead to variation in any true association; the histories of exposure have scope for recall bias; adjustment for confounding was often lacking, especially adjustment for recreational sun exposure; lastly the studies often had low power. Furthermore, because widespread use of sunbeds is a relatively recent phenomenon, most of the studies were only able to examine potential short induction period effects. Methodologically more-stringent studies are needed, with an assessment of the output of sunbeds, where possible, and an examination of potential longer induction period effects. Ideally, future research would include cohort studies, although the practical problems of these would be formidable. Given the widespread and increasing use of sunbeds in recent years, especially at young ages, and the similarity of the exposures to those believed to be aetiological for melanoma from solar

UVR (intermittent, intense exposures of skin sites that are not usually exposed in everyday life), there is reason for concern and a need to clarify the relationship.

- 137** It has been observed that mutagenic DNA is generated in human fibroblasts after exposure to artificial tanning lamps (Woollons *et al.* 1997). If this work is confirmed using normal human melanocytes rather than fibroblasts, it adds to the concern with regard to artificial tanning exposure and melanoma risk.

Therapeutic UVR

- 138** Until 1997, a raised risk of melanoma had not been found in cohort studies of patients treated with PUVA, although there had not been sufficient data to estimate the risk with precision. In a North American cohort study of 1380 patients first treated with PUVA in 1975 or 1976 (Stern *et al.* 1997), however, a significantly increased risk of malignant melanoma was reported at 15 and more years of follow-up in patients who had received 250 or more PUVA treatments. This result needs cautious interpretation for several reasons (Swerdlow and Weinstock, 1998). For instance, the analytical categories were stated to have been defined by examination of the pattern of melanoma incidence in the data; there was no adjustment for several potentially confounding variables, notably UVR exposures other than PUVA; three of the eleven melanomas occurring in the cohort were in the same patient and were counted as separate incident cases in the analysis.

- 139** Subsequently, a Swedish cohort study of 4799 patients who had received PUVA treatment between 1974 and 1985 was published (Lindelöf *et al.* 1999), with an average follow-up period of 15.9 years from first treatment for men and 16.2 years for women, which found no increased risk of melanoma in the follow-up period overall or the period 15–21 years. Thus the relation of PUVA to melanoma risk remains uncertain but of concern, and patients who have received PUVA need careful monitoring.

- 140** Cases of melanoma have been reported after dermatological treatments that include UVB (Maughan *et al.* 1980; Pittelkow *et al.* 1981), but is not clear whether a raised risk occurs.

Occupational exposure

- 141** Occupational exposure to artificial UVR sources other than lighting occurs in many circumstances, eg in arc welding and the use of arc lamps in food processing (see Chapter 2). One study has reported a borderline significantly raised risk of melanoma in relation to any such exposure (Elwood *et al.* 1986); another found no relation, based on small numbers (Holman *et al.* 1986).
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PHOTOSENSITIVITY DISORDERS

- 142** Photosensitivity disorders are a wide range of conditions of differing aetiology associated with abnormal cutaneous responses to UVR and/or visible radiation. They can be provoked by sunlight and artificial light sources, and present with clinically diverse symptomatology (see Figure 7.16a–h). Photosensitivity conditions can be broadly divided into the genodermatoses, the idiopathic (presumed immunological) photodermatoses, biochemical disorders (principally the porphyrias), and drug and chemical photosensitivity. There are also many conditions that can be aggravated by UVR, the so-called 'photoaggravated disorders'.



*FIGURE 7.16
Photosensitivity
illustrations*

*(a) Polymorphic
light eruption -
multiple small
papules and vesicles
on light-exposed
skin*



*(b) Chronic actinic
dermatitis - an acute
eczematous
eruption is present
on the face and neck,
with a sharp cut-off
where skin is
protected by the
shirt collar*

FIGURE 7.16
Continued

(c) *Solar urticaria* - an immediate intensely itchy wheal and flare reaction occurs following minimal exposure to sunlight or artificial radiation sources



(d) *Chronic discoid lupus erythematosus* - red scaly lesions occur on exposed sites, particularly on the face, resolving to leave scarring





FIGURE 7.16
Continued

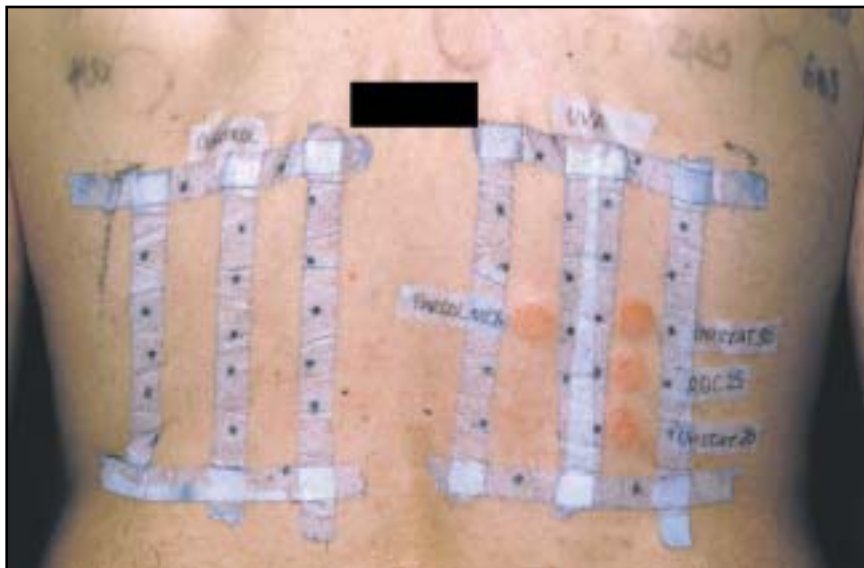
(e) Subacute lupus erythematosus - large, superficial plaques are present on the upper chest



(f) Drug photosensitivity - the patient has become photosensitive following treatment with an oral thiazide (diuretic medication)

FIGURE 7.16
Continued

(g) Photocontact allergy - the subject has reacted to the combination of sunscreen Parsol 1789 and UVA and to the creams containing this sunscreen (right side of back). There is no reaction at the control sites, where sunscreen is applied without UVA (left side of back)



(h) Xeroderma pigmentosum - severe actinic damage and multiple cancers on exposed skin treated with surgery



Genodermatoses associated with photosensitivity

- 143** Genodermatoses are conditions commonly inherited from parent to child, although the exact mode of inheritance determines how many children in the succeeding generation will be affected. Occasionally genodermatoses appear in an individual with healthy parents, due to a new mutation in that individual's DNA. There are a number of rare autosomal recessive disorders in which DNA repair processes are defective, principally xeroderma pigmentosum (XP), Cockayne's syndrome (CS), Trichothiodystrophy (TTD) and Bloom's syndrome (BS) (see Chapter 4, paragraphs 9–12). They are characterised by various degrees of photosensitivity, accompanied by increased susceptibility to skin cancer in the case of XP and BS, and increased susceptibility to internal cancers in BS.
- 144** The absence of an association with skin cancer of CS and TTD, which in some cases have the same DNA repair defect as XP, is not currently understood.

Xeroderma pigmentosum

- 145** Xeroderma pigmentosum (XP) is a rare but important genodermatosis, affecting approximately 1 in 250 000 of the population worldwide (Norris and Lehmann, 1998). The condition is determined by autosomal recessive transmission, but sporadic mutations are relatively common. It is associated with an extreme degree of photosensitivity, caused by an inability to repair DNA after UVR exposure.

Pathogenesis

- 146** Approximately 75% of cases have classic XP, associated with a defect of nucleotide excision repair (NER) (for review, see Copeland *et al.* 1997). Complementation tests have detected seven groups with identifiable defects in excision repair, ie complementation groups A–G (Hoeijmakers, 1993). The remaining 25% of cases are an excision-proficient variant, with a poorly characterised abnormality of post-replication repair. The distribution of complementation groups is uneven, with groups A, C, D and variant being the most common in Europe.

Action spectrum

- 147** Phototesting must proceed cautiously in view of the severity of photosensitivity. Most cases show low erythral thresholds to UVB, with abnormal prolongation of the erythema for several days (Cripps *et al.* 1971; Ramsay and Gianelli, 1975).

Clinical features

- 148** Patients with XP present in the first or second year of life with severe and prolonged sunburn taking several days to settle, after even minimal sun exposure (Kraemer and Slor, 1984). If the defect is not recognised and the child is vigorously protected from even minor UVR exposure, signs of premature photoageing develop, with cutaneous atrophy and mottling on light-exposed sites, with later scarring. Pigmented macules develop predominantly on sun-exposed sites. These children may develop cutaneous malignancies within the first or second decade of life (see paragraphs 66 and 116). From a survey of the medical literature, it has been estimated that the overall incidence of skin cancer in XP is up to 5000 times that of the general population (Kraemer *et al.* 1987). The predominant malignancies are SCC and BCC, while the risk of malignant melanoma is also significantly increased (Kraemer *et al.* 1987). Ocular abnormalities are common, affecting the exposed sites, ie eyelids, conjunctiva and cornea (Kraemer *et al.*

1987). These include keratitis and benign and malignant neoplasms. Approximately 20% of cases develop neurological conditions, including speech defects, sensorineural deafness and mental retardation, with a range of severity.

149 The clinical features vary depending on the complementation group, and are mild in the case of XP groups E and F. Neurological disease is frequent and often severe in group A, developing in the first decade, while it tends to develop in the second decade in group D, and is absent in group C. Skin cancer susceptibility also varies, with SCC apparently most common in group C, lentigo malignant melanoma in group D and BCC in group E and variant XP (Jung, 1986).

150 In the past the natural history of this disease was that affected individuals died of metastatic malignancy, usually SCC or malignant melanoma, before the age of 30 years. Following the recognition of the prime importance of protecting these children from any UVR exposure by avoiding outdoor activities and constant use of high SPF sunscreen and protective clothing, an increasing number are living to their fourth and fifth decades.

Cockayne's syndrome

151 This is a rare recessive disorder that usually presents by two years of age (Nance and Berry, 1992). Photosensitivity is a common presentation (Cockayne, 1936), manifesting as a red scaly rash on exposed sites, which is aggravated by sun exposure. Severe sunburn similar to that in XP may be seen, and also pigmentation and atrophic scarring of exposed skin. A characteristic facies, growth retardation and neurological and ocular abnormalities occur. Excision repair is normal, but a lack of recovery in RNA synthesis recovery is observed following UVR exposure of CS cells (Mayne and Lehmann, 1982).

Trichothiodystrophy

152 Approximately 50% cases of TTD have a photosensitivity similar to that in XP (Lucky *et al*, 1984). The condition is characterised by abnormalities in hair development, short stature, and often abnormal facies and mental retardation (Jackson *et al*, 1974; Jorizzo *et al*, 1982). However, as in CS, there are no reports of skin cancer. Cells show a varied response to UVR, those from some patients showing normal DNA repair, whilst others show the excision repair defect characteristic of XP, usually the same complementation group as XPD. It is not understood why these children do not have the very high risk of cutaneous malignancies seen in XP (see paragraph 148).

Bloom's syndrome

153 This condition is most prevalent in males and in Ashkenazi Jews (carrier rate 1 : 20). It presents with a photosensitive rash before the age of three years, comprising erythema and telangiectasia of exposed sites, particularly the face (Bloom, 1966; German and Passarge, 1989). BS is associated with an approximately 300-fold increase in incidence of external and internal malignant neoplasms, including the skin, gastrointestinal tract, and leukaemias and lymphosarcomas. A susceptibility to multiple infections is seen, associated with deficient function of both B and T lymphocytes. In contrast to XP, CS and TTD, cells in BS do not show hypersensitivity to UVR, but instead a high frequency of chromosomal aberrations and sister chromatid exchanges (Chaganti *et al*, 1974; German, 1974).

Idiopathic photodermatoses

- 154** The idiopathic conditions, suspected to be of immunological origin, comprise polymorphic light eruption (PLE), actinic prurigo (AP), hydroa vacciniforme (HV), chronic actinic dermatitis (CAD) and solar urticaria (SU). Photosensitivity dermatitis/actinic reticuloid syndrome (PD/AR) is synonymous with CAD, while juvenile spring eruption (JSE) is believed to be a variant of PLE. These conditions have distinct phenotypes and there is evidence for an immunological basis to most of them. Depending on the disorder, wavelengths of UVA, UVB and visible radiation may be responsible. The investigation and diagnosis of these patients (except clinically typical PLE, see below) takes place in a photobiology unit, where phototesting of the skin with narrow- and broad-band radiation sources serves to elucidate the erythral thresholds to a range of wavelengths from 300–600 nm and to provoke the eruption. This confirms objectively the presence of photosensitivity, determines the action spectrum and demonstrates the severity. These findings, together with serum autoantibody testing +/- skin histology, facilitate correct diagnosis and management.

Polymorphic light eruption

- 155** PLE is the most common photodermatosis. It is characterised by an intermittent pruritic skin eruption occurring in a delayed manner following UVR exposure, the lesions comprising red papules and/or vesicles and/or plaques which resolve without scarring after a few days to weeks. Although the pathogenesis is unclear, there is some evidence for an underlying disorder of cell-mediated immunity.

Prevalence

- 156** PLE is extremely common in the northern hemisphere. Surveys in Boston (USA), Sweden and the UK reported prevalences of 10, 21 and 15% of the population, respectively (Morison and Stern, 1982; Pao *et al.* 1994; Ros and Wennersten, 1986). However, these questionnaire surveys were performed in small (172–412 people) biased samples of the population, in a medical library, a pharmaceutical company, and in shopping malls, respectively, and were based on the subjects' description of their condition rather than examination of active rash by a clinician. Pao *et al.* (1994) also reported a prevalence of PLE of 5% population in Australia, supporting the observation that PLE is commoner in temperate climates than nearer the equator. It is speculated that the higher proportion of UVB to UVA at the equator might result in the inhibition of rash provocation through UVB-induced immunosuppression. PLE is much commoner in females than males, with a reported sex ratio varying from 9 : 1 to 3 : 1.

Pathogenesis

- 157** PLE has been classified as an acquired condition, but recent evidence from twin studies suggests a strong genetic influence (Millard *et al.* 2000). A questionnaire conducted on 420 pairs of adult female twins found a history suggestive of PLE in 21% of monozygotic and 18% of dizygotic pairs. A family history of PLE was reported in 12% of other near relatives of an affected twin, but in only 4% where twins were unaffected, giving evidence of familial clustering, $p < 0.0001$. The authors reported that a genetic model of additive genetic and environmental factors provided a fit for the data, with 84% (95% CI 65%, 94%) of the susceptibility to PLE attributable to genetic factors and 16% (95% CI 6%, 35%) to environmental factors.

158 It has been hypothesised that the pathogenesis of PLE may involve a photoallergen induced by sunlight, which then triggers a cell-mediated immune response (Epstein, 1942), although this has not yet been substantiated. It has been reported that heat shock protein 65 (HSP65) shows increased expression in PLE-affected skin compared with normal skin, leading to a tentative suggestion that this molecule could possibly act as a photo-induced allergen responsible for precipitating lesions (McFadden *et al.* 1994). The histological appearance in PLE is that of a perivascular lymphocytic infiltrate. These T lymphocytes peak in number at 72 hours following artificial irradiation, CD4⁺ cells occurring early on, with CD8⁺ dominating later and accompanied by increased numbers of dermal and epidermal Langerhans cells (Norris *et al.* 1989). These features, along with the pattern of adhesion molecule expression in lesional skin (Norris *et al.* 1992), resemble those occurring in allergic contact dermatitis, supporting a type IV delayed hypersensitivity mechanism for PLE.

159 UVB-induced suppression of contact hypersensitivity in normal skin is associated with the disappearance of antigen-presenting CD1a⁺ Langerhans cells from the epidermis, and the influx of CD11b⁺ cells (Cooper *et al.* 1992). These latter macrophage-like cells are producers of interleukin-10 (IL-10), a cytokine which is known to down-regulate cellular immunity. It has recently been reported that the influx of CD11b⁺ cells is lower in the UVB-irradiated non-lesional skin of PLE patients than in normal subjects, and that there is a striking persistence of LC (Kölgen *et al.* 1999). Hence, it has been speculated that there could be an imbalance between sensitisation to UVR-induced allergens and immunosuppression in PLE. However, the preliminary work of Kölgen *et al.* requires replication and clarification. The sex ratio of the patients (seven male, three female) is odd for PLE, and a very high UVB dose (six times the minimum erythral dose) was employed. Furthermore, from the description given of the clinical and phototesting features of some of the patients (older men, with severely low erythral thresholds), it is likely that a number of the study group suffered from CAD rather than PLE.

Action spectrum

160 Narrowband light testing using a monochromatic light source shows that erythral thresholds to UVB and UVA are usually normal or only borderline low (Diffey and Farr, 1986). Provocation testing with broadband sources induces a PLE rash most frequently in the UVA waveband (Hözlze *et al.* 1982; Ortel *et al.* 1986), although there are also a number of reports of successful provocation by UVB (Magnus, 1964; Miyamoto, 1989).

Clinical features

161 The onset of PLE is usually in teenage or early adult life (Frain-Bell, 1985), but it is also diagnosed in childhood. Once developed, it occurs year upon year until later adulthood. There is a spectrum of clinical severity of PLE, with mild, moderate and severe forms occurring. PLE usually causes considerable discomfort and distress, and patients report a substantial impact of the condition on their quality of life. It typically occurs from early spring to autumn each year. Light-exposed areas of skin are affected, although there is frequently facial-sparing, an effect likely to be due to skin 'hardening', caused by the constant exposure of this body site. The eruption characteristically commences several hours after sun exposure, ie on the evening of sun exposure, or the next day. A minority of patients have a rapid-onset variety, the eruption commencing at

around one hour after exposure (Mastalier *et al.* 1998). The eruption in PLE typically comprises numerous small papules and/or blisters, which may coalesce into sheets, accompanied by redness and oedema. Some patients present with larger red skin lesions, ie plaques, and occasional patients present with urticarial or haemorrhagic forms. The rash is termed 'polymorphic' since it varies in form between individuals, but it tends to show intra-individual consistency in pattern. The eruption resolves within several days – one week following light avoidance, without scarring unless there has been vigorous excoriation. The condition tends to become less troublesome as summer advances, probably due to the induction of immunological tolerance and hardening. Juvenile spring eruption (JSE) is a condition seen in children, particularly boys, where itchy vesicles occur on the rims of the ears (Berth-Jones *et al.* 1989). It usually resolves before adulthood, although can persist, and is believed to be a variant of PLE.

- 162** The clinical differential diagnosis includes the various forms of lupus erythematosus, particularly subacute lupus erythematosus (SACLE). The time course is different, LE lesions usually occurring with a latent period of two to three weeks after sun exposure, and persisting for several weeks. The presence of anti-Ro and anti-La autoantibodies supports the diagnosis of SACLE. A small minority of PLE patients are ANA positive, but there is no evidence of progression of this disorder to LE (Mastalier *et al.* 1998). The diagnosis of PLE may be made clinically, but formal investigation is required if there are atypical features. Phototesting is performed to differentiate PLE from other idiopathic photodermatoses and photopatch testing examines for coexistent sunscreen allergy or photoallergy.

Actinic prurigo

- 163** AP is less common than PLE, although the exact incidence is unknown. It also occurs most frequently in females. While AP and PLE are clinically distinct in most cases, similarities between the conditions have led to suggestions that they are related. Characteristically, AP arises in childhood, and presents with more persistent pruritic papules or nodules which become eczematized and leave residual scarring.

Pathogenesis

- 164** A heritable (autosomal dominant) form of AP with HLA associations is found in native American Indians (Bernal *et al.* 1990). Recent tissue typing studies in 26 British Caucasian AP patients revealed that all were DR4 positive, and 25/26 were DQ7 positive (Menagé *et al.* 1996a). Significantly, DR4 subtyping showed 20 of 26 patients tested to be DRB1*0407; this subtype is rare in European Caucasians without AP. DRB1*0407 was absent in 25 PLE patients tested, supporting the view that PLE and AP are distinct entities.

Action spectrum

- 165** A proportion of patients show low erythema thresholds, more frequently to UVA than UVB (Frain-Bell, 1985). The rash can be provoked with UVA, although with more difficulty than in PLE.

Clinical features

- 166** Although the condition shows a seasonal pattern with spring/summer aggravation, the lesions can also occur in the winter. The pruritic papules and nodules usually persist

for many weeks or months. In contrast to PLE, AP frequently involves the face, and scarring is common. Sun-exposed sites are predominantly affected, but covered sites can also be involved, particularly the buttock area. Lower lip inflammation (cheilitis) is a frequent association. There is sometimes diagnostic confusion with PLE since adult onset can also occur in AP, and on occasion AP can present with a more acute papular reaction following sun exposure. The clinical severity of AP equates to the more severe forms of PLE.

Hydroa vacciniforme

- 167** HV is a rare photosensitivity disorder which characteristically first appears in early childhood and clears by adult life (Sonnex and Hawk, 1988). Painful erythema and vesicles following sun exposure resolve to leave characteristic varioliform scars.

Pathogenesis

- 168** The histology is distinctive, with intraepidermal vesicles, focal keratinocyte necrosis and an infiltrate of neutrophils and lymphocytes. The underlying mechanisms have not yet been subjected to detailed examination, and it is speculated that HV may be caused by a delayed type hypersensitivity eruption, or alternatively a phototoxic reaction.

Action spectrum

- 169** Increased erythematous sensitivity has been reported to UVA (Rhodes and White, 1998; Sonnex and Hawk, 1988). Broadband UVA can provoke the typical lesions of HV (Golgeier *et al.* 1982; Rhodes and White, 1998).

Clinical features

- 170** The clinical features are typical and recur on exposed skin following sun exposure. First, painful erythema develops during or soon after sun exposure, followed by the appearance of crops of blisters. These then become umbilicated, followed by crusting and then healing to leave depressed smallpox-like scars. The effect on the quality of life is great, first in the restriction of outdoor activities in childhood, and second due to the development of scars which are carried through life.

Chronic actinic dermatitis

- 171** CAD is now the established term for chronic debilitating eczematous disorders in which are found severely low erythematous thresholds to UVB, sometimes also to UVA, and occasionally to visible light (Hawk and Magnus, 1979; Roelandts, 1993). Coexistent contact allergy +/- photocontact allergy is a frequent finding. In some cases, an infiltrated appearance reminiscent of cutaneous lymphoma can develop (Ive *et al.* 1969).

Incidence

- 172** The incidence is not known but has been estimated at 1 in 6000, while the sex ratio is reported to be the reverse of that seen in PLE, ie in CAD it is said to be nine male to one or two female (Ferguson, 1990; Menagé *et al.* 1995). It is reported to be commonest in middle-aged to elderly men with an average age of 65 years, and to be commoner in outdoor workers and those with a previous history of eczema (Menagé *et al.* 1995). However, recently a small number of cases have been reported to occur in a different group, ie in young atopic patients in their teens or early twenties (Russell *et al.* 1998; Ogboli and Rhodes, 2000).

Pathogenesis

- 173** The histology of affected skin shows the features of eczema. Occasionally in severe, long-standing cases a heavier T lymphocyte infiltrate occurs, with a pseudo-lymphomatous appearance. The pattern of the lymphocytic infiltration, which is reported to be mainly CD4⁺ (helper cells) early on and CD8⁺ (suppressor cells) later, in addition to the pattern of adhesion molecule expression, suggests that the underlying mechanism may be a delayed hypersensitivity response (Menagé *et al.* 1996b; Poulter *et al.* 1982).
- 174** Previously, there has been lengthy debate concerning whether CAD could be precipitated by earlier reactions to exogenous chemicals/drugs, ie photoallergic contact dermatitis or systemic drug photosensitivity. Persistent eczema of light-exposed sites following an episode of photoallergic contact dermatitis was described by Wilkinson (1962) and named persistent light reactivity (PLR). However, this remains a controversial area and definite progression of exogenous reactions to CAD has not been proven. Whereas topical and systemic chemical/drug photosensitivity is most often provoked by the UVA waveband, the predominant sensitivity in CAD is to UVB. However, multiple allergic contact sensitivity reactions often coexist with CAD, with compositae plant extracts the most frequent culprit followed by fragrances and colophony (Menagé *et al.* 1995), and these have been reported to precede the development of photosensitivity (Murphy *et al.* 1990).

Action spectrum

- 175** CAD shows characteristic features on phototesting, with severely low erythema thresholds to UVB, sometimes with additional UVA sensitivity, and occasionally the sensitivity additionally spreads through into the visible region. Palpable lesions are easily provoked (Frain-Bell *et al.* 1974).

Clinical features

- 176** CAD is a very disabling condition and affected individuals are unable to carry out normal daily activities. The photosensitivity is so severe that a seasonal pattern may not be evident, the less intense solar radiation present in winter months being enough to trigger the condition. Characteristically it appears as a chronic or subacute eczema of the light-exposed areas, particularly affecting the posterior and lateral aspects of the neck, chest, face, scalp and dorsal hands, with a sharp cut-off at the edges of clothing. Lichenification (thickening) of the skin occurs in long-standing cases, and in particularly severe cases an infiltrated appearance reminiscent of cutaneous lymphoma may develop (Ive *et al.* 1969).
- 177** There are occasional reports of CAD apparently developing into lymphoma. However, it is not clear whether these are due to diagnostic confusion, coincidence or causal association. Clinical experience indicates that if this occurs at all, it is infrequent. A comparison of the incidence of lymphoma in 231 CAD patients with that of age- and sex-matched national morbidity data revealed many inaccuracies in registration data, but no apparent increase in the risk of lymphoreticular or non-lymphoreticular malignancies (Bilsland *et al.* 1994). One case of lymphoreticular malignancy occurred, which was not significantly different from the number (0.96) expected in the normal population [standardised incidence ratio 1.04 (95% CI 0.03, 5.79)].

Solar urticaria

- 178** This acquired condition is a rare form of urticaria and a rare photosensitivity disorder. SU is characterised by sunlight-induced erythema and/or whealing of the skin accompanied by intense itching, typically occurring within minutes of sun exposure, and resolving within a few hours. It is frequently disabling due to its ability to be provoked by very low doses of UVR and/or visible radiation. It is reported to be slightly commoner in females (Stevanovic, 1960), with onset most commonly between the third and fourth decades, although it has presented at a range of ages between infancy and late adulthood (Ferguson, 1988).

Pathogenesis

- 179** SU is generally believed to represent an immediate type hypersensitivity reaction to a photoactivated endogenous allergen, although many questions remain concerning the exact pathogenesis (Horio, 1978; Horio *et al.* 1984; Kojima *et al.* 1986). Injected autologous serum pre-irradiated at the previously identified action spectrum for the patient can elicit an urticarial response in 75% of patients (Uetsu *et al.* 2000). Earlier, several investigators carried out transfer studies, involving the *in vitro* irradiation of serum/plasma of patients or normal subjects, followed by injection into patients' or normal subjects' skin. These studies, which can no longer be performed for ethical reasons, were reviewed (Leenutaphong *et al.* 1989) and led to the proposed classification of SU into the following two types.

Type I - whealing develops in patient or normal skin after injection of patient's, but not normal, irradiated serum/plasma, the precursor occurring only in the patient.

Type II - whealing develops in patients or normal skin after injection of either patient's or normal irradiated serum/plasma, the precursor occurring in both patients and normal subjects.

- 180** Histamine is believed to be the major mediator of the reaction (Behrendt *et al.* 1989; Hawk *et al.* 1980). This is supported by the beneficial therapeutic effect of H1 receptor antagonist antihistamines in a high proportion of patients (Diffey and Farr, 1988). However, other mediators are thought to play a role, since the response is usually only partial.

Action and inhibition spectra

- 181** SU may be precipitated by UVA, UVB and visible light. The waveband most often responsible is UVA, although broad provocation can occur throughout the wavebands (Hasei and Ichihashi, 1982). In some patients an inhibition spectrum, which is nearly always reported to be at wavelengths longer than the action spectrum, can be identified (Hasei and Ichihashi, 1982; Horio *et al.* 1984).

- 182** The histopathology is consistent with that of other urticarias, showing subtle features including dermal oedema and a scanty inflammatory infiltrate of mononuclear cells and polymorphs.

Clinical features

- 183** SU usually develops suddenly, and then persists for many years. Within minutes of sunlight or artificial light exposure, the subjects develop intense itching followed by erythema and whealing of the skin. This usually resolves within one or two hours. Some

patients may develop more generalised features of angioedema and anaphylactic shock. There are occasional reports of delayed onset of rash (Montefrecola *et al*, 1988), and of more persistent 'urticaria' which may actually represent a solar urticarial vasculitis. Fixed SU is occasionally reported, in which the rash occurs only in certain sites (Reinauer *et al*, 1993).

- 184** The differential diagnosis includes urticaria of other causes, although the subject is usually well aware that radiation is the precipitating factor. Erythropoietic protoporphyria also causes symptoms within minutes of sunlight exposure, but whealing is unusual. Contact with coal tar, and certain phototoxic drugs, may cause a sunlight-induced urticaria.

Cutaneous porphyrias

- 185** The cutaneous porphyrias are conditions associated with photosensitivity to visible radiation rather than UVR, and are mentioned briefly here (for review, see Elder, 1999). They are a group of disorders of haem synthesis, in which a variety of individual enzyme defects result in the build-up of photoactive precursor porphyrins which then photosensitise the skin (Nordmann and Deybach, 1990). Most cutaneous porphyrias are inherited, although acquired forms occur. Clinical features are precipitated by visible light around 410 nm, known as the Soret band (Magnus, 1980). Following absorption of radiation energy, the porphyrin passes into the triplet state, where it interacts with molecular oxygen to produce reactive oxygen species (ROS), particularly singlet oxygen, which then mediate skin damage.
- 186** Seven types of porphyria are recognised, five of which are associated with photosensitivity. Four conditions, porphyria cutanea tarda (PCT), hereditary coproporphyria (HCP), variegate porphyria (VP) and congenital erythropoietic porphyria (CEP), are associated with features of chronic damage of exposed skin sites, ie fragile skin with blistering and scarring. The fifth condition, erythropoietic protoporphyria (EPP), is quite different in that subjects suffer from acute features of photosensitivity. The disparity in clinical features may relate to the water or lipid solubility of the porphyrin concerned, resulting in accumulation in different cellular sites. EPP has an estimated prevalence in Western Europe of 1 in 75 000 (Went and Klasen, 1984) to 1 in 130 000 (Murphy *et al* 1985). The defective enzyme is ferrochelatase, needed for the final step in haem synthesis, and the result is the accumulation of the photoactive lipid-soluble precursor protoporphyrin IX. Singlet oxygen has been thought to be the major mediator involved, but clinical response to the singlet oxygen mopping agent, beta-carotene, is only partial (Mathews-Roth, 1984). Diagnosis may be overlooked since most patients with EPP present with pain in the skin on sun exposure, without any visible damage. Erythema and oedema occasionally accompany the pain, and linear scarring and weathering of the skin may become evident later.
- 187** HCP, VP and EPP show autosomal dominant inheritance, while CEP is autosomal recessive, and PCT is most commonly acquired, and can be provoked by alcohol, hepatitis C and oestrogens. Diagnosis is made following biochemical testing of blood, urine and sometimes faeces; phototesting is unnecessary. Accurate diagnosis of type of porphyria is essential since different therapies are employed in the different types. Moreover, two of the four conditions causing fragile skin, ie HCP and VP, are associated with acute neurovisceral porphyric attacks. These may be precipitated by various

drugs including barbiturates, anticonvulsants and progestogens, and it is important to warn patients at risk.

UVR in the treatment of photosensitivity disorders

- 188** UVR is used as a therapeutic strategy in certain photosensitivity disorders, particularly the idiopathic conditions and EPP (Plewig *et al.* 1986). This is administered using fluorescent lamps, either as phototherapy with UVB or as photochemotherapy with PUVA (UVA, with prior sensitisation with psoralen). A course of controlled UVR exposures is given over several weeks, usually in springtime. UVR therapy serves to 'harden' the skin to sunlight exposure by inducing tanning and epidermal thickening. In the case of immune-based conditions, the immunosuppressive action of UVR is important (see Chapter 5). In severe conditions such as CAD or SU, UVR therapy is administered with great care due to the risk of disease provocation. It is desirable to use radiation wavelengths other than those that induce the rash. Whereas UVB therapy was previously performed with broad-spectrum lamps also containing UVA, narrowband UVB (TL01) lamps are increasingly used. Their emission is centred at 311 nm, making them of particular value in the treatment of UVA-induced photosensitivity disorders (Collins and Ferguson, 1995).
- 189** Other than UVR, a range of treatments is available, dependent on the nature of the photosensitivity disorder. These include immunosuppressive drugs, eg azathioprine, cyclosporin and steroids, for the immune-based conditions PLE, AP and CAD, anti-histamines and plasmapheresis for SU, beta-carotene for EPP, and hydroxychloroquine for PCT. Recently, the development of a topical liposome-encapsulated DNA repair enzyme has given hope as a potential treatment in XP (Yarosh *et al.* 2001). Many therapeutic trials have been impaired by the absence of precise diagnostic terminology and sun-exposure monitoring.
- 190** All patients should be made aware of sun-protection techniques, and these may negate the need for therapy in milder cases. Measures include suitable clothing, high protection topical sunscreen of appropriate spectrum, avoidance of sunlight exposure between 11 am and 3 pm, and UVR-blocking window films. Patients should be educated in correct sunscreen application technique, since methods otherwise appear poor (Azurdia *et al.* 1999).

Photoaggravated dermatoses

- 191** The photoaggravated dermatoses are a diverse range of conditions that can be exacerbated by exposure to UVR. Some, but not all, have an underlying autoimmune aetiology. Typically, photosensitivity occurs in only a subset of patients affected with these conditions.

Lupus erythematosus

- 192** The most important photoaggravated disorder is the spectrum of inflammatory diseases encompassed by the term lupus erythematosus, the most frequently seen types being systemic lupus erythematosus (SLE), subacute lupus erythematosus (SCLE) and chronic discoid lupus erythematosus (CDLE). SLE is a multi-system autoimmune disease that involves the skin in 60%–70% of patients, SCLE is a skin disorder which can show mild systemic involvement, while CDLE is purely a cutaneous problem.

193 In LE, autoantibodies are found against cytoplasmic and nuclear components, and these are believed to mediate the different patterns of clinical disease. In SLE, serum antinuclear antibodies (ANA) are virtually always present, while antibodies to double-stranded DNA (dsDNA) are a specific finding and anti-Ro antibodies may also be present (Provost *et al.* 1985). There is a strong association of SCLE with anti-Ro and anti-La antibodies (Deng *et al.* 1984), while CDLE is usually antibody negative (Prystowsky and Gilliam, 1975). It is assumed that other immunological effector mechanisms are critical in CDLE. The presence of the anti-Ro antibody is strongly associated with photosensitivity (Provost and Reichlin, 1981). Biopsy of involved skin shows characteristic histology, with epidermal basal cell degeneration, follicular plugging and a perivascular lymphocytic infiltrate. Immunofluorescence demonstrates the presence of immunoglobulin IgG at the basement membrane zone of lesional skin in CDLE, while in SLE this is positive in most areas of sun-exposed skin. It has been suggested that UVR-induced DNA alterations may lead to the formation of immune complexes in cutaneous lesions, causing disease exacerbation and positive immunofluorescence (Biesecker *et al.* 1972).

194 Cutaneous lesions of LE are found predominantly on sun-exposed sites. CDLE appears as scaly red plaques particularly affecting the face and arms, and persisting for months before resolving with scarring. In SCLE there are many more superficial plaques, which often affect the mantle (upper chest and back) region, and resolve without, or with minimal, scarring. There is sometimes diagnostic confusion between SCLE and PLE (see paragraph 162). SLE may show similar plaques to cutaneous LE and a more diffuse photosensitivity appearing as an increased sunburn tendency.

Action spectrum

195 Phototesting may provoke new lesions of LE (Morison, 1983), but it is easier to demonstrate aggravation of existing lesions. SCLE is the most sensitive to provocation (Hölzle, 1987). Both UVA and UVB alone are effective in provoking lesions, as is the combination of UVA + UVB (Cripps and Rankin, 1973; Epstein *et al.* 1965; Kind *et al.* 1987).

Other photoaggravated dermatoses

196 Dermatomyositis is a chronic inflammatory disorder believed to be of autoimmune aetiology, characterised by a myopathy and skin involvement. The incidence and nature of the photosensitivity is poorly documented, but has been estimated to affect one-third to one-half of patients (Cheong *et al.* 1994). Other disorders with an immunological basis that have been reported to be photoaggravated include the blistering disorder pemphigus (Cram and Winkelmann, 1965) and the lichenoid eruption, actinic lichen planus (Isaacson *et al.* 1981). Viral infections including herpes simplex may be precipitated by UVR, possibly through suppression of local skin immunity (see Chapter 5). Constitutional eczemas may show aggravation by UVR, with predominant involvement of sun-exposed sites and marked worsening in the summer months (Ramsay and Kobza-Black, 1973). Photoaggravated eczemas are not as severe as CAD, but can nevertheless be very troublesome. Psoriasis is a common inflammatory dermatosis, affecting 2% of the population. Although UVR is usually beneficial and indeed used as a treatment modality in psoriasis, a minority of patients can show worsening of their disease on sunlight exposure (Ros and Eklund, 1987).

Drug and chemical photosensitivity

- 197** Photosensitisation by systemic and topical drugs and chemicals is an ever-increasing problem as new products are developed. Once in the skin, these agents may act as a chromophore for absorption of radiation, resulting in abnormal biological effects. UVR-induced reactions may be phototoxic, ie can potentially affect the entire population if the agent is given at a high enough dose in the presence of sufficient radiation, or can be reliant upon an inherent immunologically or biochemically mediated reaction which only affects a proportion of the population.

Systemic photosensitisation

- 198** The commonest mechanism underlying systemic photosensitisation is phototoxicity. Typically this occurs as an exaggerated sunburn reaction +/- blistering, which may occur after exposure to only short periods of mild sunlight (Ferguson, 1995). However, many drug reactions have their own typical clinical pattern, including acute features such as a burning/prickling sensation during exposure (Chalmers *et al* 1982), immediate erythema, and urticaria, and more chronic effects including hyperpigmentation, increased skin fragility with blistering (pseudoporphyria) (Buchbinder *et al* 1962), and nail involvement (photo-onycholysis) (Baran and Brun, 1986). These differences in presentation may relate to differences in drug structure and localisation in the skin. Certain drugs may also precipitate immune-based conditions, ie lupus erythematosus (Reed *et al* 1985) and lichenoid reactions (Harber *et al* 1959). There are occasional reports of systemic photoallergic reactions, presenting with an eczematous appearance, although these have proved difficult to substantiate.
- 199** The range of drugs responsible for photosensitivity is very large indeed. At the present time, relatively common photosensitising drugs include non-steroidal anti-inflammatory drugs (including naproxen and piroxicam), a wide range of antibiotics (including fluoroquinolones, tetracyclines and sulphonamides), antifungal agents (griseofulvin), diuretics and cardiovascular drugs (including thiazides, frusemide, amiodarone and quinidine), psychoactive drugs (including phenothiazines), and the retinoids. Psoralens are purposefully used to photosensitise to UVA in the photochemotherapy of various skin disorders. Although prescribed drugs are the main cause of systemic photosensitisation, it is important to be aware that this may also occur with dietary agents, particularly psoralen-containing vegetables, eg celery, and with herbal remedies, including St John's Wort, which has recently become a popular self-medication for depression (Anonymous, 1997).
- 200** Photosensitivity may develop shortly after a patient first uses a new drug, which makes the diagnosis relatively straightforward, or after the incriminated drug has been ingested for several months, making the diagnosis much more difficult. Withdrawal of the drug is essential, but the photosensitivity may persist for many months. This complication of drug therapy may be diagnosed clinically, or may require phototesting for confirmation and to differentiate from other causes of photosensitivity. Phototesting whilst the patient is still taking the medication will frequently show abnormally low erythema thresholds, repeat testing at six months after cessation of the drug should demonstrate a return to normality. Drug photosensitisation is in the vast majority of cases precipitated by UVA, although occasional drug reactions are reported to be activated by UVB.

- 201** The phototoxic potential of a drug has often only become known during post-marketing surveillance. However, with the use of *in vitro* cell culture studies (Arlett *et al*, 1995) and carefully designed *in vivo* phototesting studies in people, it may now be possible to predict a number of these reactions.

Topical photosensitisation

Topically applied chemicals and drugs, in the presence of UVR, can cause phototoxic and photoallergic skin reactions.

Topical phototoxic reactions can occur in anyone in the presence of sufficient chemical and radiation. A common condition, known as phytophotodermatitis, is caused by psoralen-containing sap from plants, eg Giant Hogweed, splashing on to the skin (Johnson, 1993). In the presence of UVA, severe sunburn with blistering develops in the pattern of the splashes, followed by pigmentation. Other topical phototoxic agents include polycyclic hydrocarbons (eg coal tar and pitch), fragrances (musk ambrette and Bergamot oil), dyes (eg fluorescein and rose bengal) and medications (eg phenothiazines).

- 204** Many of the above agents are also reported to be capable of causing topical photoallergic reactions. These less common responses, ie photoallergic contact dermatitis, occur in the presence of low concentrations of the drug or chemical. They present clinically as an eczematous eruption on exposed skin sites. As with phototoxic agents, topical photoallergy appears to be activated mainly by UVA. These reactions are much more serious than topical phototoxicity, since they are difficult to avoid once established. Over time, most photocontact allergens become obsolete as industry eradicates their use in favour of safer agents. However, in recent years a new group of photoallergens has become prevalent with the increasing production and use of chemical sunscreens, ie those sunscreens that act by absorbing UVB and UVA (see Chapter 12, paragraph 25).
- 205** Chemical sunscreens are used by the population generally to protect against sunburn, and by photosensitive individuals to protect against rash-induction. An ever-increasing number of agents is becoming available, and in addition to their use in sunscreens there is now a trend to add them widely to cosmetic products, including facial moisturisers and foundations, in order to protect from features of photoageing (see paragraph 15). Many of these agents are capable of producing contact allergy and/or photocontact allergy. Hence it is not surprising that sunscreens are now the commonest topical photoallergens (Ibbotson *et al*, 1997; Trevisi *et al*, 1994). The overall incidence of sunscreen photoallergy is uncertain, since no surveillance system exists to record such reactions. However, individual centres report allergy and/or photoallergy to sunscreens in 8%–20% of patients tested (Ang *et al*, 1998; Schauder and Ippen, 1997; Trevisi *et al*, 1994). These patients were either photosensitive, or normal subjects suspected of sunscreen allergy/photoallergy. Para-aminobenzoic acid (PABA) was extensively used for many years, and initially thought to be a poor photosensitiser, but numerous subsequent reports of reactions have led to a decline in its use (Dromgoole and Maibach, 1990). Benzophenones and dibenzoylmethanes are currently widely used sunscreens with reports of allergy and photoallergy. While problems with newer agents such as the salicylates and cinnamates currently appear less common, this may be a matter of time.
- 206** Photocontact allergy is diagnosed by photopatch testing, in which duplicate patches of chemical or drug are tested in the presence and absence of UVA. The British

Photodermatology Group produced guidelines for testing procedure and an updated series of chemicals (Ibbotson *et al.* 1997). In view of the rapid changes in sunscreen production, surveys are needed of the prevalence of reactions to the various agents, with periodic updating of the chemical testing battery.

SUMMARY AND CONCLUSIONS

- 207** There is strong evidence that excessive cumulative exposure to natural solar radiation causes cutaneous ageing and raises the risk of squamous cell carcinoma (SCC) of the skin and lip cancer. There is also good evidence that sun exposure is related to the risk of developing basal cell carcinoma (BCC) and malignant melanoma, although the pattern of exposure that is hazardous is still uncertain; intermittent, recreational exposure of untanned skin may be important but so, to some extent, also may cumulative exposure. The descriptive epidemiology of melanoma and BCC suggest, however, that the aetiological relation is not entirely the same for these two tumours.
- 208** Risks of skin cancer are greatest in white people with fair complexions (light skin, red or blonde hair, and blue eyes) and sun-sensitive skins, and melanoma risks are much raised in those with many and atypical naevi.
- 209** Rates of melanoma incidence have been rising in white populations around the world for several decades, and although reliable data on non-melanoma skin cancer (NMSC) are more sparse, there appear to have been large rises in incidence of these tumours also. Melanoma mortality, however, has levelled off or even fallen in recent birth cohorts.
- 210** Evidence from recall-based case-control studies, and more persuasively from migrant studies, suggests that childhood sun exposure may be particularly important to the risk of melanoma. There is also growing evidence that childhood exposure affects naevus numbers. It remains less clear, however, whether childhood exposure is intrinsically more hazardous than exposure later in life (ie whether melanocytes are more susceptible in childhood) or whether other explanations, for instance more hazardous behaviours in childhood, pertain.
- 211** There is some evidence from randomised trials, but not yet conclusive, that use of sunscreens may reduce the risk of SCC and of actinic keratosis, a precursor of SCC. Results from case-control studies taking histories of sunscreen use have found inconsistent results with regard to the risk of melanoma, including both significantly protective and significantly increased risks in relation to sunscreen use; these studies are difficult to interpret and have great potential for bias and confounding, as well as uncertainty as to whether the use of sunscreens will have reduced UVR exposure or, by affecting behaviour in the sun, increased it.
- 212** PUVA treatment shows a strong dose-response relationship to the risk of SCC. Evidence for a risk of BCC is less convincing. One study has suggested a raised risk of melanoma after a long induction period, but the relation remains uncertain. There is little, and inconclusive, information on the risk of NMSC in relation to sunlamp use, but a large epidemiological literature on the possible relation of sunlamp use to the risk of melanoma. Despite several significant positive associations, the melanoma literature overall is inconsistent, and has methodological weaknesses especially with respect to

exposure measurement, confounding, and a lack of data for long induction periods. The relation is therefore uncertain, but as the exposures are to a type of radiation that is known to be carcinogenic (UVR), and are of a pattern believed to be aetiological for melanoma with respect to sun exposures (ie intermittent, intense exposures of sites usually unexposed in everyday life), there is reason for concern.

- 213** Photosensitivity disorders are a wide range of conditions showing abnormal cutaneous responses to exposure to small amounts of UVR and/or visible radiation. Some, the genodermatoses, are inherited, others have a biochemical aetiology, while many are of immunological origin or are attributable to drug or chemical reactions. The prevalence of most is unknown, although there is evidence from questionnaire surveys that the commonest immune-based disorder, polymorphic light eruption, is present in 15%–20% of the population in temperate climates. The underlying mechanisms are poorly understood in most cases. Some immune-based disorders, such as polymorphic light eruption, chronic actinic dermatitis and solar urticaria are believed to be due to UVR-induced allergens which then trigger a variety of immune responses, but the photoallergens have yet to be identified. Photosensitisation by systemic and topical drugs and chemicals is an increasing problem as new products are developed. A large range of drugs, dietary and herbal agents are responsible for systemic reactions, while topically the most common photoallergens are chemical sunscreens. Individual clinical centres report allergic/photoallergic reactions to sunscreens in 8%–20% of patients tested; however, the prevalence of the problem has not been established. Photosensitivity disorders require sunlight avoidance, are often disabling, and can have a considerable impact on the quality of life.

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8 Non-Hodgkin's Lymphoma and Chronic Lymphatic Leukaemia

- 1 Primary and acquired immunosuppression are risk factors for non-Hodgkin's lymphoma (NHL) and the possibility has been raised that the immunosuppressive effects of UVR might be involved in causing this malignancy. NHL has become more common in both sexes in many countries over the last few decades, and Zheng *et al* (1992) and Cartwright *et al* (1994) have drawn attention to the fact that NHL shares these rising incidence rates and to some extent geographical distribution with skin cancers. There have been several studies, reviewed previously by the Advisory Group (NRPB, 1995), showing raised risks of melanoma and squamous cell carcinoma (SCC), after NHL (and after chronic lymphatic leukaemia, CLL), and of NHL after melanoma. A recent study has added evidence of a raised risk of SCC and basal cell carcinoma (BCC) after NHL and CLL (Levi *et al* 1996). Recent studies have also shown increased risks of NHL after SCC (Karagas *et al* 1998; Levi *et al* 1996, 1997) and BCC (Frisch *et al* 1996; Levi *et al* 1996, 1998), with in each study, except that by Karagas *et al* increased risks seen also for known UVR-related cancers (melanoma, lip cancer, SCC or BCC), as far as these were separately analysed, but not for other cancers. The specificity of these second cancer associations strongly suggests an aetiological factor in common between NHL (and perhaps CLL) and lip and skin cancers, although this factor need not necessarily be UVR. Several recent studies suggest that if NHL is indeed related to UVR, the association is much less strong than for cutaneous neoplasms.
- 2 In the USA, Freedman *et al* (1997) conducted a case-control study of 33 000 deaths from NHL and 66 000 non-cancer deaths as controls. They analysed the risk of NHL in relation to occupation and place of residence as recorded on death certificates, with each of these variables classified by potential solar UVR exposure. There was no positive relation of NHL with UVR exposure from either source (except a specific association with work in farming), whereas for cutaneous melanoma and non-melanoma skin cancer (NMSC) there were significant associations with the residential UVR measure and for NMSC also a borderline significant association with the occupational measure. A national cohort study in Sweden (Adami *et al* 1999) examined the relations of NHL and skin cancer incidence risks to occupation and place of residence recorded at the census, as markers of UVR exposure, with similar results to those from the USA described above: NHL, melanoma and SCC (but not CLL) showed increasing risks with decreasing latitude of residence within Sweden, but the gradient of risk was much steeper for the skin cancers than for NHL. Outdoor work was not associated with any of the cancers. In England and Wales both melanoma and NHL show north/south gradients, again stronger for the former than the latter (Swerdlow and dos Santos Silva, 1993), and the geography of NHL also correlates with that for ambient UVR (Bentham, 1996). Internationally too there is a strong correlation between melanoma incidence in white populations and ambient UVR, and a much weaker, but nevertheless positive, correlation for NHL (McMichael and Giles, 1996). In four decades of American mortality data, however, while NMSC and cutaneous melanoma rates in white populations by state showed

positive associations with measured state UVB levels, there was a negative relation for NHL (Hartge *et al*, 1996).

SUMMARY AND CONCLUSIONS

- 3 Overall, these results are not consistent with a major role for solar UVR in the aetiology of NHL, but they leave open the possibility of a minor role, or an aetiological relation for a particular subtype of NHL. Individual-based analytical studies analogous to those that have been conducted for skin cancer, investigating the relation of NHL to factors such as sun-sensitivity phenotype, personal sun-exposure history and biomarkers of sun exposure, will be needed to help to resolve these possibilities.
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9 Dietary Factors

INTRODUCTION

- 1 Dietary factors have the potential to interfere with the mechanisms of UVR-induced skin damage. Potentially, therefore, dietary manipulation might be used to combat the rising skin cancer trends and to protect the skin from other adverse UVR effects, including photosensitivity disorders and photoageing (see Chapter 7).
 - 2 The mechanisms underlying UVR-induced skin damage are complex. An early effect of UVR on the skin is the generation of excessive amounts of free radicals and reactive oxygen species (ROS), which overwhelm the skin's antioxidant defenses (Witt *et al.* 1993). ROS are well-documented as mediators in UVA-mediated effects, but also play an important role in UVB-induced damage. In excess they can cause widespread damage to lipid membranes, proteins and DNA. Inflammatory and immunomodulatory mediators including prostaglandins, cytokines and nitric oxide are released. DNA is damaged both directly by UVR and indirectly by ROS. Potential strategies for photoprotection therefore include inhibition of ROS, use of anti-inflammatory agents, augmentation of DNA repair and immune modulation. The nutritional approach to protection has mainly involved supplementation with antioxidant agents, since many of the harmful effects of UVR on the skin may be mediated by ROS, and natural supplements can be employed. Other dietary strategies that have recently shown promise involve modification of dietary fat intake, namely reduction of total fat consumption, and alteration of the balance of fats to contain more omega-3 fatty acids; these may reduce UVR-induced skin damage by effects on lipid peroxidation and/or inflammatory mediators. The relationship between vitamin D and UVR is discussed elsewhere (see Chapter 10).
 - 3 A systemic approach to photoprotection could offer continuous and even skin protection, avoiding some of the drawbacks of topical sunscreens (see Chapter 12, paragraphs 25–30). A safe nutritional agent would be the ideal, with potential application at a population level, in addition to prophylaxis for susceptible patients (Rhodes, 1998). In recent years, the nutritional approach has been studied in some detail in cell culture, animal models, in healthy people and in patients with skin cancer or photosensitivity. The salient findings are summarised below; cell culture studies are discussed briefly, since this system cannot equate to oral supplementation, and attention is focused on *in vivo* studies.
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CELLULAR STUDIES

- 4 Many harmful effects of UVR on skin cells are mediated by ROS and free radicals. The highly reactive agents interact with lipids, proteins and DNA. Their interaction with lipid membranes causes a chain reaction of lipid radical formation and lipid radical peroxidation. Several *in vitro* studies in skin cells (fibroblasts, keratinocytes) demonstrate protection by supplementation with antioxidants prior to UVR administration.

- 5 Protection by antioxidants is reported against the damage caused by UVR. Parameters against which protection is seen include membrane peroxidation, cytotoxicity, DNA damage and pro-inflammatory cytokine secretion (Fuchs, 1998). Vitamin E (alpha-tocopherol) is a powerful lipid-soluble antioxidant with chain-breaking properties, ie it terminates membrane lipid peroxidation, and can directly scavenge singlet oxygen and superoxide (Fryer, 1993). The vitamin E radical is then recycled by vitamin C (ascorbic acid), a powerful water-soluble antioxidant, or by glutathione (Packer *et al*, 1979). Vitamins C and E can reduce several aspects of UVR-induced damage when used singly (Fuchs, 1998), while other antioxidants are seen to be effective when used in combination (Stewart and Cameron, 1996). Vitamin E supplementation protected cultured human skin fibroblasts from UVB-induced phototoxicity (Kondo *et al*, 1990), while human keratinocytes were protected from cell death induced by solar-simulated radiation (Werninghaus *et al*, 1991). Vitamin C reduced UVB-induced oxidative DNA damage to mouse keratinocytes (Stewart and Cameron, 1996), and protected human keratinocytes from UVA-induced lipid peroxidation (Tebbe *et al*, 1997). Beta-carotene may operate both by serving as a precursor to vitamin A, and by its action as a lipid-phase antioxidant. Combinations of antioxidants with beta-carotene have been shown to have synergistic action against UVA effects (Bohm *et al*, 1998). Vitamin D₃ also protects keratinocytes from UVB-induced effects, which may be attributable to its capacity to prevent free-radical-related damage (Lee and Youn, 1998).
- 6 It is important to be aware that many antioxidants exhibit pro-oxidant properties in certain situations. For example, the effects of vitamin C are dose dependent, with lower concentrations protecting against UVR-induced damage, while higher concentrations cause reduced cell viability (Jones, 1998). The effects of nutrient enrichment of cell culture media are expected to be very different from those of dietary supplementation *in vivo*. Although some important principles may be elucidated with respect to the mechanisms of action of these agents, caution should be exercised when interpreting these data in a dietary context.
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ANIMAL STUDIES

- 7 Many of the dietary intervention studies performed in animals show an impressive degree of protection against UVR-induced skin damage. The endpoints studied comprise UVR-induced squamous cell carcinoma (SCC), immunosuppression and inflammation. However, studies in animals are often extreme, eg they can use excessive supplementation, and are performed in conditions of regular artificial exposure to UVR, and therefore the findings do not necessarily relate to the human situation.

Reduction in fat intake

- 8 The potential influence of dietary fat on photocarcinogenesis was first reported over 60 years ago, when a high fat diet was shown to reduce skin tumour latency in mice (Baumann and Rusch, 1939). A series of murine studies has now demonstrated that reducing fat intake, without altering dietary calorie content, protects against photocarcinogenesis (Black *et al*, 1983, 1985). These effects appear to occur at the promotion stage of carcinogenesis. They may be attributable to a reduction in suitable

target for free radical attack (unsaturated fats), resulting in less lipid peroxidation, which is believed to be a causal event in photocarcinogenesis (Black, 1999).

Omega-3 polyunsaturated fatty acid supplementation

- 9 Polyunsaturated fatty acids (PUFAs) comprise the omega-6, omega-3 and omega-9 families. The omega-6 family, largely derived from vegetable oils, includes the pro-inflammatory mediator arachidonic acid, while the omega-3 family, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are derived mainly from oily fish. A considerable body of evidence has collected over the years for the carcinogenicity of polyunsaturated fatty acids (PUFAs). A linear relationship exists between omega-6 PUFA oil intake, photoimmunosuppression and expression of photocarcinogenesis in hairless mice (Black *et al.* 1985; Reeve *et al.* 1996), supporting an immunological role in dietary fat modulation of photocarcinogenesis. However, it is now clear that a distinction must be made between omega-6 fatty acids, which are carcinogenic in many animal models, and omega-3 fatty acids, which are protective (Black *et al.* 1992). Diets rich in omega-3 PUFAs markedly inhibit photocarcinogenesis in mice (Orenge *et al.* 1989). Indeed, many of the effects of PUFAs appear to depend on the balance of omega-3 to omega-6 fatty acids (Lands, 1992). The omega-3 PUFAs compete with arachidonic acid, an omega-6 PUFA, for metabolism by cyclooxygenase, resulting in the production of less inflammatory eicosanoids. The anti-carcinogenic properties of omega-3 PUFAs may be related to the reduced formation of prostaglandin E₂ (PGE₂), an immunomodulator (Black, 1999).

Carotenoids and vitamin A

- 10 Beta-carotene is an antioxidant with a powerful ability to quench singlet oxygen. However, there are conflicting reports concerning its influence on photocarcinogenesis. While reduced skin cancer is reported in some supplementation studies in mice (Epstein, 1977; Matthews-Roth and Krinsky, 1985), others report that it does not prevent UVR-induced immunosuppression and that it actually increases photocarcinogenesis (Black, 1998). In the latter study, both beta-carotene and another carotenoid, astaxanthin, significantly shortened the tumour latent period and increased tumour multiplicity compared with control supplement, while a third carotenoid, lycopene, had no effect. The beta-carotene supplement level was comparable to that of previous studies, although there were differences in feeding methods. The response to carotenoid may depend on interaction with other available dietary factors. Beta-carotene, alpha-tocopherol and ascorbate are synergistic antioxidants (Palozza and Krinsky, 1992), which together protect against lipid peroxidation (Packer, 1993). Increased dietary beta-carotene alone may result in increased formation of carotenoid radical, which then requires the presence of increased amounts of the other antioxidants for neutralisation.
- 11 The effects of vitamin A (retinol) and its derivatives on experimental photocarcinogenesis are also controversial. Retinoids exert modulatory effects on epithelial differentiation, and oral supplements have been observed to protect against chemically induced skin tumours. However, animal studies have shown no protection against UVR-induced skin cancer (Kelly *et al.* 1989), and augmented photocarcinogenesis has even been observed (Mikkelsen *et al.* 1998).

Antioxidants

- 12** UVR generates large amounts of ROS and free radicals in the skin, which trigger a chain reaction of lipid peroxidation in cell membranes. Antioxidant supplementation shows some success in protection against UVR-induced skin damage in animal experiments. Single agent supplementation with vitamin E (Gerrish and Gensler, 1993) and vitamin C (Dunham *et al.* 1982) reduced UVR-induced skin cancers in animals. Mixed dietary antioxidants (vitamin E + vitamin C + butylated hydroxytoluene (BHT) + glutathione) also reduced photocarcinogenesis in mice, although BHT appeared to be the most active constituent (Black and Chan, 1975). Many studies have been performed to examine the photoprotective properties of topical antioxidants. While topical vitamin E protects against UVR-induced free-radical production and immunosuppression, photoageing and photocarcinogenesis (Gensler and Magdaleno, 1991; Yuen and Halliday, 1997), topical vitamin C protects against phototoxic damage (Darr *et al.* 1992). A sunscreen effect has been suspected in some topical studies, particularly with vitamin E, and, clearly, bioavailability issues are quite different for the topical and dietary routes.
- 13** Selenium is a cofactor for glutathione peroxidase, and hence conveys antioxidant properties. Selenium supplementation inhibits skin cancer in animal studies (Ip, 1985; Pence *et al.* 1994), although some studies have used unacceptably high doses (Overvad *et al.* 1985). While selenium deficiency increases skin cancer occurrence in animals, selenium supplementation protects, but the level of supplementation is important and should be at least the recommended daily dose (RDA) (Pence *et al.* 1994).
- 14** Flavonoids have both antioxidant and anti-inflammatory properties, and are available generally in fruit and vegetables, and in high concentration in certain sources such as green tea products (GTP). In hairless mice, they protect against UVR-induced suppression of contact hypersensitivity, whether given as fruit and vegetables, or as GTP or other flavonoid components (Katiyar *et al.* 1995; Steerenberg *et al.* 1998). GTP reduces UVR-induced sunburn and skin cancer in mice (Wang *et al.* 1992), while the flavonoid quercetin protects against UVR-induced immunosuppression in mice but does not affect UVR-induced tumour growth.
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HUMAN STUDIES

- 15** While UVR-induced skin cancer and immunosuppression are the endpoints used in animal supplementation studies, these rarely apply in human trials. The erythematous (sunburn) response, ie the acute inflammatory reaction of the skin to UVR, is a frequently used surrogate. A series of doses of UVR is given to the skin, and the response is assessed 24 hours later. The sunburn threshold is assessed by eye, and is usually defined as the lowest dose of UVR to result in perceptible erythematous (minimum erythematous dose, MED). The erythematous response may also be assessed quantitatively, by measuring with a reflectance instrument. The use of the acute sunburn response as an indicator for skin damage is partially justified on the grounds that the UVR action spectrum for erythema mirrors that for photocarcinogenesis in mice (de Grujil *et al.* 1993), and it is believed that the effects of repeated acute UVR insults may accumulate to result in chronic skin damage. However, it cannot be assumed that sunburn accurately

reflects susceptibility to chronic damage, ie skin cancer, photoageing and immuno-suppression, since the underlying mechanisms of these effects will differ.

- 16** Epidemiological studies designed to examine the influence of diet on UVR effects are fraught with methodological problems. Of particular concern are the complex nature of the human diet, which also changes over time, and the difficulties in analysing dietary information.

Reduction in fat intake

- 17** Encouraged by the reduction in skin cancer seen in the above studies in mice fed a low fat diet, Black performed an analogous study in people susceptible to skin cancer (Black *et al*, 1994, 1995). Seventy-six people with a previous history of a non-melanoma skin cancer (NMSC) were randomised to continue a normal diet (approximately 40% fat) or reduce fat to 20% of calorie intake, for a two-year period. The calorie content of the two groups was kept equivalent by increasing the number of calories taken as carbohydrate in the intervention group. The patients were examined for the presence of new actinic keratoses (AK, pre-malignant skin lesions) and NMSC at four-monthly intervals by physicians unaware of their assigned diets. The total number of new AK developing per patient between months 4 and 24 was ten in the control group compared with three in the intervention group ($p = 0.001$). The total number of NMSC occurring in the intervention group was noted to be significantly lower ($p < 0.02$) at two years, although it must be noted that the actual number of skin cancers was small. Since lower calorie intake is associated with a reduced cancer risk, the investigators aimed to keep calorie intake the same in the two groups, although a non-significant reduction in weight occurred in the intervention group. There was no analysis of differences in the sex ratio between the intervention and control group, or of differences between the groups in UVR exposure prior to or during the study.
- 18** Graham (1983) reported a case-control study of patients admitted as inpatients or outpatients to a cancer institute. Several dietary factors were analysed for possible association with a range of cancers. No relationship was found between skin cancer occurrence and dietary content of fat, vitamins A or C, fibre or cruciferous vegetables. However, there were a number of methodological problems, and the total number of skin cancer occurrences is not reported. There are reservations about using analysis of current dietary content since diet many years ago may be more relevant to cancer initiation, although recent diet may be relevant to promotion or inhibition of carcinogenesis. Hunter *et al* (1992) reported a prospective case-control study of diet in relationship to the incidence of first basal cell carcinoma (BCC) in a cohort of 73 366 female nurses aged 34–59 years, over a four-year period. The skin cancers were self-reported, by postal questionnaire, raising the possibility of misdiagnosis, but the data suggest that recent diet is not of major importance in the aetiology of BCC. No association of dietary fat level with skin cancer was observed. Thind *et al* (1986) undertook a different approach, by comparing the age-specific cancer death rates in 60 countries for 1980–1981, published by the World Health Organization, with the nutritional intake data for those countries from the Food and Agriculture Organization of the United Nations. A positive association was found with skin cancer for fat, protein and calorie intake when all countries were examined as a whole, but no correlation was found when 'developed' and 'undeveloped' countries were examined separately. Hence, there is clearly a need

for more large-scale long-term prospective studies, comprising randomised clinical trials and cohort studies, to approach the issue of skin cancer and relationship to fat intake, and indeed to other dietary constituents.

Omega-3 polyunsaturated fatty acids

- 19** As discussed in the animal study section above, there are also data to support the view that the composition of fat intake may be important. Following on from several studies in hairless mice, where a high omega-3 PUFA diet protected against UVR-induced photocarcinogenesis, a short-term supplementation study was performed in humans (Orengo *et al.* 1992). This randomised study showed a small, but significant rise in the sunburn threshold after four weeks of supplementation. Two uncontrolled studies then examined the effects of longer-term (three to six month) supplementation with mixed omega-3 fatty acids, ie eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in 28 subjects (Rhodes *et al.* 1994, 1995). The omega-3 PUFAs showed a pronounced uptake into epidermal lipids, from less than 2% of the total fatty acids at baseline to more than 24% after three months ($p < 0.01$). This was associated with a significant increase in the threshold to UVB-induced erythema ($p < 0.001$), which then returned to baseline after stopping supplementation (Rhodes *et al.* 1994). Moreover, the threshold to UVA-provocation of a light sensitivity condition, polymorphic light eruption, was significantly increased. The reduction in the sunburn response was accompanied by a significant reduction in skin PGE₂ (Rhodes *et al.* 1995). A double-blind randomised study of omega-3 PUFA supplementation in 42 healthy people randomised to take a purified omega-3 PUFA, ie 95% EPA, or oleic acid, 4 g daily for a three-month period, has confirmed significant protection against UVB-induced erythema (Rhodes *et al.* 2000). This was accompanied by a significant reduction in UVB-induced p53 expression, a marker of cell damage, in the skin of the EPA-supplemented group but not the oleic acid group. Bioavailability of EPA was confirmed, with an eight-fold increase in skin levels following supplementation. Further experimental data are awaited. Potential mechanisms of the protection by omega-3 PUFAs include competition with omega-6 PUFAs for metabolism by cyclooxygenase, resulting in the production of less active prostaglandins, and a buffering effect against free-radical damage by these unstable fatty acids.
- 20** Epidemiological studies designed to explore the relationship between omega-3 PUFAs and skin cancer are presently lacking. Studies have largely failed to discriminate between omega-3 and omega-6 PUFAs. A case-control study comparing the nutrient intake of 41 women with melanoma with that of 297 women sampled from the same community showed a strong inverse correlation between high intakes of PUFAs generally and melanoma, but only a non-significant association between low dietary fish intake and melanoma (Bain *et al.* 1993).

Carotenoids

- 21** Carotenoids have an important role in plants as quenchers of UVR-induced oxidative products, and they may have analogous activity in human skin. In addition to its antioxidant effects, beta-carotene may also have anti-carcinogenic properties by affecting cellular differentiation and proliferation following conversion to retinol.
- 22** Early studies of the effects of beta-carotene supplementation were reported to show a reduction in the sunburn response (Matthews-Roth *et al.* 1972), but subsequent studies have failed to confirm this effect (Garmyn *et al.* 1995; Wolf *et al.* 1988). A study

in 20 healthy female students suggested that the combination of beta-carotene and topical sunscreen could be used as a pre-holiday strategy to reduce erythema due to natural sunlight exposure, but the study was small and the effect slight (Gollnick *et al.* 1996). A substantial secondary prevention trial has shown no evidence of reduction in skin cancer (Greenberg *et al.* 1990). In this, 1805 patients who had been recently diagnosed with a NMSC were randomised to 50 mg of beta-carotene daily or placebo. Compliance was judged to be good, based on the results of annual plasma beta-carotene levels. However, after five years there was no significant difference between control and active groups in either the number of NMSC per patient or the time to new cancer development. These negative findings were confirmed in a recent, mainly primary prevention, study (Green *et al.* 1999). Here, 1383 individuals were randomised between four treatment groups: topical sunscreen + beta-carotene 30 mg per day, sunscreen + placebo tablets, beta-carotene 30 mg per day alone, or placebo only. No significant difference in the incidence of either BCC or SCC was seen between beta-carotene and placebo groups (the only significant protective effect seen in the study was protection against SCC by topical sunscreens – see Chapter 7, paragraph 74). It is possible that five years may be too short a supplementation and/or follow-up period, and longer-term studies are awaited.

- 23** Several clinical studies have also been performed in patients with photosensitivity conditions. Beta-carotene supplementation causes subjective and objective improvement in the biochemical disorder, erythropoietic protoporphyria (EPP) (Matthews-Roth *et al.* 1974). Adequate dosage is reported to be important, and much higher doses (typically 120–300 mg per day in adults) are used than in cancer prevention studies. High tissue levels of photosensitising porphyrins in EPP result, after exposure to visible radiation, in the generation of excessive amounts of singlet oxygen. Beta-carotene is a logical treatment since it is a powerful quencher for this reactive oxygen species. However, studies by other investigators have shown conflicting results concerning the efficacy of beta-carotene in EPP (Corbett *et al.* 1977), and it is clear that beta-carotene is no more than partially clinically effective in EPP. No benefit is seen in other photo-dermatoses, including polymorphic light eruption, solar urticaria and chronic actinic dermatitis (Kobza *et al.* 1973).
- 24** A case-control study in 88 males with NMSC showed an inverse relationship between the risk of NMSC and levels of serum beta-carotene ($p < 0.001$), and with high intake of foods containing beta-carotene, ie cruciferous vegetables ($p < 0.01$) (Kune *et al.* 1992). There is very little evidence at present to support a dietary role in the development of melanoma. A case-control study of 204 melanoma patients found no evidence of protection with higher plasma levels of carotenoids, or with retinol or with alpha-tocopherol (Stryker *et al.* 1990).
- 25** It has been shown that long-term, low level beta-carotene intake in humans significantly reduces the steady state plasma vitamin E level, particularly in older adults (Xu *et al.* 1992). Hence, there is a potential risk associated with carotenoid supplementation alone, and the anti-carcinogenic effects of beta-carotene may be best pursued through the consumption of foods rich in carotenoids and other natural antioxidants, including vitamins C and E. Another carotenoid, lycopene, particularly found in tomatoes, is reduced in skin following exposure to solar-simulated radiation, and could also have a role in defending against UVR-induced reactive oxygen (Clinton, 1998).

Retinoids

- 26** *Retinoids* are known to reduce chronic photodamage, and display a range of potential anti-carcinogenic mechanisms, including enhancement of differentiation, gene and oncogene regulation by nuclear receptor binding, and enhanced immune response. However, they appear to be ineffective in reducing skin cancer at low dosage. In a study by Tangrea *et al* (1992), 981 people with a history of two or more BCC were randomised to receive 10 mg of isotretinoin or placebo, daily for three years. No statistically significant protective effect was seen against development of further lesions. Even at this low dosage, significant toxicity was observed, and the side-effects of retinoids when used at higher dosage preclude them as a suitable prophylactic agents for healthy subjects. Interestingly, a recent randomised, double-blind, controlled trial of retinol 25 000 IU daily for up to five years in 2297 subjects with a history of actinic keratoses or NMSC, found that treatment significantly reduced the rate of SCC, but not BCC (Moon *et al* 1997).
- 27** Oral retinoids in high dosage have been found shown to reduce the occurrence of NMSC in specific groups of vulnerable patients. Oral isotretinoin (2 mg per kg per day) reduced the development of NMSC in xeroderma pigmentosum, the severe photosensitivity condition caused by faulty DNA repair but skin cancer rates increased on discontinuation of the treatment (Kraemer *et al* 1988). Similarly, 30 mg per day of acitretin reduced the occurrence of pre-malignant and malignant skin lesions in immunosuppressed patients following renal transplantation (Bouwes-Bavinck *et al* 1995). Unfortunately, these benefits were accompanied by troublesome skin and mucosal dryness.
- 28** A case-control study of 88 males with NMSC showed a significant inverse relationship between the risk of NMSC and the level of serum retinol ($p = 0.02$) (Kune *et al* 1992). There is very little evidence at present to support a dietary role in the development of melanoma. A case-control study of 204 melanoma patients found no evidence of protection with higher plasma levels of retinol (Stryker *et al* 1990).

Antioxidants

- 29** The protective effects of antioxidants in cell culture and animal studies have recently provoked some clinical studies. A long-term (six month) supplementation study of vitamin E 400 IU per day did not reduce clinical sunburn or the numbers of histologically assessed sunburn cells (Werninghaus *et al* 1994). Theoretically, vitamin E may be more effective if combined with vitamin C, which is needed to recycle the photosensitising vitamin E radicals formed following UVR exposure (Kagan *et al* 1992). A small placebo-controlled supplementation study of combined vitamins C and E was reported to protect against the sunburn response (Eberlein-Konig *et al* 1998). However, the supplementation period was very short (eight days), and the placebo group showed increased sensitivity. A longer-term study, in which the tissue bioavailability of nutrients was confirmed, also supports the use of combined supplements, although the doses used were very high (Fuchs and Kern, 1998). Here, 40 healthy people were randomised to receive vitamin E 2 g per day alone, vitamin C 3 g per day alone, combined vitamins E and C, or placebo, for a 50-day period. The combined supplement caused a significant rise in the sunburn threshold, while there was no change in the other treatment groups.

- 30** Double-blind trials have been performed in the photosensitivity condition EPP using antioxidant agents other than beta-carotene. There was no significant benefit with vitamin C, 1 g daily for four weeks (Boffa *et al.* 1996), or with short-term supplementation with N-acetylcysteine (Norris *et al.* 1995). A three-month placebo-controlled trial with 1800 mg per day of oral cysteine, reported some subjective and objective improvement, but statistical analysis was not presented (Roberts and Matthews-Roth, 1993).
- 31** Selenium has antioxidant properties via its action as cofactor for glutathione peroxidase. The importance of selenium in the diet has attracted interest in Europe in recent years, due to the fall in dietary selenium intake thought to be caused by a switch from selenium-rich cereal crops imported from the USA to the selenium-poor crops of Europe (Rayman, 1997). Intake in the UK has fallen to 40% of the RDA over the past 15–20 years. In a case-control study of 240 patients with NMSC, Clark (1984) found significantly lower plasma selenium levels than in controls. In addition, a case-control study showed that patients with stage 3 melanoma had the lowest levels of serum selenium (Reinhold *et al.* 1989). However, long-term supplementation with selenium had no significant effect on the occurrence of NMSC in a secondary prevention study (Clark *et al.* 1996). Here, 1312 people with a history of NMSC were randomised to 200 µg of selenium or placebo daily, treated for a mean of 4.5 years and followed up for several years. This intervention did not significantly affect the incidence of NMSC, but the blinded phase was stopped early due to reduced total cancer incidence and mortality. This study, performed in the selenium-replete North American population, suggests that the promotion phase of skin cancer is not reduced by selenium supplementation. However, a selenium-deficient population might behave differently (Fleet, 1997).

Vitamin D

- 32** An observation that vitamin D inhibited the growth of cultured melanoma cells, led to speculation concerning potential preventive effects of vitamin D on melanoma. The relationship between vitamin D and melanoma risk was examined in a case-control study in 165 melanoma patients and 209 controls (Weinstock *et al.* 1992). From their questionnaire, the authors found no evidence of an association of melanoma risk with total vitamin D intake, consumption of milk or vitamin D supplements.
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SUMMARY AND CONCLUSIONS

- 33** Nutritional strategies for protecting the skin from UVR-mediated damage have comprised the use of vitamin and non-vitamin antioxidants, flavonoids, beta-carotene, retinol, reduction in total fat intake, and modification of fat composition. The approach has been studied in cell culture and animal models, in healthy people and patients with skin cancer or photosensitivity disorders. Most emphasis here has been placed on the human studies, since supplementation of cell culture medium does not approximate dietary intake in the whole organism, and animal studies have often used excessive supplementation doses.
- 34** *In vitro* studies show that pre-supplementation of skin cells (keratinocytes and fibroblasts) with antioxidants can reduce both oxidative stress and cytotoxicity due to UVR. Antioxidant dosage is important in order to avoid pro-oxidant effects,

and combinations of antioxidants have synergistic activity against aspects of UVR-induced damage.

- 35** In animal models, a range of dietary strategies results in an impressive degree of protection against UVR-induced skin damage, the endpoints being photocarcinogenesis and immunosuppression. A reduction in total dietary lipid from 40% to 20% conveys significant protection against photocarcinogenesis. Modification of dietary fat composition also has significant effects, with omega-6 PUFAs showing a direct correlation with photocarcinogenesis, while omega-3 PUFAs are protective. Dietary supplementation with vitamin E or vitamin C reduces skin cancer formation, and dietary flavonoids can reduce both photocarcinogenesis and UVR-induced immunosuppression. While selenium deficiency is associated with increased skin cancer, supplementation can reduce photocarcinogenesis, but high doses are required.
- 36** The animal data concerning beta-carotene are conflicting, with some studies reporting protection against skin cancer while others have found augmentation of carcinogenesis. Since many reactions require the combined presence of beta-carotene and vitamin E and/or vitamin C, it is speculated that single supplementation may lead to an excess of beta-carotene radicals, which may then cause damage. Hence, it may be important to give combined supplements.
- 37** Human dietary intervention studies show some protection against UVR-induced effects. However, knowledge concerning specific dietary factors is incomplete and sometimes inconsistent. The usual endpoint examined is the sunburn response, which may or may not prove to be a suitable surrogate for various aspects of chronic UVR-induced damage. The most convincing data to date are from a double-blind, randomised secondary prevention study, in which a reduction in total fat, to 20% of total calorie intake, reduced the incidence of premalignant lesions (actinic keratoses) and NMSC. These results require replication. Supplementation with omega-3 PUFAs results in pronounced uptake of these fatty acids into the skin and this is associated with a significant reduction in the sunburn response and UVB-induced p53 expression; further data are awaited.
- 38** Important issues when exploring dietary antioxidants are dosage, bioavailability, pro-oxidant effects and use of single or combination therapies, in addition to selection of a biologically relevant endpoint. Supplementation with single agent antioxidants has been ineffective in human studies, although combined vitamins E and C protected against the sunburn response. Selenium did not protect against skin cancer in a long-term supplementation study in a selenium-replete population, despite being associated with a reduced risk of some internal tumours. However, long-term studies have not yet been performed in selenium-deficient populations.
- 39** The majority of beta-carotene human supplementation studies have shown no protective effect against the sunburn response. Epidemiological studies show some evidence that high serum beta-carotene levels and high intake of beta-carotene containing vegetables are associated with a lower risk of NMSC. However, in long-term primary and secondary prevention studies, beta-carotene did not protect against first occurrence of NMSC, or recurrence. Although study data are conflicting, beta-carotene may have partial protective effects in a photosensitivity disorder, erythropoietic porphyria (EPP), where much higher doses are used.
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10 Vitamin D

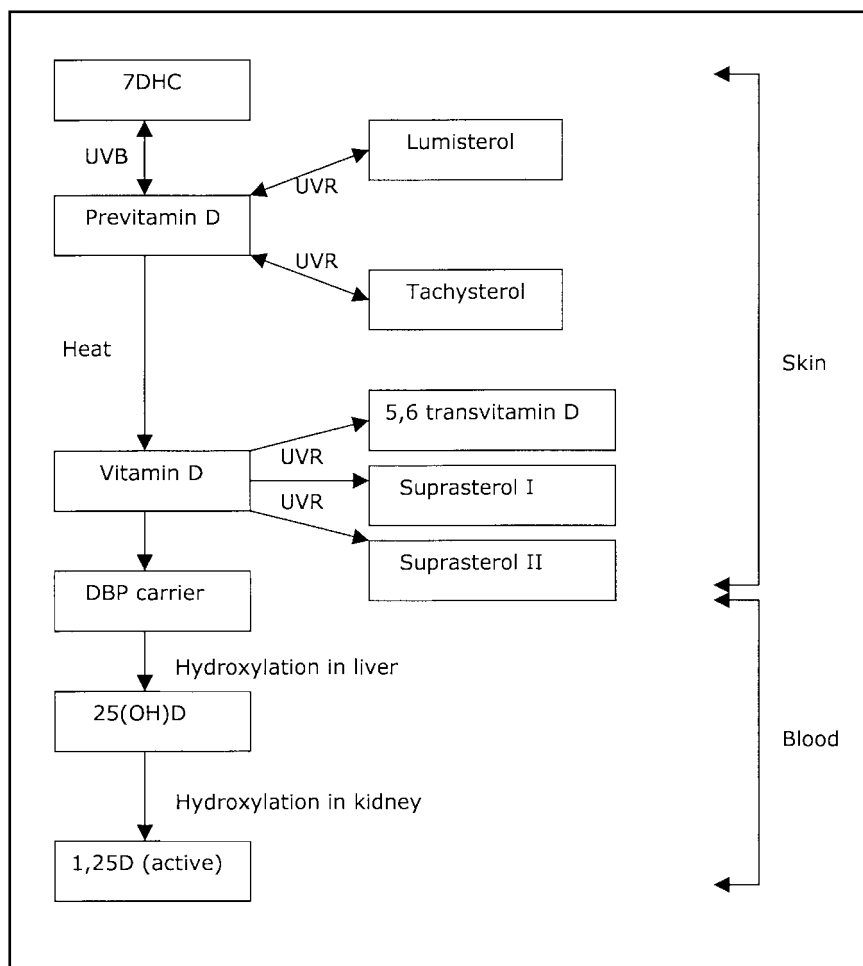
INTRODUCTION

- 1 The cutaneous synthesis of vitamin D is recognised as one of the few beneficial biological effects arising from exposure to ultraviolet radiation (UVR). It has long been known that vitamin D is essential for calcium metabolism and a healthy skeleton, and that irradiation with UVR can cure rickets – the childhood disease of vitamin D deficiency – or guard against osteomalacia, the adult form of the disease. More recently it has been suggested that vitamin D may also play a role in protecting against colorectal, breast, ovarian and prostate cancer, but at present the evidence for this protection is indirect and more work is needed to determine whether, and if so how, vitamin D might act in this capacity.
 - 2 There are two forms of vitamin D: vitamin D₂ and vitamin D₃. Vitamin D₂ (ergocalciferol) is synthesised in plants and fungi by irradiating ergosterol, the plant steroid. Vitamin D₃ (cholecalciferol) results from the irradiation of 7-dehydrocholesterol in the skin of humans and other animals. Both forms of the vitamin play equally effective roles in maintaining calcium metabolism, although not until converted to their active metabolites. Measurements of vitamin D status or intake do not usually differentiate between vitamin D₂ and vitamin D₃ and the term vitamin D is used to cover both forms. No distinction is made between vitamin D₂ and vitamin D₃ in the following discussion, but it should be understood that any vitamin D originating from cutaneous synthesis is vitamin D₃, while dietary sources of the vitamin (including supplements and fortification) may be either vitamin D₂ or vitamin D₃.
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CUTANEOUS SYNTHESIS

- 3 The production of vitamin D in the skin is essentially a two-stage process, first a rapid UVR-induced reaction, then a much slower heat isomerisation. The progression from the precursor 7-dehydrocholesterol (7DHC, also known as pro-vitamin D) to the active circulating metabolite 1,25-dihydroxyvitamin D (1,25D) is shown in Figure 10.1. The figure indicates that the basic cutaneous synthesis is part of a more complex set of photochemical reactions that control the net vitamin D available from this source.
- 4 The vital first step in vitamin D synthesis, 7DHC to previtamin D (preD), requires irradiation with UVB wavelengths (Figure 10.2), specifically wavelengths of less than 315 nm (MacLaughlin *et al.* 1982). Once preD is formed it can undergo several reversible photoreactions (to 7DHC, lumisterol or tachysterol), or a slow heat isomerisation to vitamin D. Continued irradiation of 7DHC in sunlight will result in a mixture of 7DHC, preD, lumisterol and tachysterol. There is a third reaction pathway which can be observed in the test tube, the irreversible formation of toxisterols from preD. These inert products increase very slowly with continuing irradiation, representing only a few per cent of the isomer mixture after many hours of irradiation. Apart from removing a small amount of preD from the quasi-equilibrium system of other isomers, the toxisterols

FIGURE 10.1
Synthesis of
vitamin D



seem to have no other effect and will not be discussed further. The fraction of preD in the sun-exposed mixture remains below 20% (Holick *et al.* 1981; Webb *et al.* 1988); prolonged irradiation simply increases the fraction of the inert isomers lumisterol and tachysterol (Figure 10.3). Irradiation by other UVR sources will result in a different balance of isomers as each conversion to/from preD and its various isomers has a different action spectrum (Figure 10.2) and will occur at a rate dependent on the irradiating spectrum and the amount of the target isomer.

- 5 Once preD is present in the skin no further irradiation is necessary. The heat isomerisation to vitamin D is a slower process than photoproduction, but recent research shows it to be a far quicker process than originally thought, taking a few hours rather than days (Tian *et al.* 1993; Tian and Holick, 1999). The vitamin D is then picked up by a D-binding protein (DBP) in the blood and transported to the liver, where it is

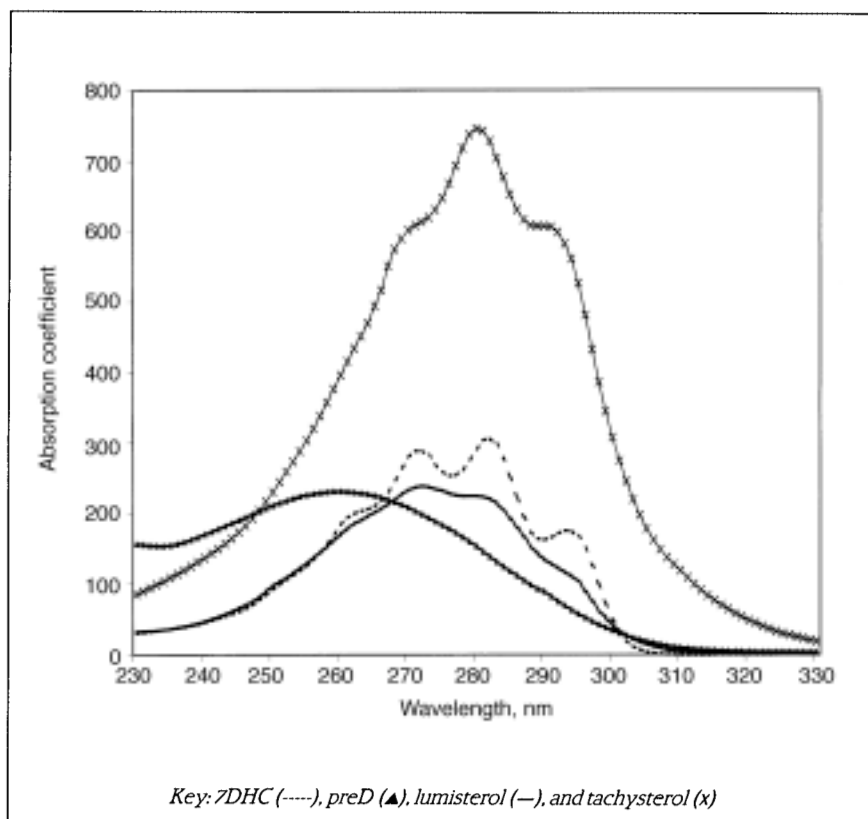
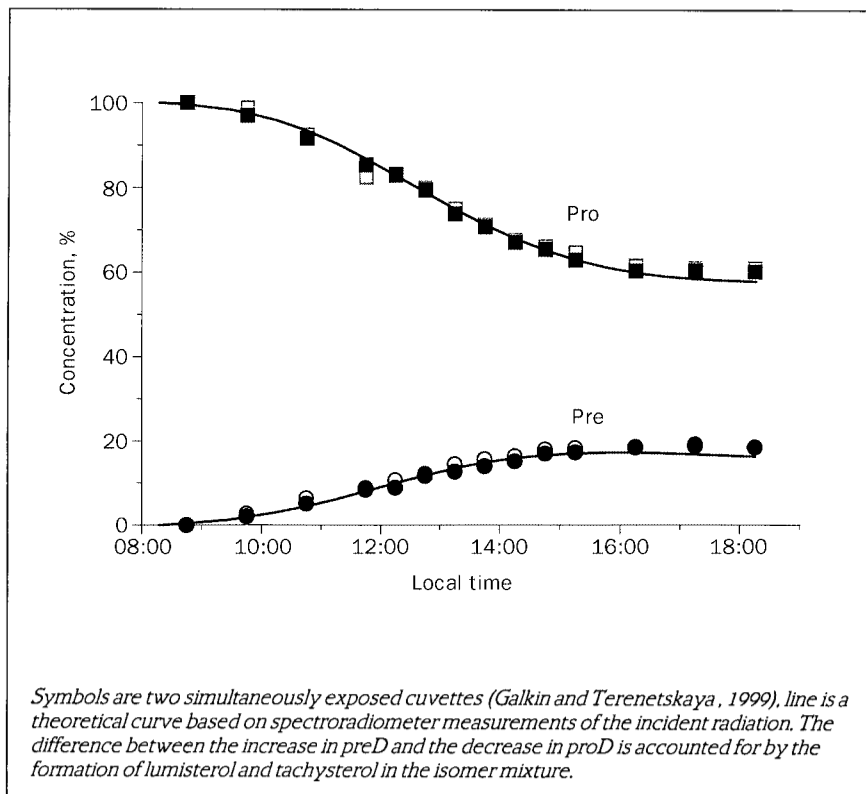


FIGURE 10.2
Absorption
coefficients (of
1% solution over
thickness 1 cm)
of
previtamin D and
its isomers
(kindly supplied by
Dr I Terenetskaya)

converted to 25-hydroxyvitamin D (25OHD), the circulating metabolite that is most commonly used as a measure of vitamin D status. The active metabolite, 1,25D, is the result of a further hydroxylation in the kidneys, a process that is tightly controlled by other metabolic factors. Vitamin D itself is photolabile, and any vitamin D not removed from the skin by DBP can be degraded to 5,6-transvitamin D and the suprasterols I and II (Figure 10.1) by radiation of both UVB and UVA wavelengths next time the skin is irradiated (Webb *et al.* 1989; Webb, 1993). Thus there are several mechanisms that limit the amount of vitamin D that can accumulate in the skin and pass into the circulatory system, preventing an overdose. This control is not present if the vitamin is taken orally, when prolonged excessive intake of vitamin D can lead to toxic effects including nausea, vomiting, kidney stones, and in extreme cases death.

- 6 A defect in the enzyme 7-dehydrocholesterol reductase (Irons *et al.* 1993) has now been recognised as the crucial genetic abnormality in the Smith-Lemli-Opitz syndrome which is a birth defect associated with mental retardation. Patients with this disease have extremely photosensitive skin with a peak sensitivity in the UVA region at 350 nm (Anstey *et al.* 1999). However, the link between DHC reductase deficiency and UVA sensitivity is unknown.

FIGURE 10.3
Production of previtamin D in a starting solution of 7DHC (Pro) during exposure to sunlight on a July day in Northern Greece



DIETARY SOURCES

- 7 The major dietary sources of vitamin D in the UK diet are oily fish, meat and eggs, plus margarine and other fat spreads, milk products and breakfast cereals. Vitamin D occurs naturally in the first group of products (new analytical techniques have shown significant vitamin D in meat), while fat spreads and breakfast cereals are fortified with the vitamin (DH, 1998; MAFF, 1996). In 1996 the average daily intake of 3.35 µg vitamin D was attributed mainly to fat products (39%, assessed by the vitamin D content of food purchased by British households), followed by cereals and fish (both 16%), meat (12%), eggs and milk products including fortified formula milk (both 7%) (MAFF, 1996). However, the daily intake, and its sources, varies significantly within the general population depending on diet, which is determined by age, region, income, religion or other personal choices (eg vegetarian). Differences will also occur between the UK and other populations where the traditional diet is different (eg a higher intake of oily fish in parts of Scandinavia), or fortification practices are different (eg milk has long been fortified with vitamin D in the USA).
- 8 The comparative importance of dietary and cutaneous sources of vitamin D is indicated by the 1998 reassessment of the Daily Reference Values (DRVs) for vitamin D for the UK population (DH, 1998). DRVs for vitamin D are given in terms of the Reference Nutrient Intake (RNI) which is the amount of the nutrient required to

meet the needs of nearly all a given population group. The 1998 reassessment left the 1991 guidelines unchanged, as follows.

- 9 For individuals aged 4–64 years an RNI of zero is upheld as adequate vitamin D status is generally achieved through the action of sunlight. It was noted that some specific groups within this population may need supplementation and those at risk should take $10 \mu\text{g d}^{-1}$.
 - 10 For people aged over 64 years an RNI of $10 \mu\text{g d}^{-1}$ is a safeguard against vitamin D deficiency. This acknowledges the fact that cutaneous synthesis of vitamin D is likely to be reduced in the more aged population for a variety of reasons. It was also noted that unsupplemented diet alone is unlikely to provide the RNI and supplementation will be needed.
 - 11 For children aged 0–6 months the RNI is $8.5 \mu\text{g d}^{-1}$, and for children aged 6 months to 3 years it is $7 \mu\text{g d}^{-1}$. This reflects the demands of rapid growth, the need to protect delicate skin from excess sunlight, and the possibility that some infant diets will contain few vitamin D rich or fortified weaning foods.
 - 12 For pregnant and lactating women an RNI of $10 \mu\text{g d}^{-1}$ is recommended to ensure that an adequate vitamin D status is maintained in both the mother and the fetus or infant.
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UVR REQUIREMENTS FOR ADEQUATE VITAMIN D

- 13 The conventional measure of vitamin D status is the plasma concentration of 25OHD, which responds to changes in both oral intake of the vitamin and sunlight exposure (concentrations of the active metabolite 1,25D are tightly controlled by other factors). People with clinical rickets or osteomalacia can present with 25OHD values within the range $0\text{--}8 \mu\text{g l}^{-1}$ ($0\text{--}20 \text{ nmol l}^{-1}$; DH, 1991), so the lower limit of adequate vitamin D status is conventionally defined as $10 \mu\text{g l}^{-1}$ (25 nmol l^{-1} ; Grunduis *et al.* 1986), although higher limits have been suggested (Gloth *et al.* 1995). As there is no information available about long-term bone health and vitamin D other than that of the diseases above, this definition is essentially one of avoiding rickets and osteomalacia.
- 14 The amount of sunlight required to maintain an adequate vitamin D status (expressed in easily recognisable terms as minutes for which bare skin is exposed to sunlight) depends upon geography, skin pigmentation and demographical factors, and when the exposure occurs. The desirability of exposing bare flesh and the availability of sunlight (specifically the UVB part of the spectrum) both vary with latitude, season and time of day. The vitamin D produced in the skin per J m^{-2} of effective incident radiation will depend upon skin pigmentation and age, while the concentrations of vitamin D in the blood will also depend upon the area of skin that has been exposed, and (for the active metabolites) the efficiency of the liver and kidney functions. Thus there is no simple guideline that will apply to every situation, rather each exposure must be assessed in a manner similar to assessing the risk of erythema. The influences of several environmental and personal factors in such an assessment are discussed below.
- 15 The initial step in the cutaneous production of vitamin D requires irradiation of the skin by radiation of strictly UVB wavelengths (UVA radiation does not contribute to vitamin D production, as it does to erythema.) UVB radiation is strongly absorbed by

ozone in the atmosphere, the absorption coefficient increasing as wavelength decreases and effectiveness for preD production increases. The pathlength of radiation through the atmosphere also influences total absorption: the longer the pathlength the greater the absorption. Pathlength is determined by solar elevation: when the sun is low in the sky the pathlength is long, when the sun is directly overhead the pathlength is at its shortest. When combined with the wavelength-dependent absorption of ozone the daily, seasonal and latitudinal changes in pathlength result in a continual changing of the incident UVB spectrum. When the sun is high in the sky (around noon/in summer/at low latitudes) significant amounts of the shorter UVB wavelengths most effective for preD formation reach the surface. When the sun is low in the sky (early or late in the day/in winter/at high latitudes) only the longer, less effective UVB wavelengths are incident at the ground.

- 16** There is evidence from exposure of 7DHC in test tubes (Ladizesky *et al.* 1995; Pettifor *et al.* 1996; Webb *et al.* 1988; Webb, 1993), exposure of excised skin (Webb *et al.* 1988) and many epidemiological studies (Beadle *et al.* 1980; Lamberg-Allardt, 1984; Rosen *et al.* 1994; Stamp and Round, 1974; Webb *et al.* 1990a) that at mid-high latitudes (from 40°–70°) there is a seasonal ability to synthesise preD and hence vitamin D. The period of the year for which it is not possible to synthesise preD (and hence when vitamin D status is likely to decrease) gets progressively longer as latitude increases. For example, in Los Angeles (34°N) preD synthesis (in a test tube) occurs all year round, while in Boston (42°N) it could not be detected between November and February, and in Edmonton (51°N) preD was not observed from October to April (Webb *et al.* 1988).
- 17** Seasonal cycles of circulating 25OHD are well documented in the UK and other mid-high latitude populations, but provided a mid-normal plasma 25OHD level can be built up during the summer then this level combined with stored vitamin D (in fatty tissues) will prevent a healthy individual from becoming vitamin D deficient through the winter (Beadle *et al.* 1980; Devgun *et al.* 1981; Lamberg-Allardt, 1984; Poskitt *et al.* 1979). Exposure to sunlight is necessary the following spring/summer to replenish 25OHD levels. A study of elderly long-stay hospital patients in Nottingham (53°N) found that exposure of the face and hands for a few hours each week in spring and summer was sufficient to raise circulating 25OHD levels above the wintertime low (Webb *et al.* 1990b). Single exposures were generally short and no volunteer reported any erythema during the study. Similar results were found during a more extended study in Boston, USA (42°N): ambulatory elderly volunteers who spent short periods outdoors during the summer months were capable of maintaining sufficient vitamin D status, while those confined to bed were more in need of dietary supplementation to maintain adequate levels of vitamin D (Webb *et al.* 1990a).
- 18** The incident radiation, however abundant, can only begin the process of vitamin D synthesis if it reaches the 7DHC in the skin. PreD production is therefore decreased if a competing UVB absorber is present, either naturally occurring melanin pigmentation or artificially applied sunscreen, or if there are fewer target 7DHC molecules in the skin. A decrease of 7DHC in skin cells is a symptom of ageing, decreasing the capacity of the skin to synthesise preD (MacLaughlin and Holick, 1985), although ambulatory elderly people with short but regular exposure to sunlight will acquire and maintain an adequate vitamin D status (Webb *et al.* 1990a,b). The low vitamin D status of many

elderly people is more likely to be due to a combination of little outdoor activity, small areas of exposed skin (many clothes), and a diet that is naturally low in vitamin D.

- 19** People with naturally pigmented skin require more UVB radiation to produce the same change in circulating 25OHD as fair skinned people (Lo *et al.* 1986). However, if the irradiation is expressed in terms of minimum erythral dose (MED) for each respective skin type then vitamin D per MED is a constant factor. Thus the evolutionary gradient in skin pigmentation with latitude provides a natural response not only to protection from sunburn, but also to vitamin D requirements. Pigmented people moving to higher latitudes are more susceptible to low vitamin D status than the indigenous population (Harris and Dawson-Hughes, 1998; Serhan *et al.* 1999), although this is partially compensated for by race-independent properties of 25-hydroxylation (Matsuoka *et al.* 1995). Thus, it is a combination of factors such as skin colour, social habits and diet that is often required before vitamin D status becomes a problem (Henriksen *et al.* 1995; Lawson *et al.* 1999). Young Asian children breast fed by mothers who already have a low vitamin D status are particularly at risk (Pugliese *et al.* 1998), while the vitamin D status of older Asian children in England has been shown to be lower than that of their white counterparts (Lawson *et al.* 1999).

- 20** The public health guidelines for avoidance of sunburn and skin cancer, ie use of sunscreens, and avoidance of sun exposure when the sun is high in the sky, could also, if carried too far, prevent cutaneous vitamin D synthesis. Sunscreens can suppress vitamin D synthesis (Matsuoka *et al.* 1987) because they prevent UVB radiation from reaching the skin. If thoroughly applied to all exposed skin no natural synthesis of the vitamin can take place. Exposure only when the sun is low in the sky is equivalent to restricting exposure to wintertime/high latitude conditions. The long radiation path-length through the atmosphere shifts the incident spectrum to longer wavelengths and significantly reduces the radiation effective for vitamin D synthesis. Sayre *et al.* (1999) have calculated that for high solar elevations sunlight is more efficient for vitamin D synthesis than for erythema and adequate vitamin D synthesis can be initiated with a short suberythral exposure. When the sun is low in the sky the erythral reaction is the most efficient process and exposure will favour erythema before suitable vitamin D synthesis (although both processes are limited by the long exposure times required). Thus, whilst the avoidance of excessive sun exposure is important, for the reasons discussed in Chapter 7 and elsewhere, overemphasis – in the extreme and where vitamin D consumption is insufficient – can be detrimental for the skeleton.
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POSSIBLE ROLE OF VITAMIN D IN NON-SKELETAL DISORDERS

- 21** The discussion above has been based on the well-known skeletal requirements for vitamin D. However, it has been known since 1979 that vitamin D receptors are present in many parts of the body (Stumpf *et al.* 1979; Tanaka *et al.* 1982), besides the more obvious locations associated with calcium metabolism (intestine, bone and kidney). Later it was found that 1,25D inhibited proliferation in some cells and lymphocytes, with implications for a role in some diseases, and function of the immune system (summarised in Holick, 1999). The treatment of the proliferative skin disorder psoriasis with topically applied 1,25D has been very successful (Perez *et al.* 1996). However, not

all potential treatments have been successful: patients with preleukemia did not, in the end, benefit from treatment with 1,25D (Koeffler *et al*, 1984).

- 22** More recently, a number of epidemiological studies have identified inverse correlations at a population level between sunlight exposure (or at least ambient sunlight) and a number of other diseases, and have suggested that a protective role might be attributed to vitamin D (Garland *et al*, 1985, 1989, 1990). Certainly vitamin D receptors have been found in cancer cells of the breast, prostate and colon, and in melanoma and squamous cell carcinoma cells (Eisman *et al*, 1981; Holick, 1995; Skowronski *et al*, 1993), but the circulating active form of the vitamin, 1,25D, is closely controlled and not directly related to sun exposure. However, it has recently been discovered that skin, prostate and prostate cancer cells can produce 1,25D (Bikle *et al*, 1986; Schwartz *et al*, 1997). Cultured human prostate cells can convert 25OHD to 1,25D (Schwartz *et al*, 1998); 1,25D inhibits proliferation in normal prostate and prostate cancer cells; 25OHD also reduces proliferation in normal prostate cells, at high concentrations, which suggests that 25OHD is metabolised to the active 1,25D form (Holick, 1999). If such metabolism can occur when high concentrations of 25OHD are present then it adds strength to the link between sunlight exposure, cutaneous vitamin D synthesis and their inverse correlation with cancer incidence (Holick, 1999; Studzinski and Moore, 1995).
- 23** Finally, a possible relationship between vitamin D and blood pressure may exist. There is an observed inverse relationship between blood pressure and latitude, with decreased hypertension in people living at low latitudes (Rostand, 1997), and it has been suggested that exposure to UVB radiation, but not UVA radiation, can reduce blood pressure (Krause *et al*, 1998). There are vitamin D receptors in cardiac and vascular smooth muscle, while vitamin D deficient rats showed an increase in blood pressure. Whether this was due to indirect effects on calcium metabolism or direct effects of vitamin D is not known (Weishaar and Simpson, 1989).
- 24** The evidence for these possible additional benefits of vitamin D remains indirect. In any case, the benefits of vitamin D can be gained through short (suberythral) exposures: the photochemistry of vitamin D limits its photosynthesis during prolonged exposure. Sunburn or significant changes in skin pigmentation (heavy tanning) remain indicators of high exposure that may increase the risk of skin cancer, with no additional benefits from vitamin D synthesis.
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SUMMARY AND CONCLUSIONS

- 25** It has long been known that vitamin D is necessary for a healthy skeleton, through its involvement in calcium metabolism. The main source of the vitamin is cutaneous synthesis following exposure to UVB radiation (usually sunlight). The diet, unless supplemented, plays a minor role in provision of the vitamin. Cutaneous synthesis of vitamin D via the production of preD is limited by the photochemistry involved; it is initiated rapidly and at suberythral doses and prolonged exposures are of no additional benefit. At mid-high latitudes cutaneous synthesis does not occur during the winter months as there is not enough UVB in sunlight to promote the formation of preD, but summer exposure can provide sufficient stores of the vitamin to last through the

winter. Naturally pigmented people require more UVB to produce the same amount of vitamin D, although their requirements normalised to their own MED are the same. The result of this is that pigmented people living at high latitudes have an increased susceptibility to vitamin D deficiency. The elderly, and pregnant women and young children, especially those with pigmented skin, are most at risk of vitamin D deficiency, because of decreased outdoor exposure and the extra demands of growth, respectively. However, care should be taken not to overexpose the skin of children since sunburn in childhood may be a risk factor for skin cancer later in life. Babies can be protected if pregnant and lactating women ensure that they have a good vitamin D status, through dietary supplementation if necessary. Most baby milk formulas are fortified with vitamin D. Other sections of the population should be able to maintain an adequate vitamin D status with short exposures to sunlight, as encountered in everyday life (eg a walk to the shops/school). Sunbathing is not necessary.

- 26** There is some evidence for a possible role for vitamin D in protecting against some cancers, but this evidence is not strong. The initial claims were based on population-based epidemiological associations and the findings have had limited support from the discovery of mechanisms within the body for extra-renal synthesis of the active form of the vitamin (1,25D), and its effect on cell growth. Whether the benefits of vitamin D are limited to the skeleton or extend to cancer prevention, its synthesis is still optimised at suberythemal doses and there is no benefit from the levels of exposure that incur sunburn and potentially increase the risk of skin cancer. However, shunning the sun completely can raise the risk of vitamin D deficiency and skeletal problems. In the absence of adequate vitamin D in the diet, modest, suberythemal exposure, the length of which differs for individual skin type and solar environment, should produce all the benefits and few of the risks.

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11 Risk Assessment

INTRODUCTION

- 1 The original report by the Advisory Group on the health effects of ultraviolet radiation (UVR) (NRPB, 1995) presented the results of calculated skin cancer risks consequent to exposure to both natural and artificial sources of UVR. This chapter is reproduced in Appendix B. At that time it was possible to estimate risks only for basal and squamous cell cancer (BCC and SCC); knowledge about the action spectrum and dose-response relationship for the induction of melanoma were inadequate to permit useful risk estimates. In the intervening period, there remains insufficient knowledge about the quantitative role of UVR in the pathogenesis of melanoma to allow risk calculations, and the models for estimating the risks of BCC and SCC have not improved appreciably to allow significantly more accurate estimates.
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RECENT INFORMATION

- 2 Recent estimates (Slaper *et al.* 1996; UNEP, 1998) suggest that the increased risk of skin cancer due to ozone depletion would not have been adequately controlled by implementation of the Montreal Protocol alone, but can be achieved through implementation of its later amendments (Copenhagen 1992 and Montreal 1997). These estimates indicate that under the Montreal Amendments, incidence rates of skin cancer (all types) in northwest Europe (Benelux, Denmark, Germany and the UK) will peak around 2050 at an additional incidence (relative to the incidence in 1980) of about 9 per 100 000 (Slaper *et al.* 1996). Compared with the incidence of skin cancer in 1980, this increase in incidence rate is equivalent to a relative increase of 7.5%. For the UK population of approximately 60 million this would imply 5400 additional cases of skin cancer in 2050 than would have been expected in the absence of ozone depletion. Thereafter the increase in disease rates attributable to ozone depletion is expected to return almost to zero by the end of the 21st century; as skin cancer typically results from several decades of UVR exposure the response of the disease follows later than changes in exposure.
 - 3 The quantitative risk estimates for skin cancer are only valid if all other factors which determine risk, notably human behaviour, remain unchanged. Public health campaigns aimed at encouraging people to reduce their sun exposure by sun avoidance and the use of photoprotective measures, such as sunscreens, clothing and shade, may achieve a reduction in average population UVR exposures, and presumably skin cancer rates, which could more than offset the adverse effects of ozone depletion. However, the calculated risks imply full compliance with restrictions on the production and consumption of ozone-depleting chemicals throughout the world. If, in the future, compliance does not continue, damage to the ozone layer could be greater than hitherto expected and biological impacts could be more severe (SORG, 1999).
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12 Protective Measures

INTRODUCTION

- 1 For most people, their greatest source of exposure to ultraviolet radiation (UVR) is the sun. In people with white skins living in the tropics (30°N to 30°S), protection against solar UVR is necessary all year, whereas for those living in temperate latitudes (40°N to 60°N) sun awareness is generally limited to the six-month period from April to September. Several methods of personal protection against solar UVR are available. These are:
 - (a) avoiding exposure to direct sunlight during the period around noon in summer.
 - (b) seeking shade.
 - (c) clothing and eyewear that are designed to provide a high level of absorption of UVR.
 - (d) hats that provide shade to the face and neck.
 - (e) topical sunscreens.

When these measures are used in combination, it is possible to reduce exposure to solar UVR to within acceptable levels without seriously limiting the range of outdoor activities that can be safely pursued.

SUN PROTECTION FACTOR

- 2 The concept of the Sun Protection Factor (SPF) was originally proposed by the Austrian scientist Franz Greiter and subsequently adopted by many regulatory authorities and the cosmetic and pharmaceutical industries (COLIPA, 1994; FDA, 1978). It is popularly interpreted as how much longer skin covered with sunscreen takes to burn compared with unprotected skin (HEA, 1996).
- 3 A more appropriate definition of the Sun Protection Factor [or Clothing Protection Factor (CPF) in the case of clothing; see below] is that it is the ratio of the least amount of ultraviolet energy required to produce a minimal erythema on sunscreen (or clothing) protected skin to the amount of energy required to produce the same erythema on unprotected skin (FDA, 1978). Ten years ago most commercially available sunscreen products had SPFs less than 10 but today there is a trend for higher factors. Most manufacturers produce products with SPFs of 15 to 20 and it is not uncommon to find products claiming an SPF of 50 or higher. The clothing industry has also embraced the notion of sun protection and there is a British Standard for its measurement (BSI, 1998).
- 4 The primary function of a photoprotective device (sunscreen or clothing) is to prevent sunburn so just how large should the SPF be to satisfy this requirement? Maximum daily ambient UVR levels under clear summer skies are about 70 SED in the tropics, 60 SED at mid-latitudes approximating to those of southern Europe, and 45 SED for UK latitudes. These maximum ambient exposures will not be received by people simply because it would be unrealistic to lie in the unshaded sun all day without moving. An extreme sunbather might spend half the time supine and half the time prone, resulting in a maximum exposure on much of the body surface of 50% of ambient. For

upright subjects engaging in a variety of outdoor pursuits such as gardening, walking or tennis, the exposure relative to ambient on commonly exposed sites, eg the chest, shoulder, face, forearms and lower legs, ranges from about 20% to 60% (Diffey, 1999). So someone who is on vacation in southern Europe would receive a daily exposure of no more than 20 SED over much of the body surface. Since an exposure of 2–3 SED is necessary for a minimal erythema in the most common British skin types (Diffey, 2000), a photoprotective device, properly applied, need only possess an SPF of 10 or more to give a sunburn-free vacation. For tropical sun exposure, an SPF of 15 or higher should be more than adequate for all-day exposure if properly applied.

PHYSICAL APPROACHES TO SUN PROTECTION

Sun avoidance

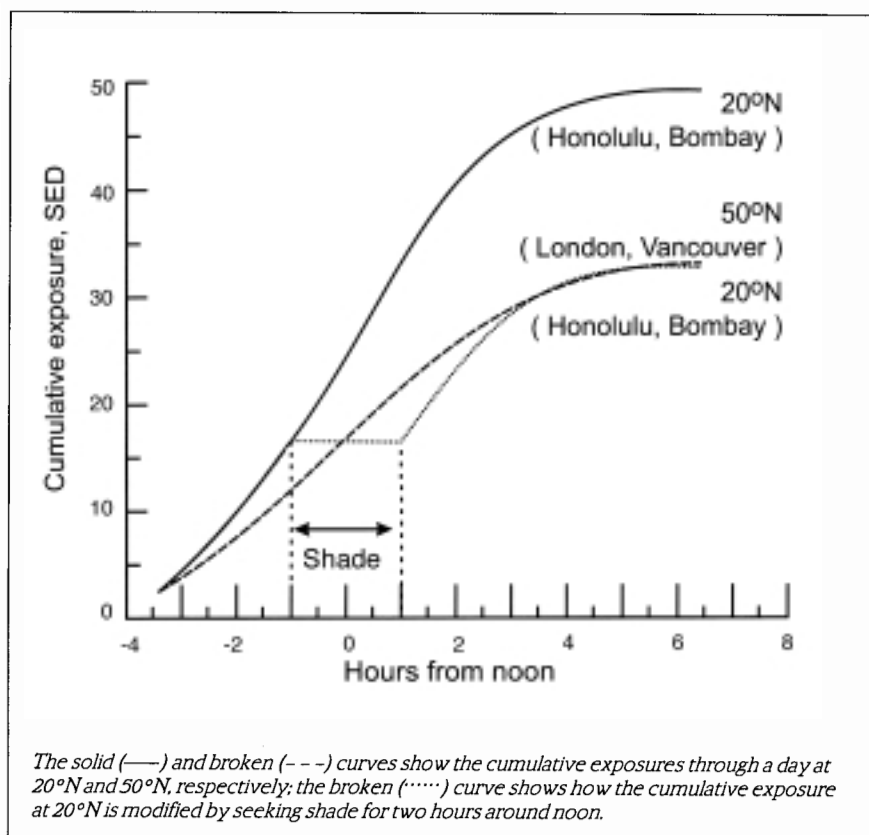
- 5 As a general rule, whenever someone's shadow is shorter than his or her height, care should be taken. The shorter the shadow, the stronger is the sun's UVR and the more likely is sunburn to occur. Under clear skies during summer months, the highest levels of solar UVR are received around noon. Figure 12.1 illustrates that seeking shade for two hours around noon at a latitude of 20°N (eg Honolulu or Bombay) results in the same UVR exposure as all-day sun exposure at 50°N (eg London or Vancouver). Consideration should be given to this issue when planning public outdoor events, as well as for personal activities. Under variable cloud conditions in summer months, breaks in the cloud cover can allow the increase of UVR to levels similar to clear sky conditions and can add significantly to the daily UVR dose.
- 6 Sunburn can occur on cloudy days as well as clear days, although heavy, overcast skies do offer some protection. It is the UVR, and not the infrared radiation, of the sun that is harmful, so a cool, windy day will not necessarily prevent sunburn. Care should be exercised in and around water in open spaces. Many people get sunburnt when they are swimming, boating or playing on a beach.

Shade

- 7 Shade can be provided naturally by trees, by utilising canopies and semi-permanent structures, or by constructed shade in areas where large numbers of people may gather. In addition to protecting against UVR exposure, shade can also provide wind and rain protection, improve acoustics, and enhance the environment. It is important that the shade structure used blocks the line-of-sight path from most of the sky, as well as that from the solar disc. A substantial proportion of solar UVR is received from the sky, as a result of scattering in the atmosphere (Björn and Murphy, 1985; Webb, 1991). At UK latitudes, a minimum of around 50% of solar UVR is received from the sky. This minimum occurs under clear skies near noon in summer, ie when the solar elevation is at a maximum. Under cloudy conditions or when the solar zenith angle is greater, the proportion of total UVR received from the sky is greater. At lower latitudes, the contribution from the sky is smaller than that from the solar disc, but is never insignificant. This effect is more pronounced for UVR than visible radiation, so that observing the amount of shade provided by a structure at visible wavelengths provides an overestimate of its UVR protective properties. Small shade structures such as

parasols leave large amounts of sky visible to the occupant and may provide only low UVR protection. For these reasons, it is not valid to determine the protection provided by a shade structure from the protection factor of its fabric, in an analogous way to the evaluation of protection factors for clothing (Wong, 1994). Measurements have been made of the ratio of the solar irradiance underneath an open-sided fabric shade structure to that outside the structure (Wong, 1994). In most locations that were shaded by the structure the shade ratio was greater than would have been predicted by the transmittance of the fabric. Only when the detector was close to the fabric did the two quantities show good agreement.

FIGURE 12.1 Effect of sun avoidance around noon on sun exposure during a summer's day



Optical filters

- 8 Materials which are visibly clear will absorb UVR to varying degrees. For example, window glass transmits radiation down to 310 nm (within the UVB), whereas plastics such as Perspex® and polycarbonate do not transmit below 370 nm. In general, windows on cars transmit UVA but block UVB, in contrast to laminated car windscreens and cockpit windscreens on airplanes, which block UVB and UVA (Diffey and Roscoe, 1990).

Clothing and hats

- 9** Most summer clothing provides CPFs greater than 10; measurements on over 5000 fabrics submitted for testing to the Australian Radiation Laboratory revealed that 97% of fabrics fell into this category (Gies *et al.* 1996). More than 85% of fabrics had CPFs of 20 or higher. Studies on the spectral transmission of textiles (Robson and Diffey, 1990) show that many materials absorb more or less uniformly over the solar UVR spectrum. In other words most clothing, in common with other forms of shade such as trees, canopies and beach umbrellas, provides principally a quantitative, rather than qualitative, change in cutaneous UVR exposure. A number of factors affect the protection offered by fabrics against solar UVR; these include weave, colour, weight, stretch and wetness (Gies *et al.* 1994). Certain fabrics are marketed as tanning accessories. These occur in certain items, such as swimwear and beach umbrellas, and such items are relatively transparent to UVR.
- 10** Clothing is an effective and reliable source of protection against solar UVR, provided consideration is given to the design of the garment and the UVR transmittance of the fabric. The garment should provide good coverage of the skin and the fabric should prevent most of the incident UVR from reaching the skin beneath it. It is not always possible for consumers to make a reliable assessment of the UVR protection properties of a fabric by visual inspection, so a method has been developed for determining the CPF provided by a fabric, which is defined as the ratio of the erythemally effective solar UVR exposure on exposed skin to that received through the fabric. It is analogous to the SPF quoted for sunscreens. In order to determine the CPF of a fabric, its spectral transmittance at UVR wavelengths is measured at several locations on the fabric sample or garment.
- 11** The penetration, P , of UVR through a fabric (BSI, 1998) is given by

$$P = \frac{\sum_{\lambda=290}^{400} E_{\lambda} \epsilon_{\lambda} T_{\lambda} \Delta\lambda}{\sum_{\lambda=290}^{400} E_{\lambda} \epsilon_{\lambda} \Delta\lambda}$$

where λ is the wavelength of the radiation, E_{λ} is the spectral irradiance of the solar radiation at the Earth's surface, ϵ_{λ} is the weighting function related to the reference erythemal action spectrum published by CIE (McKinlay and Diffey, 1987), T_{λ} is the spectral transmittance of the fabric and $\Delta\lambda$ is the wavelength interval of the measurements. The CPF of the fabric is then given by the reciprocal of the penetration (Agnew *et al.* 1998; Gies *et al.* 1992).

- 12** A wide range of CPFs has been observed from different fabrics (Agnew *et al.* 1998; Gies *et al.* 1992). Very light weight fabrics with an open structure often have CPFs of less than 5. By contrast, a heavier fabric with a closed structure, such as a knitted fabric containing elastane, may have a CPF of 500 or more. Darker coloured fabrics often absorb more UVR than lighter fabrics, but the protection provided by a fabric cannot be reliably predicted from its colour. Off-white and cream fabrics often provide lower CPFs, but white fabrics frequently offer higher protection. This is because white fabrics usually contain fluorescent whitening agents that absorb UVR.
- 13** The conditions under which a fabric is used can also affect its CPF. If it is stretched during use, its CPF will decrease. This reduction in CPF should be assessed by

laboratory testing, as the exact decrease depends on the fabric structure and the degree of stretch. A reduction in CPF of more than 50% has been seen for some fabrics (Agnew *et al.* 1998). The CPF of a fabric can also change when it is wet. This effect is more complicated, with both increases and decreases in CPF observed for different fabrics (Agnew *et al.* 1998; Gies *et al.* 1992; Roy and Gies, 1997). To date the largest increases and decreases in CPF have been seen on fabrics containing a substantial proportion of cotton. In most cases the changes in CPF were reversed when the fabric dried but some showed a permanent increase in CPF after drying. This was attributed to shrinkage of the fabric. Polyester and nylon fabrics, many of which also contained a small amount of elastane, have to date shown smaller changes in CPF when wet.

- 14** Hats can provide substantial shading of the head and neck from solar UVR. Those with wide brims provide the greatest protection (Diffey and Cheeseman, 1992). Legionnaire style hats, with a flap of fabric covering the neck, are also effective and are becoming more popular. The fabric from which the hat is constructed should have a high CPF. The actual protection provided is not accurately predicted by the CPF, since the brim of a hat, which provides much of the protection, is not close to the skin. Most hats provide the best protection to the forehead and the relative amounts of protection over the whole of the head and neck are very dependent on the design of the hat. In measurements made on rotating mannequins, used to simulate the motion of a person during outdoor activities, most styles of hat reduced the UVR exposure to the forehead to less than 10% of the ambient levels (Diffey and Cheeseman, 1992). Other sites on the head and neck which were at greater distances from the hat received less protection and were frequently exposed to greater than 50% of ambient UVR levels. As for the shade structures discussed below, a hat provides greatest protection where it shields the skin from most of the sky, in addition to the solar disc. Since the exact reduction in intensity provided by a hat depends on both the hat design and the prevailing solar elevation and cloud cover, sunscreens may also need to be applied to the face and neck to provide additional protection.

Eyewear

- 15** Several forms of eyewear exist for protection of the eye. Sunglasses are frequently used to reduce the amount of solar radiation reaching the eye. The main casual use of sunglasses is usually to reduce glare by decreasing the intensity of visible radiation reaching the eye. UVR is also attenuated by sunglasses, but the degree of attenuation is not apparent by visual inspection of the lenses. Several countries have standards specifying the classification of sunglasses according to their UVR transmittance (BSI, 1997; Standards Australia, 1990). The design of sunglasses is important, with 'wrap-around' glasses that fit close to the eyes providing better protection than more open designs. Photokeratitis and photoconjunctivitis are the main short-term effects of UVR exposure of the eye. These conditions commonly occur when exposure takes place on a surface with a high UVR reflectance, such as snow or sand. The presence of the high reflectance surface significantly increases the solar irradiance reaching the eye. In addition, skiing often takes place at high altitudes where the solar UVB irradiance can be higher than that at sea level. Enclosed UVR protective goggles should be used to reduce the intensity of UVR reflected from the snow reaching the eye.

Protection of the eye by spectacles and contact lenses

- 16** The wearing of optical devices, whether prescription or not, offers the possibility of providing some protection to the eye from the effects of UVR exposure.

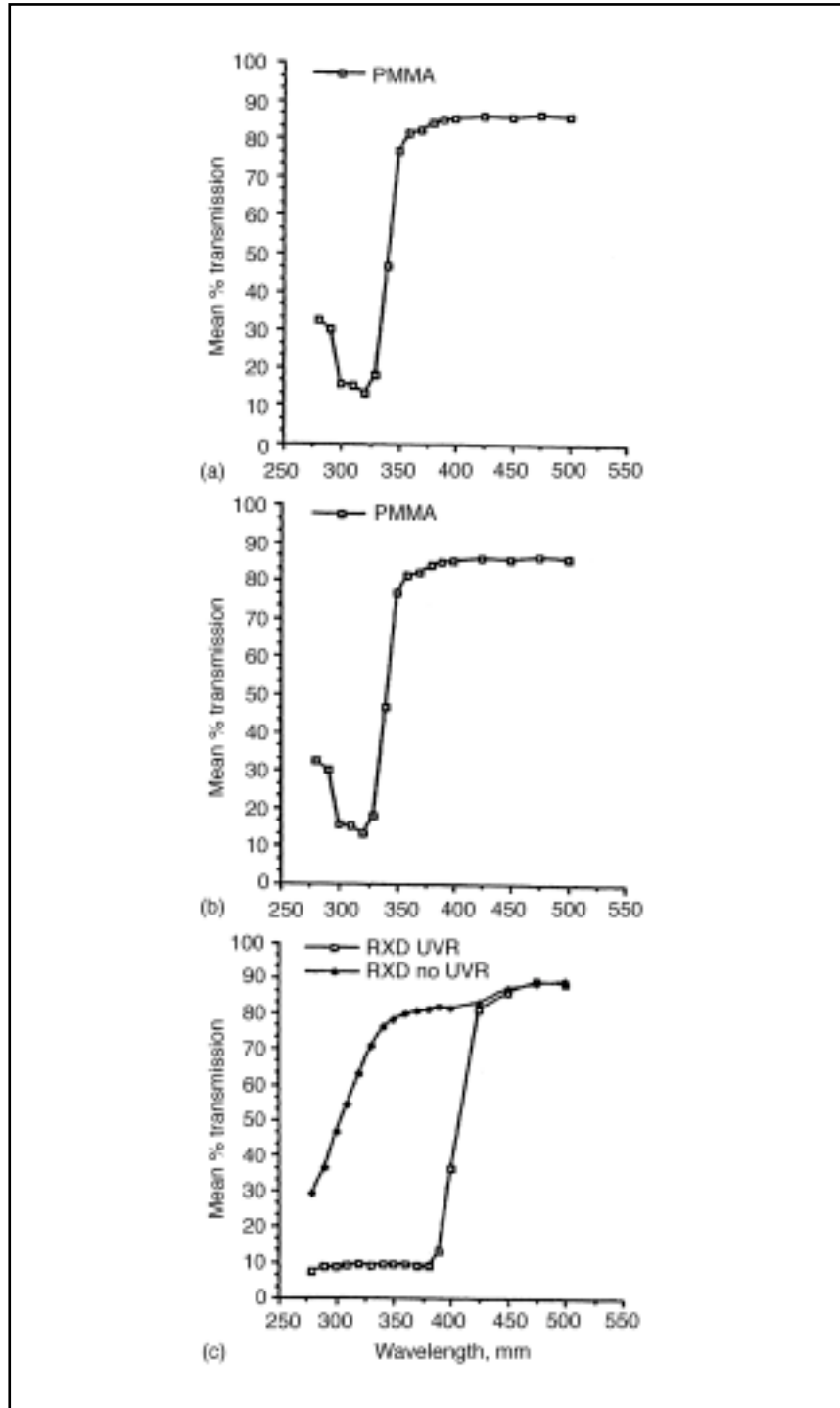
Spectacles

- 17** Standard spectacles with lenses of crown glass offer some protection to the eye from exposure to direct UVR. Such lenses still allow reflected, oblique rays to reach the anterior eye and periocular skin, which may amount to 50% of the solar UVR normally reaching these regions when the eye is unprotected. The level of protection is further reduced when the lenses are of small size, for stylistic reasons. Some UVR may be reflected on to the eye from the back surface of the lens (Bergmanson *et al.* 1996; Lauren, 1988).
- 18** Crown glass gives incomplete protection against UVR and blue light. It begins to transmit radiant energy at 290 nm (Pitts and Kleinstein, 1993). One plastic commonly used in spectacle lens production (CR-39) blocks UVR transmission below 350 nm, but transmits wavelengths above this level. Polycarbonate lenses, which have gained favour because of their impact-resistant properties, absorb radiant energy below 380 nm and have some value in reducing direct UVR exposure (Pitts and Kleinstein, 1993).
- 19** UVR-blocking sunglasses are of several varieties. Such coatings capable of blocking UVR up to 400 nm, may be applied to prescription glasses. As a coating is used, the degree of absorption is independent of the thickness of the lenses. Non-prescription sunglasses usually contain a blocker as an integral component of the plastic. Such sunglasses are usually highly effective in blocking the transmission of all direct UVR. The FDA recommendation is that all sunglasses, whether prescription or non-prescription, must block 99% of the incident UVB and UVA. However, unless they have a wrap-around construction, with enclosing sidepieces, all such glasses are no better at preventing obliquely-directed radiation from hitting the eye, than ordinary spectacles. Such glasses may permit up to 20% (10%–25%) of the UVR to reach the cornea, whereas wrap-around sunglasses, goggles or Inuit whalebone slit goggles reduce radiance to less than 1% (Slaney, 1995a,b).

Contact lenses

- 20** Although some untreated contact lenses show a moderate absorption of UVB, the majority provide little protection from UVR. However, rigid gas permeable (RGP) and hydrogel lenses are now available, which contain UVR blockers that will absorb between 80% and 100% of incident UVR (Chou *et al.* 1988; Harris *et al.* 1994) (Figure 12.2). Many such lenses transmit at the low, visible end of the spectrum and would therefore not remove the risk of blue-light toxicity. Such absorbers are chemically integrated with the lens material, so the degree of absorption is related to lens thickness and for this reason the UVR-blocking lens is defined in relation to its thinnest specification. The American National Standards Institute (ANSI) designates a contact lens as UVR-blocking when it absorbs a minimum of 95% of the UVB and 70% of the UVA (Bergmanson *et al.* 1987, 1988). Experimentally, UVR-absorbing hydrogel lenses may provide complete protection from damage caused by UVR (Bergmanson *et al.* 1987; Pitts and Lattimore, 1987).
- 21** The degree of protection afforded by a UVR-blocking contact lens is in part determined by its size and location. An RGP lens will be 10 mm or less in overall diameter

FIGURE 12.2
 Mean percentage transmission by contact lenses of optical radiation between 280 and 500 nm:
 (a) transmission by a PMMA lens
 (b) comparison of the Boston RXD lens with (open figures) and without (closed figures) a UVR filter
 (c) transmission by a Sontakt lens. Note that there is substantial absorption between 400 and 500 nm
 (from Harris et al, 1994)



(smaller than the diameter of the cornea, 11.5 mm) and will not cover the limbal region, which houses the corneal epithelial stem cells. Hydrogel lenses are of 12 mm or more in diameter and can therefore perform some screening role in this region, although it must be accepted that UVR absorption at the periphery of the lens, its thinnest part, will be less than at its centre. The limbus is a common site for intra-epithelial neoplasia or squamous cell carcinoma and it may be considered, in view of the accepted role of UVR in causation of skin carcinomas, that protection of the interpalpebral limbus from UVR exposure may be beneficial (Bergmanson *et al.* 1987, 1988). In the rabbit, UVR-absorbing contact lenses protect the cornea from damaged caused by UVR (Cullen *et al.* 1989).

- 22** Subjects wearing UVR-absorbing contact lenses exhibit a significant increase in visual comfort and a reduction in glare in conditions of snow and sun (Dumbleton and Cullen, 1986). This has been interpreted as due to a reduction in the UVR-induced lenticular fluorescence, which would normally give rise to symptoms of glare and photophobia in these conditions.
- 23** For exposure to artificial sources in the workplace, greater levels of protection may be needed. These can take the form of enclosed goggles or faceshields. The highest levels of UVR commonly encountered are during electric arc welding, which produces high levels of all wavelengths of UVR, including substantial irradiance in the UVC region. Close-fitting face masks with low transmittance to UVR and visible and infrared radiation are used for protection.
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CHEMICAL APPROACHES TO SUN PROTECTION

Systemic sunscreens

- 24** Systemic agents such as beta-carotene, antimalarials, antihistamines, and psoralens are sometimes used in the management of photodermatoses, but would not be recommended for photoprotection of normal skin.

Topical sunscreens

- 25** Topical sunscreens act by absorbing or scattering UVR. In addition, antioxidants such as vitamin C or beta-carotene are occasionally added to sunscreens as free-radical quenchers. Sunscreens traditionally contained organic filters which absorb mainly UVB (eg octylmethoxycinnamate), although the majority of sun care products now offer some protection from UVA, either by the addition of organic filters absorbing in this waveband (eg avobenzene) or mineral pigments (eg TiO₂ or ZnO). Although the majority of sun care products currently available provide UVA protection, there is (as of 2001) no industry standard for its declaration on the pack.
- 26** The most common purpose for adopting sun protection behaviour is to avoid sunburn. Surprisingly, whilst this expectation was realised for natural measures of sun protection (clothing and shade), people who usually or always wore SPF15+ sunscreen reported a higher incidence of sunburn than people who rarely or never used sunscreen (Dixon *et al.* 1997). However, no allowance was made in these analyses for different skin types.
- 27** The protection offered by a sunscreen – defined by its SPF – is assessed after phototesting *in vivo* at an internationally agreed application thickness of 2 mg cm⁻². Yet a

number of studies have shown that consumers apply much less than this (Azurdia *et al.* 1999; Bech-Thomsen and Wulf, 1993; Diffey and Grice, 1997; Gottlieb *et al.* 1997; Stenberg and Larkö, 1985), typically between 0.5 and 1.5 mg cm⁻². Application thickness has a significant effect on protection with most users probably achieving a mean value of between 20% and 50% of that expected from the product label as a result of common application thicknesses (Stokes and Diffey, 1997). Compounded with this is the likely variability of protection over the skin surface due to uneven application technique (Rhodes and Diffey, 1996). Once a sunscreen has been applied to skin, its effectiveness can become compromised due to factors such as immersion in water (Stokes and Diffey, 1999) and abrasion with beach sand (Stokes and Diffey, 2000). So a likely explanation for people getting sunburnt despite using high factor sunscreens is that inadequate amounts of sunscreen are applied, areas of the body are missed, and sunscreens are washed and/or rubbed off. This emphasises the point that sunscreens should be applied generously and spread evenly over the skin in order to be effective. Approximately 35 ml of sunscreen are needed to be applied to the total body surface of an adult to achieve the SPF quoted on the pack.

- 28** In contrast to clothing, it is difficult to see which parts of the body have been missed when sunscreens are applied, thus increasing the risk of sunburn as there is some evidence to suggest that sunscreen use encourages a longer time to be spent in the sun (Autier *et al.* 1999). Furthermore, there is ample evidence that the numerical measure of protection indicated on the product pack is generally higher than that achieved in practice (Diffey, 2000). This mismatch between expectation and realisation may be one contributing factor to why sunscreens have been reported to be a risk factor in melanoma (La Vecchia, 1999) (see Chapter 7).
- 29** Conventional photoprotection by sunscreens is entirely prophylactic and of no value once DNA damage has occurred. An intriguing development, which has yet to be exploited commercially, is to incorporate the DNA-repair enzyme photolyase into sunscreens (Stege *et al.* 2000). On exposure to photoreactivating light, this enzyme converts cyclobutane dimers into their original DNA structure. It is suggested that this enzyme could be combined as an after-sun strategy with conventional sunscreens to provide photoprotection and repair at the same time.
- 30** With specific reference to sunscreens, the following recommendations were made by IARC (2001).
- (a) Sunscreens should be developed that by virtue of their content, consistency and ease of application achieve adequate protection against UVR when in common use.
 - (b) Educational strategies should be devised to inform people who expose themselves intentionally to the sun to use sunscreens as only one part of a sun protection strategy.
 - (c) Studies should be conducted to evaluate whether qualitative rating of the potential protective function of sunscreens against UVR, such as low, medium, high and ultra-high, rather than SPF, would promote appropriate use of sunscreens.
 - (d) Once the optimal method for specifying protection against broad-spectrum UVA has been agreed, a labelling method should be introduced that is internationally accepted and comprehensible to the public.
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SUMMARY AND CONCLUSIONS

- 31** For most people, their greatest source of exposure to UVR is the sun. Several methods of personal protection against solar UVR are available. These are: avoiding exposure to direct sunlight around noon during summer; seeking shade; wearing suitably protective clothing and eyewear; providing shade to the face and neck with a hat; applying a topical sunscreen. Using these measures in combination, personal UVR exposures can be reduced to acceptable levels without seriously limiting the range of outdoor pursuits.
- 32** As a general rule, sunburn is more likely to occur when the length of a person's shadow is less than his or her height. The shorter the shadow, the stronger is the sun's UVR. Sunburn can occur even on cloudy days and many people get sunburnt when they are swimming, boating or playing on a beach. Seeking shade during summer is a sensible means of protection. Shade can be provided naturally by trees, by using canopies, buildings or by constructed shade at outdoor assemblies. The shade structure should block the solar disc and the line-of-sight path from most of the sky. Hats can provide substantial shading of the head and neck from solar UVR. Those with wide brims provide the greatest protection, while legionnaire style hats, with a flap of fabric covering the neck, are also effective and are becoming more popular. The fabric from which the hat is constructed should have a high protection factor.
- 33** Clothing is an effective and reliable source of protection against solar UVR, provided consideration is given to the design of the garment and the UVR transmittance of the fabric. The garment should provide good coverage of the skin and the fabric should prevent most of the incident UVR from reaching the skin beneath it. Although it is not always possible for consumers to make a reliable assessment of UVR protection of a garment by visual inspection, it has been found that most summer clothing provides protection factors greater than 10, which should be an adequate level of protection against sunburn in the UK. For tropical sun exposure, clothing with a protection factor of 15 or higher should be more than adequate for all-day exposure.
- 34** In contrast to clothing, it is difficult to see which parts of the body have been missed when sunscreens are applied. Sunscreen with a protection factor of at least 15 should be applied generously and, if necessary, reapplied to skin surfaces that are not covered directly by clothing or a hat. There is evidence that the numerical measure of protection indicated on the sunscreen pack is higher than that achieved in practice; thus the need for applying sunscreen generously and evenly. In addition, once a sunscreen has been applied to the skin, its effectiveness can be compromised by water immersion and abrasion; thus the need for reapplication.
- 35** Several forms of eyewear exist for protection of the eye against UVR both in the workplace and in the natural environment. The design of sunglasses is important, with 'wrap-around' glasses that fit close to the eyes providing better protection than more open designs. The UVR transmission through optical filters in the everyday environment varies. For example, window glass transmits UVA and long-wave UVB but will absorb short-wave UVB within about 310 nm; car windscreens transmit UVA but generally absorb UVB; while aircraft cockpit windscreens block all UVR.
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13 Summary and Conclusions

SOLAR RADIATION AND ARTIFICIAL UVR

- 1 For most people the major source of ultraviolet radiation (UVR) exposure is the sun. However, for some individuals, for at least some of the time, UVR from artificial sources may contribute significantly to their total exposure. Such sources include those used for medical therapy, cosmetic tanning and a few industrial sources.
 - 2 Ground-level measurements of solar UVR have been made worldwide for many years but provide only a limited database for assessing personal exposure to solar UVR. Although localised spasmodic variations in UVR levels have been reported, there is no convincing evidence to indicate a global trend of changing solar UVR at the Earth's surface with time or with stratospheric conditions. It is likely that any trend will have been obscured by atmospheric absorption and scattering processes, localised atmospheric pollution and cloud cover. However, some temporal and geographical variations have been reported, particularly with respect to Antarctica.
 - 3 Incandescent sources such as tungsten filament bulbs generally emit levels of UVR believed to be insignificant to human health, although some unshielded tungsten halogen lamps can emit amounts of UVR sufficient to cause erythema. Fluorescent lamps for general lighting emit very small amounts of UVR at the levels of light exposure normally encountered in the home and in the workplace. However, special-applications fluorescent lamps, such as those used for cosmetic tanning, emit levels of UVR sufficient to cause skin and eye injury. The most potent artificial sources of UVR, and particularly of UVB and UVC, are those characterised as high intensity discharge (HID) lamps, which include high pressure mercury, mercury metal halide and xenon lamps. HID lamps used in an open situation without secondary containment are likely to constitute a UVR hazard, but used for lighting purposes within properly designed luminaires they do not.
 - 4 Gas welding, brazing and cutting processes operate at temperatures insufficiently high to cause the emission of intense UVR, but advised limits for protection may be approached if exposures at short distances are very prolonged. Arc welding processes are particularly potent sources of UVR and even very short exposures may be hazardous to the eyes and to the skin. Both gas and arc welding also emit light and infrared radiation which may be hazardous to the retina. Appropriate personal protection always needs to be worn during gas or arc welding.
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CELLULAR STUDIES

- 5 Several lines of evidence show convincingly that UVB radiation causes damage to DNA by direct absorption. UVA radiation also leads to potentially mutagenic base damage (eg 8-OHdG) but via oxidative pathways. DNA repair processes are critical for removal of all types of base damage. The role of antioxidant enzymes is still being elucidated. Glutathione is known to be the major endogenous antioxidant that protects against UVA damage. Both glutathione and the antioxidant enzyme, catalase,

are progressively destroyed by UVA radiation. While UVR is intimately involved in the process of melanogenesis, melanin can act as a photosensitiser and generate both oxidative damage and cytotoxicity under certain conditions. UVB and UVA radiations activate expression of a wide variety of genes, the functional significance of which is still under investigation. UVB and UVA radiations can activate oncogene and metallo-proteinase expression in skin, both of which are implicated in carcinogenesis.

ANIMAL STUDIES OF PHOTOCARCINOGENESIS

- 6 The carcinogenicity of solar radiation and artificial UVR in experimental animals, mostly mice, is well established: squamous cell carcinomas (SCC) are readily induced in rodents. However, there are few natural animal models of melanoma and UVR-induced basal cell carcinomas (BCC) have rarely been produced. The International Agency for Research on Cancer considered that the evidence was sufficient to conclude that solar radiation, broad-spectrum UVR, UVA, UVB and UVC radiation were all carcinogenic to experimental animals.
 - 7 Mutation of the *p53* tumour suppressor gene seems to occur as an early event in the development of UVB-induced SCC in both humans and mice but may be less important in UVA-driven skin carcinogenesis. An action spectrum has been produced for the induction of SCC in mice showing the greatest sensitivity around 290 nm in the UVB region. A lower, secondary peak around 380 nm in the UVA region may be indicative of increased levels of oxidative DNA damage in this region.
 - 8 Mutations of the *PTCH* tumour suppressor gene, part of the sonic hedgehog (SHH) signalling pathway, are thought to be responsible for the nevoid BCC syndrome and are implicated in the aetiology of familial and sporadic BCC. The experimental evidence supports the view that UVR-induced dysregulation of the SHH signalling pathway and target gene activation are essential events in the initiation of BCC tumourigenesis.
 - 9 Most UVR-induced animal melanomas arise in the dermis with negligible epidermal involvement. Spontaneous melanomas and the strong genetic predisposition to melanoma seen in humans have been identified only in Sinclair swine and certain hybrid fish. The other common experimental animal melanoma model is the South American opossum in which young animals develop metastasising tumours following exposure to UVB but not UVA radiation. However, significant differences in tumour aetiology and growth remain, suggesting caution in extrapolating these results to humans.
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IMMUNE RESPONSES

- 10 In most immune systems assessed to date, UVR induces significant changes, frequently in multiple parameters which makes the understanding of the sequences of events complex. It is apparent that measurable immunological effects are caused by UVR doses that could be encountered easily in natural sunlight. The initiating events following UVR exposure of skin and the differential effects on T cell subsets have become clearer recently. The acute exposure of animals or volunteers to UVR frequently results in a suppression of immune responses. The chain of events leading to the immunomodulation is known to be complex and is initiated by chromophores in the

skin which, on absorption of UVR, trigger the production of various mediators, particularly cytokines, both locally and systemically. There are associated changes in the populations of antigen presenting cells in the skin and in their function. The final step is the induction of T cells capable of down-regulating immunity and a probable imbalance in various T cell subsets.

- 11** Details of the above steps have been elucidated both in cellular systems *in vivo* and in animal models, generally rodents. It has been demonstrated that modulation of the normal host defences by UVR in mice may be important in allowing a tumour to progress and in causing a significant suppression of resistance to several microbial diseases, both skin-associated infections and systemic infections with no skin involvement. Fewer studies have been published to date examining the effects of UVR on immunity in human subjects, but generally they have produced results similar to those obtained in rodents. There is some evidence to indicate that there may be UVR-susceptible and UVR-resistant individuals, as in mice, with the former group more prone to develop skin cancers than the latter. With regard to infectious diseases, a link has been demonstrated between recrudescence of the herpes simplex virus (HSV) and sun exposure in a proportion of latently infected individuals, and a high risk of conversion of benign papillomas caused by various human papillomavirus (HPV) types to SCC in immunocompromised subjects on areas of the body normally exposed to the sun. The significance of UVR-induced changes in immune system responses regarding susceptibility to other infections or in reducing the effectiveness of vaccination given to sun-exposed people is not, however, clear.
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THE EYE

- 12** In recent years it has been recognised that exposure of the eyes to solar UVR is strongly influenced by facial geometry and the protection afforded by the nose, brow, lids and lashes. Further protection is afforded by aversive behaviour, which directs the eyes away from the direct rays of the sun and includes inclination of the head and 'squinting', to avoid exposure in conditions of intense sunlight. This information has been incorporated into several models used to measure individual, lifetime exposure to UVR. It is also appreciated that optical radiation incident on the eye from the temporal side may be focused on the region of the nasal limbus and adjacent conjunctiva by the optics of the eye and this probably explains why pterygium is confined to this region. Spectacle wear provides some protection from direct UVR exposure and protection is increased by sunglasses incorporating adequate UVR filters. However, unless such spectacles have a wrap-around construction, they do not protect from the influence of UVR obliquely incident on the eye from the temporal side. Indirect exposure of this kind is likely to arise in conditions of intense sunlight, when there is high reflectance from the surrounding terrain. In geographical regions such as the Dahlak islands, high UVR reflectance from the white coral sands accounts for a major incidence of pterygium and climatic droplet degeneration.
- 13** UVR is a cause of acute photophthalmia, due either to UVR exposure from arc welding or as a feature of snow blindness. Chronic UVR exposure is a major contributor to corneal and conjunctival disorders such as climatic droplet degeneration, pterygium and, probably, pinguecula and BCC of the eyelids. Only the first two of these are blinding

conditions. In geographical regions of high solar exposure and to a lesser extent in regions with lower exposure rates, UVR contributes to the occurrence of cortical cataract. Its role in the causation of other forms of cataract is less clear. The UVB component of UVR is thought to be the main causative factor in the above conditions, but UVA may also play a part. Protective behaviour, including avoidance of direct exposure to solar radiation, the wearing of hats and the wearing of UVR-absorptive sunglasses, appears to reduce risk.

- 14 Direct viewing of the sun may cause irreversible visual loss through the mechanism of solar retinitis. Retinopathy may also occur occasionally through laser injury or as a response to arc welding, in unprotected individuals. The longer UVA wavelengths, and wavelengths at the blue end of the visible spectrum, contribute to this damage. There is limited evidence to support solar radiation exposure as a contributor to age-related macular degeneration.
 - 15 There is no good evidence to suggest a relationship between solar UVR exposure and choroidal melanoma, although a weak relationship may exist for iris melanoma. Studies have supported a relationship between choroidal melanoma and exposure to sunlamps and arc welding sources.
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THE SKIN

- 16 There is strong evidence that excessive cumulative exposure to natural sunlight causes cutaneous ageing and raises the risk of SCC of the skin and lip. There is also good evidence that sun exposure is related to the risk of developing BCC and malignant melanoma, although the pattern of exposure that is hazardous is still uncertain; intermittent, recreational exposure of untanned skin may be important but so, to some extent, may be cumulative exposure. The descriptive epidemiology of melanoma and BCC suggests, however, that the aetiological relation is not entirely the same for these two tumours.
- 17 Rates of melanoma incidence have been rising in white populations around the world for several decades and, although reliable data on non-melanoma skin cancer (NMSC) are more sparse, there appear to have been large rises in incidence of these tumours also. Melanoma mortality, however, has levelled off or even fallen in recent birth cohorts.
- 18 Risks of skin cancer are greatest in white people with fair complexions (light skin, red or blonde hair, and blue eyes) and sun-sensitive skins, and melanoma risks are much raised in those with many and atypical naevi.
- 19 Evidence from recall-based case-control studies, and more persuasively from migrant studies, suggests that childhood sun exposure may be particularly important to the risk of melanoma. There is also growing evidence that childhood exposure affects naevus numbers.
- 20 There is some, but not yet conclusive, evidence from randomised trials that use of sunscreens may reduce the risk of SCC and of actinic keratosis, a precursor of SCC. Results from case-control studies taking histories of sunscreen use have found inconsistent results with regard to the risk of melanoma, including both significantly protective and significantly increased risks in relation to sunscreen use; these studies are difficult to interpret.

- 21** Oral psoralen plus UVA irradiation (PUVA) treatment shows a strong dose–response relationship to the risk of SCC. Evidence for a risk of BCC is less convincing. One study has suggested a raised risk of melanoma after a long induction period, but the relation remains uncertain. There is little, and inconclusive, information on the risk of NMSC in relation to sunlamp use, but a large epidemiological literature on the possible relation of sunlamp use to the risk of melanoma. Despite several significant positive associations, the melanoma literature overall is inconsistent, and has methodological weaknesses especially with respect to exposure measurement, confounding, and a lack of data for long induction periods. The relation is therefore uncertain, but as the exposures are to a type of radiation that is known to be carcinogenic (UVR), and are of a pattern believed to be aetiological for melanoma with respect to sun exposures (ie intermittent, intense exposures of sites usually unexposed in everyday life), there is reason for concern.
- 22** Photosensitivity disorders are a wide range of conditions in which there are abnormal cutaneous responses to exposure to small amounts of UVR and/or visible radiation. Some, the genodermatoses, are inherited, others have a biochemical aetiology, while many are of immunological origin or are attributable to drug or chemical reactions. The prevalence of most is unknown, although there is evidence from questionnaire surveys that the commonest immune-based disorder, polymorphic light eruption, is present in 15%–20% of the population in temperate climates. The underlying mechanisms are poorly understood in most cases. Some immune-based disorders, such as polymorphic light eruption, chronic actinic dermatitis and solar urticaria are believed to be due to UVR-induced allergens which then trigger a variety of immune responses, but the photoallergens have yet to be identified. Photosensitisation by systemic and topical drugs and chemicals is an increasing problem as new products are developed. A large range of drugs, dietary and herbal agents are responsible for systemic reactions, while topically the most common photoallergens are chemical sunscreens. Individual clinical centres report allergic/photoallergic reactions to sunscreens in 8%–20% of patients tested; however, the prevalence of the problem has not been established. Photosensitivity disorders require sunlight avoidance, are often disabling, and can have a considerable impact on the quality of life.
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NON-HODGKIN'S LYMPHOMA

- 23** Overall, the data are not consistent with a major role for solar UVR in the aetiology of non-Hodgkin's lymphoma (NHL), but they leave open the possibility of a minor role, or an aetiological relation for a particular subtype of NHL.
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DIETARY FACTORS

- 24** Nutritional strategies attempted for protection of the skin from UVR-mediated damage have comprised the use of vitamin and non-vitamin antioxidants, flavonoids, beta-carotene, retinol, reduction in total fat intake, and modification of fat composition by supplementation with omega-3 polyunsaturated fatty acids (PUFAs). The approach has been studied in cell culture and animal models, in healthy humans and patients with skin cancer or photosensitivity disorders.

- 25** Cell culture studies have served to give valuable information concerning the mechanisms underlying effects and the interactions between agents. *In vitro* studies show that pre-supplementation of skin cells with antioxidants can reduce both oxidative stress and cytotoxicity caused by UVR. Antioxidant dosage is important in order to avoid pro-oxidant effects, and combinations of antioxidants have synergistic activity against aspects of UVR-induced damage.
- 26** In animal models, a range of dietary strategies result in an impressive degree of protection against UVR-induced skin cancer and immune suppression. Reduction in total dietary lipid from 40% to 20% significantly protects against photocarcinogenesis. Modification of dietary fat composition also has significant effects, with omega-6 PUFAs showing a direct correlation with photocarcinogenesis, while omega-3 PUFAs are protective. Dietary supplementation with vitamin E, vitamin C or flavonoids reduces photocarcinogenesis. Selenium deficiency is associated with increased skin cancer; supplementation can reduce photocarcinogenesis, but high doses are required. In the case of beta-carotene, some studies report protection against skin cancer while others have found augmentation of carcinogenesis. Since many reactions require the combined presence of beta-carotene and vitamin E/vitamin C, it is speculated that single supplementation may lead to an excess of damaging beta-carotene radicals, which may then cause damage. Hence, it may be important to give combined supplements.
- 27** Human dietary intervention studies show some evidence for protection against UVR-induced effects. However, knowledge concerning specific dietary factors is incomplete and sometimes inconsistent. The usual endpoint examined is the sunburn response, which may or may not prove to be a suitable surrogate for aspects of chronic UVR-induced damage. Bioavailability of the agent in the skin is clearly important, although frequently not assessed. The most convincing data to date are from a double-blind, randomised, secondary prevention study, in which a reduction in total fat, to 20% of total calorie intake, was associated with a reduced incidence of premalignant lesions (actinic keratoses) and NMSC. These results require replication. Composition of fat intake may also be important. Supplementation with omega-3 PUFAs results in their pronounced uptake into skin lipids; this is associated with a significant reduction in the sunburn response and UVB-induced p53 expression in skin.
- 28** Supplementation with single agent antioxidants has been ineffective in human studies, although combined vitamins E and C are reported to protect against the sunburn response. Selenium did not protect against skin cancer in a long-term supplementation study in a selenium-replete population, despite being associated with reduced risk of some internal tumours. However, long-term studies have not yet been performed in selenium-depleted populations. The majority of beta-carotene human supplementation studies have shown no protective effect against the sunburn response. Epidemiological studies give some evidence that a high intake of beta-carotene-containing vegetables is associated with a lower risk of NMSC. However, in primary and secondary prevention studies, beta-carotene did not protect against first occurrence of NMSC, or recurrence. Although study data are conflicting, beta-carotene may have partial protective effects in a photosensitivity disorder, erythropoietic porphyria (EPP), where much higher doses are used.

- 29** Dietary manipulation might potentially offer an approach to combat the hazardous effects of UVR. There are some promising data from human studies, particularly in relation to fat intake, but so far these findings have not been confirmed.
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VITAMIN D

- 30** Vitamin D is essential for healthy bone growth and maintenance. Absence of sufficient vitamin D causes rickets in children and osteomalacia in adults. There are two sources of the vitamin: the diet and cutaneous synthesis on irradiation of the skin by UVB wavelengths. Dietary vitamin D is often insufficient to maintain adequate levels of the vitamin and the main source of the vitamin comes from casual exposure to sunlight. At mid to high latitudes a seasonal cycle in circulating vitamin D levels is observed, following the seasonal cycle in availability of sunlight. Provided that sufficient amounts of the vitamin are synthesised in the summer months, vitamin D stored in fat is available to the body throughout the winter when little or no exposure to UVB occurs. A brief exposure to sunlight containing the requisite short wavelength part of the spectrum is all that is needed to initiate vitamin D synthesis: 10–15 minutes on unprotected hands and face in summer for a fair skinned person in the UK. Such a suberythral dose several times a week is sufficient and additional exposure will be of little benefit. Dark-skinned people living at high latitudes can require a greater exposure, and people who get no exposure to sunlight are likely to require vitamin D supplements. Vitamin D has also been successfully used in the treatment of the skin disorder psoriasis and although other beneficial actions have been hypothesised there is not at present any strong evidence for such effects.
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RISK ASSESSMENT

- 31** The original Advisory Group report on the health effects of UVR in 1995 presented the results of calculated skin cancer risks consequent on exposure to both natural and artificial sources of UVR. At that time the Advisory Group was able to estimate risks only for BCC and SCC; knowledge about the action spectrum and dose–response relationship for the induction of melanoma was inadequate to permit useful risk estimates. It is still the case that there are insufficient quantitative data on the role of UVR in the pathogenesis of melanoma to allow risk calculations. Also data on the risks of BCC and SCC have not improved appreciably to allow substantially more accurate estimates.
- 32** The risk estimates above imply that limiting exposure to UVR is sensible, as noted above. However, a complete lack of exposure to solar UVR carries its own risks to the skeleton through a deficiency of vitamin D.
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PROTECTIVE MEASURES

- 33** Efforts should be made to increase public awareness of the ocular risks of solar radiation exposure and of the value of effective protective measures, such as the wearing of wrap-around sunglasses incorporating adequate UVR filters. As a corollary, the public should be advised of the additional risks that might be incurred by the wearing of sunglasses providing limited protection for reasons of style of manufacture.

or because they lack adequate UVR filtration properties. The wearing of darkly tinted sunglasses, lacking a UVR filter, may be associated with some pupil dilatation which will increase retinal UVR/blue-light irradiance.

- 34** Personal solar UVR exposures can be reduced to acceptable levels without seriously limiting the range of outdoor pursuits by using a combination of suitable protective measures. These include avoiding exposure to direct sunlight around noon during summer, seeking shade, wearing suitably protective clothing and eyewear, providing shade to the face and neck with a hat, and applying a topical sunscreen.
- 35** Shade can be provided naturally by trees, by utilising canopies and semi-permanent structures, or by constructed shade in areas where large numbers of people may gather.
- 36** Sunscreens applied at the thickness tested by manufacturers need only possess a Sun Protection Factor (SPF) of 15 to prevent sunburn even for all-day exposure in tropical sunshine. However, behavioural studies show that high SPF (more than 15) sunscreens do not always prevent sunburn. That the protection achieved is often less than that expected depends upon a number of factors: application thickness and technique; type of sunscreen applied; resistance to water immersion and sand abrasion; and when, where and how often sunscreen is re-applied. These factors provide ample evidence that the numerical measure of protection indicated on the product pack is generally higher than that achieved in practice. A useful rule-of-thumb is that the protection most people get from a sunscreen is numerically equal to about one-third the SPF.
- 37** Clothing, however, does not suffer from the uncertainties of sunscreen application, and the Clothing Protection Factor (CPF) of a fabric indicates its actual level of sun protection. Measurements on several thousand samples of fabric indicate that almost 90% of summer clothing has CPFs greater than 10 and, in practice, provides equivalent protection to sunscreens of SPF 30 or higher, and 80% of summer clothing has CPFs greater than 15 and under normal exposure patterns will offer virtually complete protection.
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14 Overall Conclusions

- 1 For most people, the main source of ultraviolet radiation (UVR) exposure is the sun, but for some individuals substantial exposures occur from artificial sources including sunbeds, industrial lamps, arc welding, and medical UVR therapies. UVR can cause damage to DNA, and in animal experiments it has been shown to be carcinogenic.
 - 2 The main tissues of the body affected by UVR are those of the skin and eye. There is considerable experimental evidence in animal models and human subjects of suppressive effects of UVR on the immune system, but their significance for human health is generally unclear. Excessive short-term UVR exposure to the skin causes sunburn, and to the eye can cause acute damage to the cornea and conjunctiva; staring at the sun can damage the retina permanently. Certain individuals have abnormal skin responses to UVR exposure ('photosensitivity') because of genetic, metabolic or other abnormalities, or show photosensitive responses because of intake of, or contact with, certain drugs or other chemicals.
 - 3 There is evidence that chronic UVR exposure of the eye contributes to a raised risk of certain conjunctival diseases and cortical cataract, and possibly to the development of age-related macular degeneration of the retina, a major cause of blindness. The relation to eye melanoma is unclear.
 - 4 Chronic sun exposure leads to skin ageing and can raise the risk of both non-melanoma and melanoma skin cancers; the latter are the main cause of skin cancer death. Short, intense exposures of the type arising from sunbathing appear to be important in the causation of melanoma and possibly basal cell skin cancer. Childhood exposures may be particularly important. Although it has not been established directly whether the use of sunbeds causes skin cancer, they are an appreciable source of intense, intermittent UVR exposure, and as such represent a potential health risk.
 - 5 The main known benefit of UVR exposure is the generation of vitamin D, which is essential for healthy bone growth and maintenance. Dietary levels of vitamin D are often low, but short periods outdoors in everyday life will produce sufficient vitamin D, and additional or intensive exposures will not confer further benefit.
 - 6 Research is underway into the possibility that dietary factors may affect risks of UVR-associated skin cancer, but this is not yet established. The health risks of UVR can be greatly diminished by sensible reductions in UVR exposures, especially intense, intermittent exposures such as sunbathing. This can be achieved without seriously affecting outdoor pursuits, by avoiding exposure to direct sunlight around noon during summer, seeking shade, wearing suitable protective clothing, hats and sunglasses when in the sun, and, although in general less effectively, by applying a topical sunscreen to unprotected parts of the body. There is also a need to avoid unnecessary exposure to artificial sources of UVR, including sunbeds.
 - 7 In brief, there is good evidence that excessive exposure to UVR can cause serious eye and skin disease: individuals can greatly reduce their risks by sensible protective measures.
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15 Research Recommendations

SOLAR RADIATION AND ARTIFICIAL UVR

- 1 The major source of ultraviolet radiation (UVR) exposure for most people is the sun and the major risk is associated with personal habits in relation to solar radiation. It is recommended that co-ordinated national ground-based measurements of solar UVR levels should be maintained to obtain baseline data and to monitor variations resulting from climatology and environmental impacts, such as ozone depletion. National measurement programmes should be subject to internationally agreed quality assurance procedures and the data should be available to a co-ordinated international database of solar UVR measurements to provide a reliable and topical global picture of solar UVR levels and their variations.
 - 2 With regard to artificial sources of UVR, it is recommended that a database of spectral emissions from artificial optical sources is established, although the optical radiation hazards from such sources will be required to be assessed on an individual basis, depending on the operating conditions. As the most potent artificial sources of UVR, and particularly of UVB and UVC, are those characterised as arcs and high intensity discharge (HID) lamps, which include high pressure mercury, mercury metal halide and xenon lamps, particular attention is required in their use and in their hazard assessment. Training and information on the potential hazards of such sources should be made available to workers, and employers need to be aware of the hazards and the training and protection required.
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CELLULAR STUDIES

- 3 Investigations should be carried out to further elucidate the molecular basis of DNA repair of UVR-induced damage using biochemical and molecular genetic techniques. The role of the UVR-induced modulation of gene expression in the acute and chronic effects of UVR exposure on the skin, particularly in relation to apoptosis, cellular defence mechanisms and mutagenesis, should also be studied. In addition, the role of DNA damage/repair in melanogenesis is incompletely understood and should be further investigated. Much human exposure is to UVA radiation and it would be of value to characterise the chromophore(s) involved in UVA responses and the nature and wavelength dependence of UVR-induced oxidative damage to key cellular targets, particularly DNA but also lipids and proteins. It would also be of value to clarify the role of oxidative/nitrative stress in melanogenesis, the cellular antioxidant defence pathways and the potential role for dietary antioxidants such as carotenoids, and flavonoids in UVR protection. Finally, the molecular basis of UVA-sensitive syndromes such as the Smith-Lemli-Opitz syndrome should be determined.
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ANIMAL STUDIES OF PHOTOCARCINOGENESIS

- 4 Future research should focus on studies of the molecular mechanisms underlying the development of UVR-induced skin cancers, especially malignant melanoma. The use of various primary and tumour cell lines and animal models, particularly the transgenic or knockout models of human skin cancers that have recently been developed, is especially relevant. In this context, studies of the genetic and other changes that occur during UVR-induced neoplastic progression from normal skin cells through to fully malignant phenotypes and their wavelength dependence would be of considerable value. The contribution of UVA-induced oxidative damage to these processes remains to be clearly elucidated. In addition, the genetic basis of the variation in susceptibility to UVR-induced skin cancer that exists within the general population warrants further investigation.
 - 5 There are no natural animal models of malignant melanoma. However, recently developed transgenic and knockout mouse models are likely to prove useful in the study of the role of UVR in the aetiology of this disease. One of the most promising is one in which mice homozygous for *Ink4a* deletions and bearing an activated *H-ras* mutation developed locally invasive melanomas. The investigation in this mouse model of a possible role of receptor tyrosine kinases in the development of metastasis may also be of value. In addition, studies based on the use of immune-compromised mice on to which is grafted full-thickness human skin show promise.
 - 6 Further studies clarifying the role of UVR in the induction of basal cell carcinomas (BCC) via dysregulation of the sonic hedgehog signalling pathway would seem appropriate. The recently developed *Ptch* heterozygous knockout (*Ptch*^{+/-}) mouse model may be particularly helpful in this context.
 - 7 With regard to UVR-induced squamous cell carcinomas (SCC), further study of the sequence of genetic events underlying their development, particularly *p53* mutations, should be carried out. The use of *p53* knockout mice may prove valuable in this context. In addition, the contribution of UVA radiation to this process, and the significance of chronic low dose exposure in enhancing the predisposition of mammalian skin to skin carcinogenesis, also deserve further attention.
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IMMUNE RESPONSES

- 8 Although very rapid progress has been made in the area of photoimmunology in recent years, many important questions remain unanswered that merit investigation. The first of these is to assess the wavelength dependency of the immunological effects of UVR. This would best be done using a monochromatic source and the construction of action spectra, particularly for certain immune parameters, for example delayed type hypersensitivity (DTH) responses. There is a special need to examine the mechanisms leading to immunomodulation following UVA exposure, about which little is known in comparison with UVB. Some evidence at present indicates that there might be waveband interactions on immunity, such as the finding that UVA may reverse the immunosuppressive activity of UVB, and this area requires further work. The use of solar simulators is also indicated so that doses can be related more easily to natural sun exposure.

- 9** In the majority of studies to date, acute exposure to UVR is followed by application of an antigen, and then various aspects of immunity to that antigen are monitored. A more common circumstance may be that the antigen-specific immune response has already been generated prior to the UVR. Therefore an assessment of the effect of UVR on memory immune responses is required. In addition, it is not known whether adaptation to the immunomodulation induced by UVR may develop on prolonged UVR exposure of the type that would be experienced over the summer months. Epidermal thickening and tanning, which are the skin's response to long-term sun exposure, may well influence local immunological mechanisms.
- 10** The remaining areas where further investigation is recommended concern human subjects directly. First, it is desirable to establish whether people can be divided into UVR-susceptible and UVR-resistant for the local and systemic immunological effects of UVR, and whether this parameter relates to the risk of developing skin cancer. Second, reliable epidemiological data are required on the frequency and severity of episodes of infectious and autoimmune diseases and respiratory allergies in relation to personal sun exposure. Third, it is important to find out if immune responses generated to vaccines administered in the summer months are different from those generated in the winter months, and in sun-exposed compared with unexposed individuals. A similar study is needed to examine whether UVR exposure reduces already established immune responses to vaccines, thus lowering the resistance to re-infection. Finally, a consensus view is required regarding the most relevant endpoint or endpoints for assessing the immune protection factors of particular sunscreens.
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THE EYE

- 11** Although a role for UVR in the causation of pterygium, climatic droplet degeneration and cortical cataract appears to have been established, the role of UVA remains uncertain. Further studies should be mounted to address this problem. The role of UVR-induced oncogene mutation in the causation of pterygium should be explored further and particularly its potential role in the causation of epithelial carcinomata at the ocular surface. The role of sunlight in the aetiology of BCC of the lids should be kept under review. SCC, a tumour for which UVR exposure plays an important aetiological role, accounts for about 10% of lid carcinomata. Attention should be focused on the role of UVR in the occurrence of this tumour.
- 12** Age-related macular degeneration (AMD) is a major cause of blindness on a world scale. There is sufficient information in the literature concerning a role for blue-light exposure and possibly long wavelength UVR exposure as an initiating factor for AMD, to suggest that this area should remain under intensive scrutiny.
- 13** The role of solar radiation exposure in the causation of choroidal melanoma remains controversial and needs further investigation. Any hypothesis as to cause should address the question of access of long wavelength UVR to the choroid, across the retinal pigment epithelium. The transmission characteristics of the retinal pigment epithelium should be studied, to answer this question.
-

THE SKIN

- 14** Trends in skin cancer incidence and mortality need continued monitoring, because of the large rises in rates over recent years. Research is needed to define more clearly the patterns of sun exposure responsible for the aetiology of BCC and cutaneous melanoma, the degree of importance of UVR exposures at different ages to risks of these tumours, and especially of childhood exposures to the risk of melanoma, and the effects of different protective measures, especially sunscreens, on risk. The relations of specific signs of benign photodamage to risks of these tumours also need clarification.
- 15** Although there are strong reasons to believe that sunbed exposure may contribute to the risk of skin cancer, especially melanoma, this remains unproven and needs clarification by methodologically stringent studies that include good quality assessment of sunbed exposure and of confounding variables, notably solar UVR exposure. Ideally such studies would be of prospective cohort design, although this will not be easy. The recent report of an association of oral psoralen plus UVA irradiation (PUVA) treatment with the risk of melanoma needs investigation in further data, both because of its clinical importance and because it is an unusually well-quantified UVR exposure from a well-defined spectral source and therefore may help to clarify the UVR spectral associations of melanoma.
- 16** Recent studies have started to unravel the relation of UVR to the development of naevi but further investigation is needed of this relation and its contribution to melanoma aetiology, as well as investigation of genetic aspects of susceptibility to UVR-induced skin cancer and the interactions of genetic and UVR effects. There is potential for epidemiological studies of the effects of UVR, and of UVR protection, in relation to intermediate endpoints, be they precancerous lesions such as actinic keratoses or markers of DNA damage or mutations.
- 17** Methodologically, the epidemiological literature on skin cancer has been dominated by case-control studies, with their attendant defects in relation to retrospective recall of such a complex exposure as UVR and confounding by skin sensitivity. Further repetition of such studies is unlikely to add much unless they include better exposure measures or unusual exposure groups whose circumstances can be used to imply their exposure. Recent years have seen the emergence of randomised controlled trials to investigate the possible preventive effects of sunscreens, although the difficulties in conducting these trials have been considerable, and so far they have only produced data in relation to SCC and intermediate endpoints. There is potential for further information of value from trials, and also from cohort studies, which potentially could employ better exposure measures. A major methodological need is for the development of better measures of:
- (a) cumulative, intermittent and extreme UVR exposures – there is limited potential to do this by better retrospective questionnaires and hence there is a need to develop biological or physical markers,
 - (b) sun-sensitivity phenotype, and hence the ability to adjust for this as a confounder and to examine the potential modifying effects of phenotype on UVR-related risks.
- 18** There is little knowledge of the relation of cumulative UVR exposure, and of acute, intermittent, intensive exposure, to specific features of benign photodamage, and this needs investigating.

- 19** The photosensitivity disorders are a very under-researched group of conditions. There is a need to perform larger surveys to examine prevalence, including geographical variation. The impact on quality of life should be examined, particularly for the commoner conditions. Investigation should be performed into the underlying mechanisms of many of the disorders, with a view to ultimately developing more effective treatments. In the idiopathic (presumed immunological) conditions, further exploration is required into the relationship between UVR induction of allergens and UVR-induced immunosuppression. The contribution of genetic and environmental factors requires further research. Therapies reported to be effective should be subjected to randomised controlled trials, and their underlying mechanisms of action explored with the aim of elucidating the pathogenesis of disease. Accurate diagnostic terminology and monitoring of sun exposure are essential in clinical trials. Systems are needed both to predict and to monitor the occurrence of photosensitisation by systemic and topical exogenous agents.
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NON-HODGKIN'S LYMPHOMA

- 20** Individual-based analytical studies analogous to those that have been conducted for skin cancer, investigating the relation of non-Hodgkin's lymphoma (NHL) to factors such as sun-sensitivity phenotype, personal sun-exposure history and biomarkers of sun exposure, will be needed to help to resolve the possible relation of UVR exposure to NHL.
-

DIETARY FACTORS

- 21** The data from dietary intervention studies in humans suggest the need for further research, particularly in two areas. First, reduction in total fat intake was found to protect against an UVR-induced disease endpoint, ie actinic keratoses (pre-malignant skin lesions) in humans in one study. This requires replication and study in larger groups of subjects, and, if replicated, examination of underlying mechanisms. The effect of composition of fat intake also requires study. Reports suggest that omega-3 polyunsaturated fatty acids protect against UVR-mediated effects including sunburn in humans; studies are required to examine the effects of longer-term supplementation, and to examine disease endpoints. Second, work is needed to explore further the effects of combined antioxidant supplementation, particularly the combination of antioxidant vitamins C and E, which has been reported to protect against the sunburn response.
- 22** Important issues which should be addressed in future studies are bioavailability of any nutritional supplements, examination of mechanisms of action, and selection of biologically relevant endpoints.
-

VITAMIN D

- 23** While the exposures required to maintain an adequate vitamin D status are known to be suberythral, there has been little work on the optimisation of exposure in different situations. For example: as the solar spectrum changes with solar elevation the balance between vitamin D synthesis and erythema risk will change; skin area exposed

does not alter the erythema risk, but it does influence circulating vitamin D levels. There is also some circumstantial evidence that vitamin D may have actions other than the well-accepted influences on the skeleton. These issues require further research and clarification.

RISK ASSESSMENT

- 24** A serious shortcoming that presently exists is the absence of a robust quantitative model of the association between UVR exposure and melanoma. The development of such a model would permit targeted preventive campaigns to achieve maximum benefit for a given effort.
-

PROTECTIVE MEASURES

- 25** Research into certain key areas of personal protection, such as the suitability of certain sunscreen preparations and the development of appropriate sun-protective eyewear, clothing and shade structures should continue, particularly with regard to their development into international standards.
- 26** With specific reference to sunscreens, in line with IARC recommendations, research should be continued into the optimal active ingredients of sunscreens, their distribution on the skin and the best spectral profile in terms of wavelength interactions. In addition, methods should be developed to increase the accuracy of measures of use of sunscreens and of individual cutaneous sun sensitivity and sun exposure.
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Appendix A

DOSEMETERS FOR MEASURING PERSONAL EXPOSURE TO ULTRAVIOLET RADIATION

INTRODUCTION

A number of systems have been developed for measuring personal exposure to ultraviolet radiation (UVR). Exposure doses are generally recorded by determining chemical or biological changes in the dosimeter. Clinical measures have been developed to attempt to assess the degree of photoageing of the skin.

REQUIREMENTS OF PERSONAL UVR DOSEMETERS

Whilst radiometers and spectroradiometers are used to monitor ambient UVR either from the sun or from artificial sources, these instruments are not suited to determining the UVR exposure of individuals, especially at multiple sites over the body, because of their bulk and generally high cost. Ideally UVR dosimeters designed for personal use should have the following characteristics.

- (a) The dosimeter should be easy to handle and not impose restrictions on the activities of the wearers.
 - (b) The physical, chemical or biological change produced in the dosimeter should increase linearly with UVR dose. If not, the dose-response curve should at least be monotonic, that is, any given dosimeter response is effected by only one radiation dose.
 - (c) The dosimeter should exhibit photoaddition; each wavelength acts independently and the effect of polychromatic radiation is the sum of the effects of all wavelengths involved.
 - (d) The dosimeter response should depend only on dose and be independent of dose rate.
 - (e) The spectral sensitivity of the dosimeter should, ideally, match the action spectrum of the photobiological effect being monitored.
 - (f) The dosimeter response should be independent of temperature and humidity, it should exhibit no 'dark effect' (continuing response when radiation exposure is terminated), and it should be stable on long-term storage.
 - (g) The dosimeter should not require laborious processing and should be easy to convert the physical, chemical or biological response to a measure of UVR exposure dose.
 - (h) The cost per dosimeter should be low so that large-scale monitoring is feasible.
-

TYPES OF PERSONAL UVR DOSEMETERS

Polysulphone film

The most commonly used material for studies of personal UVR dosimetry has been the thermoplastic, polysulphone, which was first suggested as a possible dosimeter for UVR by Davis *et al* (1976). The basis of the method is that when film is exposed to UVR at wavelengths principally in the UVB waveband, its UVR absorption increases. The increase in absorbance measured at a wavelength of 330 nm increases with UVR dose (Diffey, 1989). In practice the film (around 40 µm thick) is mounted in cardboard or plastic photographic holders. Applications of UVR dosimetry with polysulphone film have included:

- (a) sun exposure of children,
- (b) sun exposure from different leisure pursuits,
- (c) sun exposure from different occupations,
- (d) anatomical distribution of sunlight in humans and animals,
- (e) clinical photosensitivity studies,
- (f) UVR exposure of patients from therapeutic light sources,
- (g) UVR exposure of workers in industry.

Plastic films incorporating photosensitising drugs

In field studies of drug-induced photosensitivity the possibility of using a dosimeter which incorporates the relevant drug is an attractive proposition. To this end, several drugs which are known to have photosensitising effects in humans have been incorporated as the chromophore in a polyvinyl chloride (PVC) film. Photoactive drugs which have been used in this way include phenothiazine, 8-methoxypsoralen, nalidixic acid and benoxaprofen (Diffey and Davies, 1978; Diffey *et al*, 1982, 1989; Tate *et al*, 1980).

Diazo systems

Diazo systems, which are based on diazonium compounds, are one of the oldest photochemical non-silver processes. The two fundamental properties of the diazo type process which make it suitable for use as a UVR dosimeter are:

- (a) the ability to be decomposed by UVR,
- (b) the ability of the undecomposed diazonium compound to couple with a colour former to produce a stable image.

Diazonium compounds are sensitive principally to the UVA and blue regions of the spectrum. Their spectral sensitivity, together with the simplicity, economy, and convenience of the diazo system, have led to their use as film badge dosimeters for UVA and blue-light radiation (Jackson, 1980; Moseley *et al*, 1984).

Photosensitive papers

One drawback of the film dosimeters described above is that they require laboratory equipment to facilitate readout. An alternative approach is to use a system whereby the photochemical process initiates a colour change so that visual comparisons with stable printed colour standards enable the user to obtain a reasonably accurate and continuously readable integrated measure of his exposure to UVR. An example of a

dosemeter based on this principle has been described by Zweig and Henderson (1976). This dosimeter is a polycarbonate film matrix incorporating a chromophore which converts to a red photoproduct following exposure to UVR of wavelengths less than 350 nm. The depth of red colour developed depends solely on the radiant exposure.

Another type of photodosimeter is based on the reversible colour change of photochromic aziridine formulations (Fanselow *et al.* 1983). The colourless aziridine undergoes isomerization following UVR exposure to form the blue-coloured azomethine ylide.

Photosensitive papers form the basis of dosimeters designed for consumer use whilst sunbathing (Moseley *et al.* 1993).

The main drawback of photosensitive papers is that, at best, they provide a semi-quantitative estimate of exposure.

Thermoluminescent materials

Several thermoluminescent (TL) materials have been investigated as possible UVR dosimeters. Many materials (eg LiF:Mg, CaSO₄:Tm and CaF₂:natural) require pre-irradiation with high doses of gamma radiation and partial annealing before showing sensitivity to UVR (so-called 'transferred thermoluminescence'), whereas others (eg MgO, Al₂O₃:Si and CaF₂:Dy) have proved directly sensitive to UVR. TL materials have never found an established role as dosimeters for UVR.

Polycarbonate plastic

On exposure to UVR the transparent plastic, CR-39 (polyallyl diglycol carbonate), alters its optical properties. These changes are the basis of its use as UVR dosimeter (Wong *et al.* 1989). After exposure, the plastic is etched in 6N KOH at 80°C for three hours, rinsed and allowed to dry. The degree of UVR dose-dependent front surface damage, visible as opacification, is quantified by measuring the transmission at 700 nm. A comparison of CR-39 with polysulphone film has shown the latter to be a more reliable UVR dosimeter (Sydenham *et al.* 1994).

Electronic dosimeters

The use of integrating dosimeters, such as the polysulphone film badge, does not permit an assessment of short-term exposure (ie a few hours or less). However, following the availability of miniature electro-optical UVB sensors it has been possible to construct small lapel badges incorporating a UVR sensor that is electrically coupled to a portable data logger carried in a trouser pocket, worn on a belt or clipped to spectacles. By this means it is possible to record UVR exposure on a second-by-second basis, which permits a much clearer understanding of human behaviour in sunlight (Wong *et al.* 1989; Sydenham *et al.* 1994).

Biological systems

The bacteriophage T7 has been described for use as a UVR biosensor (Rontó *et al.* 1992). It has been used to monitor ambient UVR (Rontó *et al.* 1994) and, when combined with an appropriate optical filter, a spectral response similar to the action spectrum for erythema in human skin can be achieved (Quintern *et al.* 1997).

Repair deficient bacterial spores were originally proposed as a useful system for biological dosimetry of sunlight (Tyrrell, 1978). They are extremely sensitive to UVR at all wavelengths in the UVR range. They are easily used as suspensions in water in field

measurements and can be stored at room temperature for long periods before assay. Several studies on this system and other potential biomarkers are now available (Tyrrell, 1995). The bacteriophage T7 has also been described for use as a UVR biosensor. It has been used to monitor ambient UVR, and when combined with an appropriate optical filter, a spectral response similar to the action spectrum for erythema in human skin can be achieved.

An extremely useful biomarker of oxidative (including UVA radiation) DNA damage is 8-OHdG (see Chapter 3). A multicentre programme (ESCODD) is currently evaluating this marker in several laboratories throughout Europe.

CLINICAL MEASURES OF PERSONAL UVR EXPOSURE

The salient features of photoaged human skin are wrinkles and actinic lentigines. The amount of sun exposure required to produce wrinkles, actinic lentigines and other clinical signs of photoageing is poorly understood – for instance is it chronic or acute intermittent sun exposure that is responsible for these features? It is proposed that microtopography of the skin surface could be used as a clinical indication of sun exposure – by measuring skin wrinkling. The caveat of course is that different racial groups and different phototypes photoage differently and that wrinkling *per se* is not an absolute hallmark of photoageing (Gos, 1990; Griffiths *et al*, 1992). Cutaneous microtopography for assessment of severity of photoaged skin was first developed by Beagley and Gibson (1980). The technique involves taking silicone rubber moulds of small areas of the dorsa of the hands and visual reading of the resultant microtopography. Microtopographs are graded from 1 – normal – to 6 – large, deep lines consistent with coarse wrinkles. The thesis is that severe photoageing resulting from chronic sun exposure is represented by coarse lines, ie grade 6. A refinement of this technique, namely optical profilometry, has been described by Grove (1989). This is very similar to the method of cutaneous microtopography but the site of application of silicone moulds differs – crow's foot region (Figure A1), instead of dorsa of hands and reading of the surface relief of the mould by laser shadowing.

Epidemiological studies of 'premature skin ageing' have been performed in Australia using the technique of microtopography (Green, 1991). It appears that microtopography is a representative measure of clinical photoaged skin with a modest correlation with histological elastosis. Concern about the inter-observer agreement of this method was raised by Fritschi *et al* (1995) implying that the grading anchors were rather limited and subjective. As a consequence, Fritschi *et al* suggested a modification, the Σ system, whereby a defined 15 mm diameter circle was graded within each silicone replica which appeared to enhance validity. Despite these concerns, there have been studies finding microtopograph grade related to the risk of non-melanoma skin cancer (see Chapter 7). Not all studies, however, have found wrinkling relates positively to skin cancer risk (see Chapter 7), which might be because microtopography is not a good index of UVR exposure unless weighted for skin type and anatomical site, or because wrinkling is not a good surrogate of the type of UVR exposure relevant to risk.

Appendix A: Dosemeters for Measuring Personal Exposure to Ultraviolet Radiation



(a)

*FIGURE A1 Optical profilometry:
(a) application of silicone rubber to crow's foot region,
(b) Silicone rubber impression of crow's foot wrinkles*



(b)

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Appendix B

RISK ANALYSIS OF HUMAN SKIN CANCER*

INTRODUCTION

Estimates of the risk of inducing skin cancer from exposure to ultraviolet radiation (UVR) demands knowledge of dose-response relationships and the relative effectiveness of different wavelengths in the spectral power distribution of the source in causing skin cancer. These data remain unknown for malignant melanoma and so it is unwise to make predictions about the relative risk of inducing melanoma from either elective or adventitious exposure to UVR. However, data on dose-response relationships and action spectra are available to some extent to allow quantitative estimates to be made of the risk of inducing non-melanoma skin cancer (NMSC) from exposure to natural and/or artificial UVR.

DOSE-RESPONSE RELATIONSHIPS

The application of multivariate analysis to population-based epidemiology of NMSC has shown that, for a group of subjects with a given genetic susceptibility, age and environmental UVR exposure are the two most important factors in determining the relative risk (Fears *et al.* 1977). Other epidemiological studies have confirmed these findings, and this has led to a simple power-law relationship which expresses the risk in terms of these factors (Slaper and van der Leun, 1987):

$$\text{Risk} \propto (\text{annual UVR dose})^\beta (\text{age})^\alpha \quad (\text{B1})$$

The symbols α and β are numerical constants associated with the age dependence of the incidence and the biological amplification factor, respectively. This equation is applicable to situations where the annual exposure received by an individual remains unaltered throughout life. In most instances changes in lifestyle with age mean that the annual UVR exposure does not remain constant. This situation applies, for example, when cosmetic tanning equipment is used for a limited period during life.

The situation of changes in annual exposure was examined in a series of experiments with mice (de Gruijl, 1982), and led Slaper and van der Leun (1987) to modify the above equation to estimate the risk of NMSC at age T , as

$$\text{Risk} \propto (\text{cumulative UVR dose at age } T)^{\beta-1} \sum (\text{annual dose at age } [T-t]) t^{\alpha-\beta} \quad (\text{B2})$$

Values of the exponents α and β are normally derived from surveys of skin cancer incidence and UVR climatology.

* Reproduced from *Health Effects from Ultraviolet Radiation, Doc NRPB, 6(2)*, Chapter 7, pp 143-58 (1995).

Note that exposures have been expressed in standard erythema dose (SED) rather than minimum erythemal dose (MED) as used in the original text.

Age exponent α

The value of the parameter α can be estimated from published incidence data on basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) from the slope of the logarithm of incidence plotted against the logarithm of age. This relation is consistent with certain two-stage models of carcinogenesis as well as a multistage model with α and $\alpha + 1$ stages (Gaffrey and Altshuler, 1988). Estimates of the exponent α for BCC and SCC are given in Table B1. The value is greater for SCC than for BCC, and for men than for women.

TABLE B1
Estimates of the age exponent obtained using a power function model of BCC and SCC incidence

| Carcinoma | Country | Exponent \pm standard error | | Reference |
|-----------|-------------|-------------------------------|-----------------|------------------------------|
| | | Males | Females | |
| BCC | USA | 3.54 \pm 0.24 | 2.89 \pm 0.22 | Scotto <i>et al</i> (1983) |
| | USA | - | 2.82 \pm 0.37 | Hunter <i>et al</i> (1990) |
| | USA | 3.49 \pm 0.11 | 2.93 \pm 0.13 | Chuang <i>et al</i> (1990) |
| | Switzerland | 4.03 \pm 0.33 | 3.16 \pm 0.17 | Levi <i>et al</i> (1988) |
| | Netherlands | 4.21 \pm 0.15 | 3.70 \pm 0.13 | Coeburgh <i>et al</i> (1991) |
| | Wales | 3.38 \pm 0.47 | 3.44 \pm 0.54 | Roberts (1990) |
| | Australia | 2.63 \pm 0.29 | 1.96 \pm 0.32 | Marks <i>et al</i> (1993) |
| SCC | USA | 4.44 \pm 0.25 | 4.19 \pm 0.08 | Scotto <i>et al</i> (1983) |
| | USA | 5.56 \pm 0.27 | 5.44 \pm 0.27 | Glass and Hoover (1989) |
| | Switzerland | 6.47 \pm 0.22 | 4.91 \pm 0.40 | Levi <i>et al</i> (1988) |
| | Netherlands | 6.32 \pm 0.55 | 5.26 \pm 0.60 | Coeburgh <i>et al</i> (1991) |
| | England | 5.64 \pm 0.53 | 4.47 \pm 0.38 | Whitaker <i>et al</i> (1993) |
| | Australia | 4.71 \pm 0.79 | 3.30 \pm 1.12 | Marks <i>et al</i> (1993) |

TABLE B2
Estimates of the biological amplification factor for BCC and SCC

| Carcinoma | Country | Biological amplification factors | | Reference |
|-----------|---------|----------------------------------|---------|----------------------------|
| | | Males | Females | |
| BCC | USA | 1.3-2.6 | 1.1-2.1 | Scotto <i>et al</i> (1983) |
| | USA | 1.8-2.2 | 1.1-1.5 | Rundel (1983) |
| | Norway | 1.5-2.0 | 1.6-2.1 | Moan <i>et al</i> (1989) |
| SCC | USA | 2.1-4.1 | 2.2-4.3 | Scotto <i>et al</i> (1983) |
| | USA | 2.4-2.8 | 1.6-2.1 | Rundel (1983) |
| | Norway | 1.2-1.5 | 1.6-1.8 | Moan <i>et al</i> (1989) |

Biological amplification factor β

Estimates of the biological amplification factor β from epidemiological studies carried out in the USA and Norway are summarised in Table B2.

The estimates of β from the USA were based on the 1977-78 survey of NMSC incidence in eight regions of the USA with corresponding measurements of ambient erythemal UVR obtained from Robertson-Berger meters (Scotto *et al*, 1983). The difference in the ranges of values shown for Scotto *et al*(1983) and Rundel (1983) arises because the former used an exponential model of age-standardised incidence, whereas

the latter fitted a log-normal distribution to the age-incidence data in each geographical area and estimated the mean onset time for both BCC and SCC. The reciprocal mean onset times were then modelled as a linear function of erythemal UVR dose across the different geographical areas.

The estimates of α and β from the Norwegian study were derived from incidence data on BCC and SCC collected by the Norwegian Cancer Registry (Moan *et al.* 1989) and estimates of erythemal UVR obtained by modelling solar spectral irradiance and combining with the CIE reference action spectrum for UVR erythema in human skin (McKinlay and Diffey, 1987).

Mean values of α and β (pooled for males and females) from the data given in Tables B1 and B2 are summarised in Table B3. Both the age exponents α and the biological amplification factors β are higher for SCC than for BCC.

| Parameter | Mean \pm standard deviation | |
|---------------------------------|-------------------------------|---------------|
| | BCC | SCC |
| Age exponent | 3.2 \pm 0.6 | 5.1 \pm 0.9 |
| Biological amplification factor | 1.7 \pm 0.3 | 2.3 \pm 0.5 |

TABLE B3
Summary of age exponents and biological amplification factors for BCC and SCC

ACTION SPECTRUM FOR PHOTOCARCINOGENESIS

Clearly, an action spectrum for skin cancer can only be obtained from animal experiments. The most extensive investigations to date are those from groups at Utrecht in the Netherlands and Philadelphia in the USA. These workers exposed a total of about 1100 albino Skh:hr1 mice to 14 different broadband UVR sources and by a mathematical optimisation process derived an action spectrum referred to as the *Skin Cancer Utrecht-Philadelphia (SCUP)* action spectrum mice (de Gruijl *et al.* 1993). The SCUP action spectrum is that for skin tumour induction in Skh:hr1 mice, a species which has a thinner epidermis than human beings.

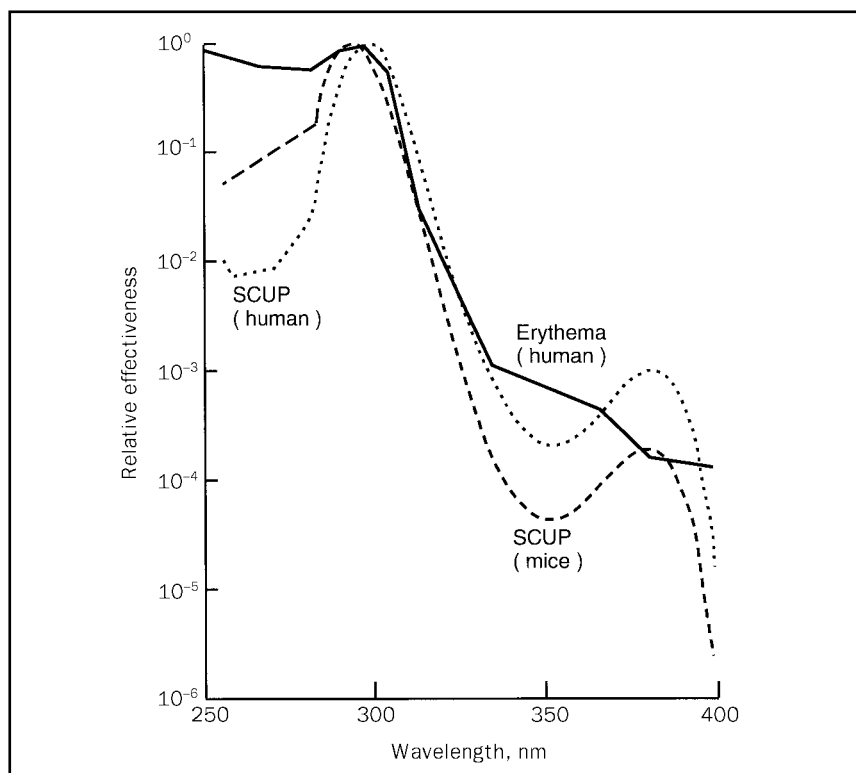
By taking into account differences in the optics of human epidermis and Skh:hr1 albino mouse epidermis, the experimentally determined action spectrum for tumour induction in mouse skin can be modified to arrive at a postulated action spectrum for human skin cancer mice (de Gruijl, 1993). The resulting action spectrum resembles the action spectrum for erythema (Figure B1), suggesting that this action spectrum may be used as a surrogate for human skin cancer (Parrish *et al.* 1982). For this reason erythemal doses expressed in units of standard erythema dose (SED) can be used to express carcinogenic-effective exposure.

HUMAN EXPOSURE TO NATURAL UVR

The solar UVR exposure received by an individual depends on three factors:

- (a) ambient solar UVR,
- (b) the fraction of ambient exposure received on appropriate anatomical sites,
- (c) behaviour outdoors.

FIGURE B1
Carcinogenic action
spectra in mice and
human beings
compared with the
action spectrum for
erythema in human
skin (de Gruijl, 1993)



Differences exist between the assessed environmental and personal solar radiation exposures. The distribution of UVR exposure across the body can also vary greatly, depending on posture and personal habits in the sun. Estimates of personal exposure can be obtained in two ways: by direct measurement using UVR-sensitive film badges normally worn on the lapel site (Challoner *et al*, 1976; Gies *et al*, 1992; Holman *et al*, 1983; Larkó and Diffey, 1983; Leach *et al*, 1978; Melville *et al*, 1991; Rosenthal *et al*, 1990; Slaper, 1987) or by modelling the variables above (Diffey, 1992; Rosenthal *et al*, 1991). The results obtained from both methods indicate that indoor workers in the UK receive around 200 SED per year mainly from weekend and vocational exposure, and principally to the hands, forearms and face. This value is approximately 6% of the total ambient available (see Chapter 1). Children have a greater opportunity for outdoor exposure and receive an annual dose of around 300 SED. For indoor workers the annual exposure associated with occupation (travelling to and from work, going outside at lunchtime) is about 40 SED, about 80 SED is contributed by weekend exposure, and the remaining 60 SED from vocational exposure. In the case of children, 'occupational' exposure (playtime and lunchtime exposure) may be about 60 SED, recreational about 180 SED (because children are at school for only about 190 days per year), and vacation with parents about 60 SED. It must be stressed, however, that there will be large variations in the annual exposure doses received by individuals within a given population group depending on propensity for outdoor activities and to what extent these are influenced by shade.

VALIDATION OF THE MODEL

Australia has the highest recorded incidence of non-melanoma skin cancers of any country (Giles, 1988). The second national survey of NMSC incidence has recently been published giving age-standardised rates and age-specific incidence separately for BCC and SCC (Marks *et al*, 1993). The model described by equation B2 was used as the basis to predict these data.

Age-standardised rates for BCC and SCC by latitude

The age-standardised incidence rate for the population in a particular geographical area for either BCC or SCC is calculated as

$$\sum N_i R_i / \sum N_i \tag{B3}$$

where N_i is the world standard population (Doll, 1979) in 100 000s for age group i and R_i is the age-specific incidence rate per 100 000 population, calculated as

$$R_i = \Gamma \left(\sum_{j=0}^{j=1} D_j \right)^{\beta-1} \sum_{j=0}^{j=1} D_{i-j} t^{\alpha-\beta} \tag{B4}$$

where Γ is a factor which accounts for the genetic susceptibility of the population for a particular type of cancer (BCC or SCC), and D_j is the annual dose at age j . In the Australian survey NMSC rates were given for three latitudinal zones: $< 29^\circ\text{S}$, $29^\circ\text{--}37^\circ\text{S}$, and $> 37^\circ\text{S}$. Data on population exposure at these different locations are not available and so the assumption is made that childhood and adult exposures in each region are the same fractions of ambient as for the UK (ie 9% and 6%, respectively).

Values of annual ambient erythemal UVR at each of six locations in Australia (two in each latitude zone) were obtained from measurement data published by the Australian Radiation Laboratory (Gies *et al*, 1994). These measurements are summarised in Table B4. From these data representative annual personal doses equivalent to ambient values of 14 200, 10 800 and 8000 SED were used in equation B4 as the values for the latitude zones $< 29^\circ\text{S}$, $29^\circ\text{--}37^\circ\text{S}$, and $> 37^\circ\text{S}$, respectively.

Appropriate values of α and β for BCC in males were taken from Table B3. The numerical value of Γ ($2.83 \cdot 10^{-7}$) for BCC was obtained by linear regression of the observed rates on those calculated from equation B3. The calculated rates from equation B4 are compared in Table B5 with the observed rates.

A similar approach was used in comparing calculated and observed rates for SCC (Table B5). Appropriate values of α and β were used (Table B3), but a value of $1.64 \cdot 10^{-12}$ was taken for Γ , reflecting the lower prevalence of SCC compared with BCC.

| City | Latitude ($^\circ\text{S}$) | Annual SED |
|------------|-------------------------------|------------|
| Townsville | 19 | 10 800 |
| Brisbane | 27 | 9 100 |
| Perth | 32 | 8 800 |
| Sydney | 34 | 7 300 |
| Melbourne | 38 | 6 400 |
| Hobart | 43 | 5 000 |

TABLE B4
Calculated annual ambient erythemal exposure dose for different cities in Australia

TABLE B5
Observed and
calculated age-
standardised rates
for BCC and SCC by
latitude

| Latitude | BCC | | SCC | |
|----------|----------------------|------------|-------------------|------------|
| | Observed | Calculated | Observed | Calculated |
| < 29°S | 1182 (1017, 1347) | 1147 | 421 (323, 518) | 428 |
| 29°-37°S | 791 (716, 866) | 785 | 297 (252, 342) | 256 |
| > 37°S | 323 (256, 390) | 428 | 47 (23, 71) | 113 |

Note Figures in parentheses are 95% confidence intervals.

For both types of cancer the agreement between observed and calculated rates for the two zones nearest the equator are very similar. However, the predicted rates for the latitude zone > 37°S are outside the 95% confidence intervals of the observed rates. The ratio of the observed rate of NMSC (BCC and SCC combined) between < 29°S and > 37°S is 4.3 : 1 (95% CI 3.5, 5.5), whereas the ratio of the calculated rate is 2.9 : 1. This value is much closer to the observed rate of 2.5 : 1 (95% CI 1.8, 3.7) for these latitude zones obtained in the first national survey of NMSC incidence in Australia carried out in 1985 (Giles *et al.* 1988).

Age-standardised rates for BCC and SCC by country of birth

The survey found that the rates of both BCC and SCC were higher in native-born Australians than for those Australian residents who were born in the UK. Age-standardised rates were calculated for both these groups (native-born and UK-born) using the same values of Γ (reflecting equal genetic susceptibility) determined previously for BCC and SCC, respectively. An average ambient exposure of 12 000 SED was assumed for Australia, giving an adult exposure of both groups of 720 SED (6% of ambient). For native-born Australians annual childhood exposure (up to the age of 18 years) was taken as 1080 SED (9% of 12 000 SED), whereas the childhood exposure of UK-born Australians was taken as 300 SED per year (see above). The observed and calculated incidence rates are compared in Table B6, where good agreement is seen for both BCC and SCC, implying that the model is sufficiently robust to cope with differences between childhood and adult exposure.

Repeating the calculations with a childhood annual exposure of 300 SED and adult exposure of 200 SED, as might be expected in the UK, gives age-standardised rates for BCC and SCC of 99 and 16, respectively. These compare favourably with rates observed in a population-based epidemiological study of NMSC incidence carried out in South Wales during a six-month period of 1988 in which the age-standardised rates for BCC

TABLE B6
Observed and
calculated age-
standardised rates
for BCC and SCC by
country of birth

| Country of birth | BCC | | SCC | |
|------------------|-------------------|------------|-------------------|------------|
| | Observed | Calculated | Observed | Calculated |
| Australia | 847 (780, 913) | 853 | 284 (247, 322) | 287 |
| UK | 421 (306, 535) | 332 | 124 (62, 186) | 83 |

Note Figures in parentheses are 95% confidence intervals.

and SCC were found to be 83 (95% CI 68, 96) and 19 (95% CI 14, 24), respectively (Roberts, 1990). A more recent population-based study over a 14-year period in the North Humberside area of England found the 1991 age-standardised rates for BCC and SCC to be 110 and 25, respectively (Ko *et al.* 1994).

RISK PROGNOSSES

Estimates of the risk of BCC and SCC, either separately or combined, based on the above model have been made for a number of both elective and adventitious exposure conditions. These include subjects undergoing phototherapy for skin diseases or seasonal affective disorder, people who are sunbathing or using sunbeds, or receiving occupational exposure from hospital phototherapy lamps or indoor fluorescent lighting, and those experiencing a reduction in risk as a consequence of using sunscreens during sun exposure (Diffey, 1987, 1988, 1989, 1993; Lytle *et al.* 1993; Slaper and van der Leun, 1986, 1987; Slaper *et al.* 1986). The risk of BCC and SCC as a result of elective or adventitious exposure relative to an individual who is exposed only to the 'baseline' exposure given above can be estimated from equation B2. The uncertainties on these estimates were derived using a Monte Carlo approach whereby the values assigned to the age exponent α and the biological amplification factor β for a given cancer were taken as

$$\alpha = \alpha_0 + \left[\left(\sum_{i=1}^{i=12} r_i \right) - 6 \right] \sigma_\alpha \quad (B5)$$

and

$$\beta = \beta_0 + \left[\left(\sum_{i=1}^{i=12} r_i \right) - 6 \right] \sigma_\beta \quad (B6)$$

where α_0 and β_0 are the means and σ_α and σ_β are the standard deviation of the age exponent and biological amplification factor, respectively, given in Table B3, and r_i is a random number between 0 and 1. For both α and β , 100 values were generated and the risk calculations performed for each estimate. In this way it was possible to determine the 95% confidence intervals directly by ranking the resulting 100 risk values.

UVA sunbed use

The relative risk from whole-body tanning using sunbeds will depend on the number of sessions per year that equipment is used and the number of years that the practice continues. Calculations have been carried out on the assumption that each tanning session results in a whole-body dose of 2 SED. In carrying out these calculations a non-user is assumed to have sun exposure only to the face, hands and forearms (approximately 20% of the body surface area), amounting to an annual exposure of 300 SED in childhood (up to age 18 years) and thereafter 200 SED per year. The sunbed user receives, in addition to this exposure, a whole body exposure of either 20, 60, 200 or 600 SED per year for different periods during life. The risks for BCC and SCC relative to a non-user are summarised in Tables B7 and B8, respectively, for a variety of usage patterns.

Health Effects from Ultraviolet Radiation

TABLE B7 Relative risks of BCC at age 70 years as a result of whole-body exposure to tanning equipment

| Equipment used every year in age range (years) | Annual exposure from tanning equipment (SED) | | | |
|--|--|----------------------|----------------------|----------------------|
| | 20 | 60 | 200 | 600 |
| 20-30 | 1.03 (1.01, 1.05) | 1.10 (1.06, 1.14) | 1.44 (1.36, 1.52) | 2.97 (2.71, 3.23) |
| 20-40 | 1.05 (1.03, 1.07) | 1.19 (1.13, 1.25) | 1.91 (1.71, 2.11) | 5.39 (4.29, 6.49) |
| 20-50 | 1.07 (1.05, 1.09) | 1.27 (1.19, 1.35) | 2.34 (2.04, 2.64) | 7.74 (4.04, 11.4) |
| 20-60 | 1.09 (1.07, 1.11) | 1.34 (1.24, 1.44) | 2.70 (2.06, 3.34) | 9.70 (6.70, 12.7) |
| 30-40 | 1.02 (1.00, 1.04) | 1.08 (1.06, 1.10) | 1.33 (1.21, 1.45) | 2.44 (2.04, 2.84) |
| 30-50 | 1.04 (1.02, 1.06) | 1.14 (1.09, 1.19) | 1.65 (1.37, 1.93) | 4.05 (2.40, 5.70) |
| 30-60 | 1.06 (1.03, 1.09) | 1.20 (1.10, 1.30) | 1.93 (1.43, 2.43) | 5.44 (1.64, 9.24) |
| 40-50 | 1.02 (1.00, 1.04) | 1.06 (1.02, 1.10) | 1.24 (1.12, 1.36) | 1.98 (1.68, 2.28) |
| 40-60 | 1.03 (1.01, 1.05) | 1.10 (1.04, 1.16) | 1.44 (1.10, 1.78) | 2.92 (1.32, 4.52) |
| 50-60 | 1.01 (1.00, 1.03) | 1.04 (1.01, 1.07) | 1.16 (1.02, 1.30) | 1.61 (1.00, 2.22) |

Note Figures in parentheses are 95% confidence intervals.

TABLE B8 Relative risks of SCC at age 70 years as a result of whole-body exposure to tanning equipment

| Equipment used every year in range (years) | Annual exposure from tanning equipment (SED) | | | |
|--|--|----------------------|----------------------|----------------------|
| | 20 | 60 | 200 | 600 |
| 20-30 | 1.03 (1.01, 1.05) | 1.10 (1.07, 1.15) | 1.39 (1.31, 1.51) | 2.73 (2.22, 3.42) |
| 20-40 | 1.06 (1.04, 1.08) | 1.18 (1.11, 1.26) | 1.76 (1.49, 2.12) | 5.11 (2.90, 7.26) |
| 20-50 | 1.08 (1.05, 1.12) | 1.25 (1.15, 1.39) | 2.13 (1.70, 3.08) | 7.73 (3.50, 16.7) |
| 20-60 | 1.09 (1.06, 1.15) | 1.31 (1.20, 1.53) | 2.48 (1.87, 3.52) | 10.4 (3.82, 25.9) |
| 30-40 | 1.03 (1.01, 1.04) | 1.08 (1.04, 1.12) | 1.28 (1.17, 1.48) | 2.15 (1.49, 3.02) |
| 30-50 | 1.04 (1.02, 1.08) | 1.14 (1.07, 1.26) | 1.54 (1.31, 2.08) | 3.53 (2.11, 6.96) |
| 30-60 | 1.06 (1.02, 1.10) | 1.20 (1.09, 1.37) | 1.80 (1.41, 2.77) | 4.95 (2.24, 12.7) |
| 40-50 | 1.02 (1.01, 1.04) | 1.06 (1.03, 1.13) | 1.22 (1.06, 1.45) | 1.80 (1.28, 2.70) |
| 40-60 | 1.04 (1.01, 1.07) | 1.12 (1.04, 1.26) | 1.43 (1.14, 1.99) | 2.64 (1.32, 5.82) |
| 50-60 | 1.02 (1.01, 1.03) | 1.06 (1.02, 1.10) | 1.19 (1.06, 1.34) | 1.63 (1.26, 2.49) |

Note Figures in parentheses are 95% confidence intervals.

A course of ten sessions to acquire a tan before going on holiday is associated with a small (< 10%) increased risk of inducing NMSC compared with non-users. Some may argue that this risk is acceptable for the perceived psychological and cosmetic benefit of a tanned skin. Of greater concern are the users of sunbeds at home who may expose themselves two or more times a week throughout the year for several years. Here the relative risks can become appreciable.

Occupational UVR exposure

In a study carried out in Sweden, staff working with phototherapy equipment wore polysulphone UVR film badges to record their daily occupational exposure (Larkö and Diffey, 1986). The results showed that on most working days staff received UVR doses lower than those required to produce acute clinical symptoms such as erythema. Occasionally, however, due to factors such as a particularly heavy workload or an uncooperative patient, sufficient exposure was received to result in erythema. This pattern of day-to-day exposures could be described by a log-normal distribution (Diffey, 1988), and from this distribution it was possible to estimate the annual occupational UVR exposure from the number of occasions on which erythema was apparent.

The data in Table B9 and B10 show the annual occupational exposure (expressed in SED) estimated in this way, and the relative risk of BCC and SCC compared with that of an indoor worker who is not occupationally exposed to UVR.

Risk estimates have been calculated at age 70 years for different periods during which staff are occupationally exposed. The risks are small provided that staff adopt

| Frequency of erythema | Estimated annual occupational exposure (SED) | Number of years occupationally exposed | | | |
|-----------------------|--|--|----------------------|----------------------|----------------------|
| | | 5 | 10 | 20 | 40 |
| Once per week | 400 | 1.32 (1.19, 1.42) | 1.58 (1.35, 1.81) | 2.06 (1.61, 2.54) | 2.80 (1.61, 4.17) |
| Once per month | 184 | 1.14 (1.10, 1.19) | 1.25 (1.15, 1.34) | 1.45 (1.27, 1.67) | 1.74 (1.29, 2.37) |
| Once per year | 30 | 1.02 (1.01, 1.03) | 1.04 (1.03, 1.05) | 1.07 (1.04, 1.10) | 1.11 (1.06, 1.17) |

TABLE B9
Relative risks of BCC at age 70 years as a result of occupational exposure to UVR from medical phototherapy equipment

Note Figures in parentheses are 95% confidence intervals.

| Frequency of erythema | Estimated annual occupational exposure (SED) | Number of years occupationally exposed | | | |
|-----------------------|--|--|----------------------|----------------------|----------------------|
| | | 5 | 10 | 20 | 40 |
| Once per week | 400 | 1.41 (1.18, 1.57) | 1.75 (1.38, 2.16) | 2.41 (1.46, 3.73) | 3.64 (1.83, 7.93) |
| Once per month | 184 | 1.18 (1.11, 1.24) | 1.31 (1.16, 1.52) | 1.56 (1.26, 1.94) | 2.00 (1.35, 3.09) |
| Once per year | 30 | 1.03 (1.02, 1.04) | 1.05 (1.02, 1.07) | 1.08 (1.05, 1.14) | 1.14 (1.05, 1.25) |

TABLE B10
Relative risks of SCC at age 70 years as a result of occupational exposure to UVR from medical phototherapy equipment

Note Figures in parentheses are 95% confidence intervals.

good working practices so that acute erythema develops no more than once or twice a year. With modern phototherapy equipment in which the lamps are enclosed inside a cubicle, this is perfectly feasible. It is with the older type of unenclosed lamps (eg the Alpine Sunlamp) that inadvertent exposure generally occurs.

Stratospheric ozone depletion and the risk of NMSC in a British population

Concern has been expressed widely that depletion of stratospheric ozone by chemical reactions involving the degradation products of chlorofluorocarbons will lead to a rise in the incidence of skin cancers as a consequence of increased levels of solar UVR at the Earth's surface (MacKie and Rycroft, 1988; Russell Jones, 1987; UNEP, 1991).

Significant global scale decreases in total ozone occurred during the period 1979-89 (UNEP, 1991; Science and Policy Associates Inc, 1992) and the loss of ozone in the northern hemisphere is now proceeding faster than previously thought with a rate of loss over mid-latitudes (30°-60°N) seen in winter and early spring of about 8% per decade (SORG, 1991). Measurements of total column ozone at several ground stations in Europe during the period from November 1991 to February 1992 reported values ranging up to 20% below average for the winter months (EASOE, 1992). The loss in summer months, when UVR levels are much higher and people are exposed more frequently to the sun, is about 2%-4% per decade.

Calculations for the northern hemisphere based on the measured ozone trends for the period 1979-89 indicate that, all other factors being constant, the terrestrial carcinogenic-effective UVR (which lies mainly within the UVB waveband of 280-315 nm) should have increased by about 1.3% to 4.7% during this decade (Madronich, 1992). Paradoxically these predictions are not confirmed consistently by ground-based UVR monitoring programmes (see Chapter 2).

By combining UVR climatological data for the UK with models of human behaviour (Diffey, 1992), it is possible to estimate the monthly exposure to the face (the most

*TABLE B11
Estimated monthly solar UVR exposure dose to the face of a child and an adult indoor worker, and total ozone trends for the UK*

| Month | Exposure dose to face (SED) | | % ozone decrease per year |
|-----------|-----------------------------|-------|---------------------------|
| | Child | Adult | |
| January | 0.6 | 0.4 | 0.6 |
| February | 2 | 1 | 0.3 |
| March | 6 | 2 | 0.8 |
| April | 28 | 12.8 | 0.6 |
| May | 40 | 26 | 0.8 |
| June | 50 | 32 | 0.3 |
| July | 64 | 44 | 0.3 |
| August | 80 | 66 | 0.1 |
| September | 20 | 12 | 0.3 |
| October | 7 | 3.2 | 0.6 |
| November | 2 | 0.2 | 0.5 |
| December | 0.4 | 0.2 | 0.4 |
| Annual | 300 | 200 | 0.4 |

common site for NMSC) in subjects taken to be representative of different population groups. These exemplary exposures are given for a child aged ten years and an adult indoor worker in Table B11.

In the absence of ozone depletion the adult indoor worker continues to receive an annual facial exposure dose of 200 SED. The child receives 150 SED per year until the age of 18 years and thereafter 200 SED each year (on the assumption that he/she becomes an indoor worker). However, if ozone depletion continues indefinitely at the rates shown in Table B11, it is possible to calculate the expected lifetime exposure, and hence the increased risk of developing skin cancer, for each subject compared with that expected if ozone levels remained at present values. Implicit in these estimates is that behaviour, time spent outdoors and climate remain unchanged.

The facial exposure dose (in SED) received by each subject during the 12-month period t years from now would be

$$\sum_{m=1}^{m=12} H_m \left\{ 1 + RAF \left[1 - \left(1 - \delta_m \right)^t \right] \right\} \quad (B7)$$

where H_m is the monthly exposure from the relevant column in Table B11, δ_m is the fractional ozone depletion in month m (ie 1/100 of the values given in Table B11), and RAF is the radiation amplification factor defined such that a 1% decrease in ozone results in a RAF% increase in carcinogenic-effective radiation at the Earth's surface. Using the most recent action spectrum for photocarcinogenesis in hairless mice, a factor of 1.4 for RAF is obtained (UNEP, 1991). By incorporating annual exposure doses into the model for skin cancer risk, it is possible to estimate the increased risk of BCC and SCC at different ages throughout life (Table B12).

The above calculations of the lifetime risk of skin cancer assume that ozone depletion continues indefinitely at present rates and would imply that at 50 years from now the number of skin cancers occurring each year in the UK will increase from the present number of about 30 000 to around 33 000 (because of under-reporting the real incidence of NMSCs each year could be two or three times this number). However, if there is global adherence to international undertakings for the phasing out of ozone depleting chemicals, as agreed in the Montreal Protocol (Niu *et al*, 1992), ozone levels should begin to recover slowly in the next century (Niu *et al*, 1992).

| Age (years) | Cumulative dose to face (SED) | | | Risk of skin cancer | | | |
|-------------|-------------------------------|----------------------------------|-------|---------------------|-------|-------|-------|
| | No ozone depletion | Ozone depletion at current rates | | BCC | | SCC | |
| | | Child | Adult | Child | Adult | Child | Adult |
| 50 | 11800 | 12530 | 11908 | 1.07 | 1.01 | 1.10 | 1.01 |
| 60 | 13800 | 14908 | 14088 | 1.09 | 1.02 | 1.13 | 1.03 |
| 70 | 15800 | 17356 | 16350 | 1.11 | 1.03 | 1.16 | 1.05 |

TABLE B12
Cumulative solar UVR exposure dose to face and the risk of skin cancer

Note It is assumed that ozone depletion continues indefinitely at current rates relative to an intact ozone layer calculated for a child presently aged 10 years and an adult indoor worker presently aged 35 years.

TABLE B13 Risk of BCC in a child presently aged 10 years when aged 70 years relative to that under an intact ozone layer

| T_c (years) | τ years | | | | | |
|---------------|--------------|------|------|------|------|------|
| | 5 | 10 | 15 | 20 | 25 | 30 |
| 20 | 1.04 | 1.05 | 1.05 | 1.05 | 1.06 | 1.06 |
| 30 | 1.06 | 1.07 | 1.07 | 1.08 | 1.08 | 1.08 |
| 40 | 1.08 | 1.09 | 1.09 | 1.10 | 1.10 | 1.10 |
| 50 | 1.10 | 1.11 | 1.11 | 1.11 | 1.11 | 1.11 |
| 60 | 1.11 | 1.11 | 1.11 | 1.11 | 1.11 | 1.11 |
| 10 | 1.02 | 1.02 | 1.03 | 1.03 | 1.03 | 1.03 |

Note Data are given on the assumption that ozone depletion continues at present rates until a period T_c years from now and thereafter the ambient UVR levels at that time return exponentially to present levels with a half recovery time of τ years.

TABLE B14 Risk of SCC in a child presently aged 10 years when aged 70 years relative to that under an intact ozone layer

| T_c (years) | τ years | | | | | |
|---------------|--------------|------|------|------|------|------|
| | 5 | 10 | 15 | 20 | 25 | 30 |
| 10 | 1.02 | 1.03 | 1.03 | 1.04 | 1.04 | 1.04 |
| 20 | 1.05 | 1.06 | 1.06 | 1.07 | 1.07 | 1.08 |
| 30 | 1.07 | 1.09 | 1.10 | 1.10 | 1.10 | 1.11 |
| 40 | 1.11 | 1.12 | 1.12 | 1.13 | 1.13 | 1.13 |
| 50 | 1.14 | 1.14 | 1.15 | 1.15 | 1.15 | 1.15 |
| 60 | 1.16 | 1.16 | 1.16 | 1.16 | 1.16 | 1.16 |

Note Data are given on the assumption that ozone depletion continues at present rates until a period T_c years from now and thereafter the ambient UVR levels at that time return exponentially to present levels with a half recovery time of τ years.

Models of atmospheric chemistry and transport are not capable of predicting reliably the details of any future ozone depletion resulting from the increasing concentrations of chlorine compounds that are largely responsible (UNEP, 1987). There will also be a time lag of several years before stratospheric chlorine concentrations respond to a decrease in chlorine loading. The implication is that stratospheric ozone destruction may continue to increase for several years after the chlorine loading of the troposphere has passed its peak value (SORG, 1990).

Given these uncertainties, the approach used here is to assume that ozone depletion continues at present rates for a period T_c years from now and thereafter the ambient UVR levels at that time return exponentially to present levels with a half recovery time of τ years. The child's risk of BCC and SCC at age 70 years for a range of T_c and τ have been calculated and the results are shown in Tables B13 and B14, respectively, where it can be seen that if ozone depletion continues at present rates for another 20 years, say, and then recovers with a half recovery time of 20 years, the risk of SCC by age 70 will be 1.07 compared with 1.16 if ozone depletion continues indefinitely at present rates.

COMMENT

This approach to estimation of dose–response using a power model has assumed, among other things, that:

- (a) the erythral dose is an adequate surrogate for carcinogenic-effective radiation,
- (b) all members of the populations giving rise to the incidence rates which have formed the basis for estimating the age exponents and biological amplification factors have lived their whole lives in a single environment,
- (c) skin cancer incidence rates have been measured accurately and, in particular, that their error does not correlate with ambient UVR,
- (d) possible confounding of ambient UVR with constitutional sensitivity to the sun and sun-related behaviour is either unimportant or has been taken adequately into account,
- (e) the fraction of ambient exposure received in different countries is the same,
- (f) all NMSCs are caused by exposure to UVR,
- (g) photocarcinogenesis is basically similar in mouse and human skin.

Although none of these assumptions is likely to be entirely correct (Armstrong, 1993), they do permit the development of a simple mathematical model relating UVR exposure to the risk of NMSC which gives encouraging agreement between observed and calculated age-standardised incidence rates both by latitude and by country of birth.

It should be noted that even if dose–response relationships between UVR and NMSC incidence determined at the population level are accurate, they may not reflect dose–response relationships at the individual level. This is because of the averaging of exposure and risk that occurs at the population level. The actual population exposure of the skin at any level of ambient UVR is an average of many different exposures and the actual population incidence of skin cancer is an average of many individual risks of skin cancer. The association of individual risk to individual exposure may be quite complex (as has been postulated for melanoma – see Armstrong, 1993) but at the population level this could still translate into a simple power relationship between ambient exposure and incidence. For this reason the use of the model described above is probably only valid in estimating the relative risks associated with elective or adventitious UVR exposure at the population level.

CONCLUSIONS

A model for estimating the risks of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) from exposure to UVR is described. The model was shown to give close agreement between observed and calculated age-standardised incidence rates (both by latitude and by country of birth) of BCC and SCC in a recent national survey in Australia, the country with the highest recorded incidence of NMSC. The model was used to estimate the risks (together with 95% confidence intervals) of BCC and SCC associated with elective UVR exposure (use of UVA sunbeds for whole-body tanning) and adventitious UVR exposure (occupational exposure in a hospital phototherapy department).

For British adults alive today ozone depletion continuing indefinitely at current rates is predicted to result in a relatively small additional lifetime risk (<5%; Table B12) of NMSC on the assumption of no changes in climate, time spent outdoors, behaviour or clothing habits. The lifetime risk incurred by today's children, however, is predicted to be 10%–16% greater than expected in the absence of ozone depletion (Table B12). However, if the production and use of substances that deplete ozone are reduced as expected under the current provisions of the Montreal Protocol, the increased lifetime risk of skin cancer is likely to be less than these estimates (Tables B13 and B14). It is to be hoped that public awareness about the adverse health effects of sun exposure will achieve these changes, which could lead to a reduction – rather than the anticipated increase – in skin cancer incidence. If there is no change in sun-exposure habits and the rate of ozone depletion, the calculations suggest that 50 years from now the number of skin cancers occurring each year in the UK will be about 10% higher than the present incidence. This is a much smaller increase than has occurred over the previous 50 years and illustrates that changes in leisure time, fashion and activities in the sun have had a much greater effect on skin cancer rates than expected as a consequence of ozone depletion. Clearly it will prove difficult to identify the real effect of ozone depletion on skin cancer incidence over the next few decades.

It is stressed that the nature of the assumptions associated with the derivation of the model parameters are such that the model is probably only valid for estimating population risks; it is not applicable to calculating risk for a given individual. Furthermore, it cannot be assumed that because knowledge does not allow risk estimates to be made for malignant melanoma (see Chapter 11), ozone depletion will have no effect on the incidence of this disease.

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Glossary

PHYSICAL TERMS

Absorption (atmospheric) the reduction in the intensity of any form of radiated power resulting from power or energy conversion in an absorbing medium, such as the atmosphere.

Artificial UVR sources UVR sources, other than the sun, eg arcs, discharge tubes and tungsten halogen lamps.

Atmospheric pollution pollution of the atmosphere by processes, usually industrial, used by human beings. Pollutants include hydrocarbon compounds, carbon monoxide and oxides of nitrogen and sulphur (see tropospheric ozone).

Berger meter a UVR detector designed to measure erythemally weighted UVR.

Biological action spectrum represents the effectiveness of a particular biological effect as a function of wavelength. It is the relative plot of the reciprocal of the dose required to produce the effect against wavelength normalised at one chosen wavelength (normally the most efficacious).

Broadband measurements (detectors) integrated measurements over a range of wavelengths, often inherently incorporating a weighting function representative of a biological action spectrum.

Blue light light in the wavelength range between about 400 and 500 nm.

Cathode ray tube an electronic tube in which a controllable beam of electrons is produced and directed on to a surface resulting in the emission of optical radiation.

Clothing Protection Factor (CPF) is the ratio of the least amount of ultraviolet energy required to produce a minimal erythema on clothing-protected skin to the amount of energy required to produce the same erythema on unprotected skin.

Cloud cover the effectiveness of cloudiness on the solar irradiation of a horizontal plane can be approximated by the expression $F = 1 - 0.056 C$, where C is the cloudiness factor, usually quoted in tenths of sky covered from 0 to 10 (10 being complete sky cover). Thus, for complete cloud cover, the terrestrial UVR intensity would decrease to 44% and for half cloud cover to 72%. This expression does not account for cloud quality.

Electromagnetic radiation radiation considered as a wave of electric and magnetic energy travelling through a medium.

Erythemally weighted UVR integrated UVR that has been multiplied (as a function of wavelength) with a function representative of the action spectrum for the biological effect of erythema.

Greenwich Mean Time (GMT) time measured by the hour angle of mean sun and referred to the zero meridian of longitude through Greenwich, UK.

Harmonic(s) multiple(s) of the fundamental frequency of fields emitted by a source, eg 50 Hz harmonics are 100, 150, 200 Hz etc.

Hertz (Hz) a frequency (of electromagnetic field or radiation) of one cycle per second.

Illuminance the areal density of luminous flux incident at a point on a surface (unit = the lux, ie lumen per square metre, or, practically for solar light, the kilolux where 1 klux) = 10^3 lux).

Integrated (function) either time integrated (eg dose) or wavelength integrated (eg erythemally weighted UVR) functions summed over all relevant time or wavelength intervals.

Irradiance the areal density of radiant flux incident at a point on a surface (unit = watt per square metre (W m^{-2}), or mW m^{-2}).

Liquid crystal (display) a display based on changes in reflectivity of a liquid crystal cell when an electric field is applied.

Minimum erythema dose (MED) the UVR dose that produces a just noticeable erythema on previously unexposed skin.

Network a coordinated collection of measurement sites.

Optical radiation electromagnetic radiation comprising UVR, visible and/or infrared radiation.

Ozone O_3 produced photochemically by the action of solar UVR at wavelengths below 242 nm on oxygen molecules and located in a layer between 20 and 30 km above the earth's surface.

Photometric quantities/units a system of quantities/units used to quantify the amount, rate and spatial and spectral distributions of visible radiation relative to the response of the human eye.

Photon (energy) a quantum of electromagnetic radiation equal to a constant (Planck's Constant) times the frequency of the radiation (unit = the hertz).

Photopic (response) response of the human eye under normal conditions of illumination.

Radiant exposure the time-integrated irradiance falling on a surface (unit = joule per square metre (J m^{-2})).

Radiometric quantities/units a system of absolute quantities/units used to quantify the amount, rate and spatial and spectral distributions of electromagnetic radiation; they do not depend on the response of any detector.

SED (Standard Erythema Dose) is a measure of erythema UVR equivalent to an erythema effective radiant exposure of 100 J m^{-2} .

Scattering (atmospheric) irregular reflection or dispersal of electromagnetic radiation by particles, water droplets and pollutants in the atmosphere.

Scotopic response of the human eye under conditions of low illumination.

Spectral measurements measurements made at small wavelength intervals (often 1 nm) to which any suitable biological action spectrum can be subsequently fitted.

Stratosphere the Earth's atmosphere above the troposphere, extending from about 8 km and 16 km above the Earth at the poles and equator, respectively, to about 50 km.

Stratospheric ozone depletion reduction in the ozone content in the stratosphere by the action of certain chemicals such as chlorofluorocarbons (CFCs) and halons.

Sun Protection Factor (SPF) is the ratio of the least amount of ultraviolet energy required to produce a minimal erythema on sunscreen-protected skin to the amount of energy required to produce the same erythema on unprotected skin.

Terrestrial solar UVR UVR from the sun in the wavelength range from about 290 to 400 nm which penetrates to the Earth's surface.

Tropospheric ozone generated by the action of UVR on molecules of nitrogen dioxide (NO₂), the formation of which is accelerated by solar UVR acting on atmospheric pollutants, particularly NO₂ emissions from transport and industry and hydrocarbon emissions from car exhausts.

Ultraviolet radiation (UVR) electromagnetic radiation in the wavelength range 100 to 400 nm.

UVA (ultraviolet A) UVR in the wavelength range 315 to 400 nm.

UVB (ultraviolet B) UVR in the wavelength range 280 to 315 nm.

UVC (ultraviolet C) UVR in the wavelength range 100 to 280 nm.

UVR (biologically) effective UVR at a particular wavelength which has been multiplied by a factor indicating the efficacy of a given biological effect at that wavelength; each weighted component is then summed over a wavelength interval (unit W m⁻² effective).

Visible radiation electromagnetic radiation in the wavelength range 380/400 to 760/780 nm.

Wavelength the distance between two similar and successive points on an alternating wave (unit for optical radiation = the nanometre (nm) or 10⁻⁹ m).

Weighting function represents the relative effectiveness of a particular effect normalised at a given point (generally the most efficacious) (*see biological action spectrum*).

CLINICAL AND BIOLOGICAL TERMS

Acral lentiginous melanoma (ALM) an uncommon type of melanoma, but the most common type seen in non-white individuals, occurring chiefly on the palms and soles, especially on the distal phalanges of the fingers and toes, often on the tip of the digit or nail fold or bed, and sometimes involving mucosal surfaces, such as the vulva or vagina.

Actinic keratosis spontaneously regressing keratinised patch having aberrant cell differentiation and proliferation.

Actinic damage damage caused by light beyond the violet end of the spectrum producing photochemical effects.

Antigen something the immune system recognises as foreign; an antigenic determinant is the small part, of a larger foreign target, which is actually recognised.

Antigen presenting cell specialised cells which perform antigen presentation, a process involving the uptake of foreign molecules and their degradation to fragments which are displayed on the cell surface in a form recognisable to T lymphocytes.

Apoptosis programmed cell death, during which cells deliberately degrade their own DNA to short fragments.

Aphakic crystalline lens of the eye is absent.

Basal cell attaching cell in lowest layer of stratified tissue.

Basal cell carcinoma epithelial tumour of skin originating from basal cells – usually occurs as pearly nodule or plagued with central depression.

Carcinogen an agent that induces cancer.

Carcinogenesis production and development of cancer.

Cataract an opacity, partial or complete, in the lens of the eye which may impair vision and if dense enough cause blindness.

Choroid part of uveal tract – that part behind ciliary body.

Chromophores an atom or group of atoms in a molecule responsible for spectral absorption.

Ciliary body part of uveal tract – joins iris to choroid.

Climatic droplet keratopathy bilateral, symmetrical corneal degeneration due to extreme heat or cold.

Collagen insoluble fibrous proteins forming part of connective tissue.

Cone photoreceptor in the eye responsible for normal colour vision and visual acuity.

Conjunctiva the membrane that lines the eyelids and covers the exposed surface of the sclera (white of the eye).

Conjunctivitis inflammation of the conjunctiva.

Connective tissue supporting tissues that consists of large amounts of non-living material.

Contact hypersensitivity allergic response caused by direct contact with certain substances.

Cornea the transparent structure forming the front part of the eye.

Cytokine factor which induces cell growth and division.

Cytolysis dissolution of cells.

Dermis see Figure 7.1.

Desquamation shedding of surface layer of skin.

Dyskeratosis abnormal, premature or imperfect keratinisation of the keratinocytes.

Eicosanoids arachidonic acid and its derivatives; includes many compounds with potent biological activities such as prostaglandins and thromboxanes.

Elastin protein that forms elastic fibres in connective tissue.

Endothelium squamous epithelium that lines internal body surfaces.

Epidermis see Figure 7.1.

Epithelioma malignant growth derived from epithelium.

Epithelium arrangement of cells covering a free surface.

Erythema a redness of the skin.

Eumelanin dark-brown or black form of melanin.

Extinction gradual and progressive reduction in the frequency of performance of a given response caused by withdrawal of reinforcement.

Fibroblasts flattened connective tissue cells that secrete the fibrous components of extracellular matrix.

Fibrosarcoma tumour of fibrous connective tissue.

Foveomacular retinitis inflammatory process of central retina.

Homozygous having inherited a given genetic factor from both parents.

Hyperplasia excessive multiplication of cells in the body; overgrowth.

Immunosuppression suppression of an immune response.

Interpalpebral conjunctiva that part of the conjunctiva seen between the eyelids and covering the sclera.

Keratin simple insoluble protein with structural and protective functions. Present in skin, hair, and nails.

Keratinisation intracellular deposition of keratin.

Keratinocyte the skin cell which synthesises keratin.

Keratitis inflammation of the cornea and iris.

Keratoacanthoma (KA) firm skin nodule with a centre of keratotic material.

Langerhans cells (LC) major antigen presenting stellate dendritic cells in normal epidermis.

Late post-implantation death death occurring in the later stages of fetal development when the organs and organ systems have formed.

Lentigines (S lentigo) a brownish or yellowish spot on the skin, most often on hands, arms or face.

Lentigo maligna melanoma (LMM) a cutaneous malignant melanoma (cancer) found most often on the sun-exposed area of skin.

Leucocyte white blood cell; protects against infection.

Lupus erythematosus a group of connective tissue (autoimmune) disorders primarily affecting women aged 20 to 40 years.

Lymphocyte type of leucocyte found in the lymphglands and spleen; major component of the immune system.

Macrophage large migratory white blood cell that ingests invading organisms and scavenges damaged cells.

Macula depression of the retina with the fovea at its centre. Important for visual acuity.

Macular degeneration degenerative changes of the central retina.

Malignant melanoma a malignant cancer of melanocytes.

Melanin group of black, dark-brown, or reddish pigments present in the skin. Produced in melanocytes and stored in melanosomes.

Melanocyte dendritic clear cell of the epidermis that synthesises the pigment melanin.

Melanocytic naevus a localised benign proliferation of cells of the melanocyte system. The term *atypical naevus* is used clinically to describe melanocytic naevi which are greater than 5 mm in diameter and which have an irregular edge, irregular pigmentation and sometimes also a degree of inflammation.

Melanoma tumour arising from the melanocyte system of the skin and other organs. When used alone refers to malignant melanoma.

Metastasis process where cells break away from a tumour and spread around the body (verb: metastasise).

Naevus (plural: naevi) a birthmark – a stable malformation of the skin (or occasionally oral mucosa), presumably of hereditary origin, consisting of an excess (or deficiency) of epidermal, connective, nervous or vascular tissues.

Neoplastic transformation the genetic alteration of a cell so that it will form a tumour if injected into a suitable host animal; transformed cells also exhibit characteristic growth changes in culture.

Neurodermatitis an extremely variable dermatitis presumed to be a response to prolonged vigorous scratching, rubbing or pinching.

Nodular melanoma a type of malignant melanoma that is in the form of swelling or knot of tissue, most often occurring on the head, neck and trunk.

Non-melanoma skin cancer cancers that are not melanomous, eg squamous and basal cell carcinomas.

Oedema swelling of tissue due to build up of intercellular fluid.

Oncogene a mutated or foreign gene that contributes to cancer in a dominant fashion.

Optical axis of the lens the hypothetical straight line that passes through the centres of curvature of the front and back surfaces of the lens of the eye.

Papilloma benign epithelial tumour in which the proliferating cells grow outward from a surface to form a branching structure interlaced with connective tissue.

Phaeomelanin reddish-brown melanin.

Phakic crystalline lens of eye is not absent.

Photophobia abnormal intolerance of (sensitivity to) light.

Photoreceptor sensory cell in the eye stimulated by light.

Pigment epithelium epithelium at the back of that containing granules of pigment.

Pinguecula a proliferative yellow lesion of the conjunctiva covering the sclera near the sclerocorneal junction, usually on the nasal side.

Porphyria group of disorders group of disturbances of porphyrin metabolism (products of amino acid breakdown), characterised biochemically by marked increase in formation and excretion of porphyrins or their precursors and clinically by various neurologic and cutaneous manifestations.

Prostaglandin one of several physiologically active compounds.

Psoralen any of the constituents of certain plants that are photoreactive.

Psoriasis a common chronic, dermatitis with polygenic inheritance and a fluctuating course.

Pterygium a wing-like structure, in the interpalpebral fissure, attached to the cornea and the sclera and merging with the conjunctiva at its base – may grow over cornea to impair vision.

Ptosis drooping of the upper eyelid.

PUVA clinical treatment used primarily for psoriasis consisting of ingestion of psoralens and interval irradiation with UVA.

Pycnotic nuclei small, irregular nucleus of degenerating cells.

Retina inside layer of the eye which is sensitive to light. Contains photoreceptors, nerve cells and pigment epithelium.

Retinal photoreceptor cell body the sensing cell in the retina.

Retinitis inflammation of the retina.

Rhodopsin purple pigment found in the rods of the retina.

Rod photoreceptor required to see low intensities of light (night vision).

Scleroproteins large class of proteins occurring in connective tissue. Includes collagen, elastin and keratin.

Sebaceous gland secretes sebum, a fatty fluid that protects and lubricates the skin and hair.

Solar pertaining to the sun.

Splenocytes leucocyte derived from the spleen.

Squamous cell carcinoma scaly or platelike malignant tumour.

Stratum corneum keratinised layer of exfoliating epidermis; outer layer of the skin.

Stroma a supporting framework of connective tissue.

Superficial spreading melanoma most common type of malignant melanoma, characterised by a period of radial growth of atypical of melanocytes in the epidermis, usually associated with a lymphocytic cellular host response that is sometimes accompanied by partial or complete regression.

Syngenic of the same inbred strain; genetically very similar.

Telangiectasia permanent dilation of pre-existing blood vessels, creating small focal red lesions, usually in the skin or mucous membranes.

Tumour suppressor gene normal cellular gene involved in regulating cell behaviour. Mutations can contribute to cancer in a recessive fashion.

Ulceration destruction of the epithelial surface to form an open sore.

Uvea melanoma uvea is the middle coat/layer of the eye and includes the iris, ciliary body and choroid and other structures – the structures are collectively also known as the uveal tract.

Uveal melanoma most common type of ocular malignant melanoma, consisting of overgrowth of uveal melanoma cytes and often preceded by a uveal naevus.

Uveitis inflammation of any part of the uvea, ie the iris, ciliary body and choroid.

Vasodilation relaxation, or enlarging, of blood vessels.

Vermilion border the lips (red/pink part).

Xeroderma pigmentosum a rare pigmentary and atrophic autosomal recessive disease affecting all races, in which there is extreme cutaneous photosensitivity to UVR, as a result of a deficient enzyme in the excisional repair of UVR-damaged DNA. Problems start in infancy or early childhood with erythema and vesicles and progresses to freckle-like pigmentation/telangiectasia with further superficial ulceration, warty-growths and areas of atrophy – epithelial cancers are very likely.

EPIDEMIOLOGICAL TERMS

Case-control study an investigation into the extent to which a group of persons with a specific disease (the cases) and comparable persons who do not have the disease (the controls) differ with respect to exposure to putative risk factors.

Cohort study an investigation involving the identification of a group of individuals (the cohort) about whom certain exposure information is collected, and the ascertainment of the occurrence of diseases at later times. For each individual, information on prior exposure can be related to subsequent disease experience.

Confidence interval (CI) an interval calculated from data when making inferences about an unknown parameter. In hypothetical repetitions of the study, the interval will include the parameter in question on a specified percentage of occasions (eg 95% for a 95% confidence interval).

Odds ratio the ratio of the odds of disease occurrence in a group with exposure to a factor to that in an unexposed group; within each group, the odds are the ratio of the numbers of diseased and non-diseased individuals.

Relative risk (RR) the ratio of the disease rate in the group under study to that in a comparison group, with adjustment for confounding factors such as age, if necessary. For rare diseases, the relative risk is practically the same as the odds ratio.

Statement by the Advisory Group on Non-ionising Radiation

CHAIRMAN: SIR RICHARD DOLL

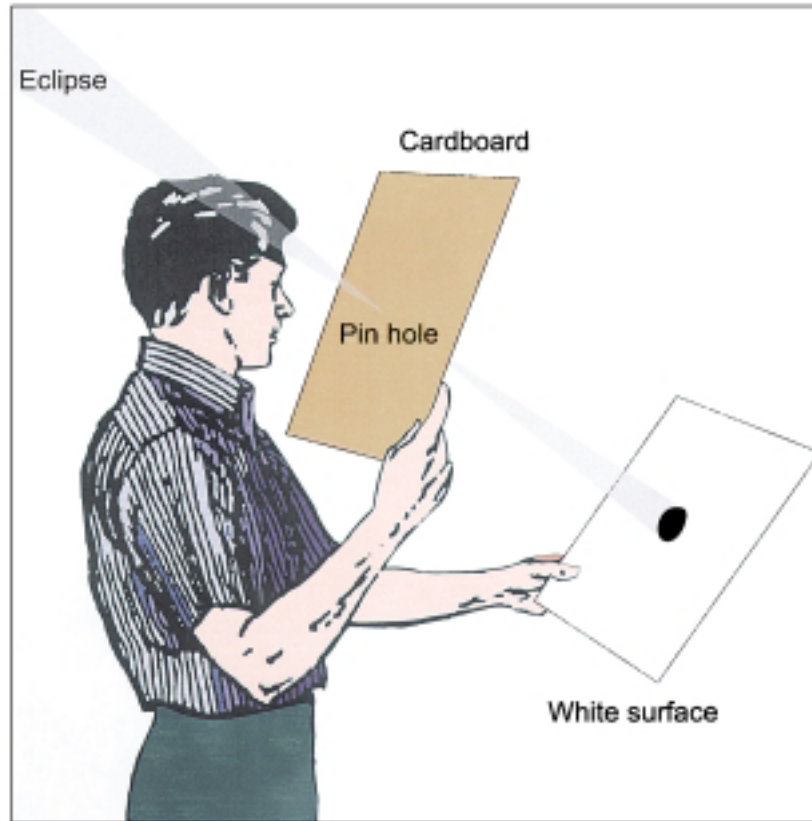
THE SOLAR ECLIPSE

Supplementary Report by the Advisory Group on Non-ionising Radiation (prepared by a Subgroup on the Effects of the Eye)*

- 1** There will be a solar eclipse in the UK on the morning of Wednesday 11th August 1999. The eclipse will be total in most areas of Cornwall, in south-west Devon, the Isles of Scilly and the island of Alderney. The moon will completely cover the disc of the sun for up to two minutes. In other areas of the UK, the eclipse will be partial.
- 2** This is a once in a lifetime event as the next total eclipse in the UK is in 2090. It should be enjoyed, but considerable care is needed. It is never safe to look at the sun, even when almost all of the sun's disc is obscured during the partial phases of an eclipse. In most of the UK it will, therefore, be unsafe to view the sun during the time of the eclipse, either directly or through unfiltered optical devices such as a telescope or binoculars. Even in areas where the eclipse is total, very great care is needed to avoid direct viewing, both before and after totality.
- 3** Exposure of the retina to intense light can cause damage to its light sensitive cells. The result can be partial impairment of sight or blindness, which may be temporary or permanent, depending on the severity of the damage. When a person stares at the sun directly, without proper protection for the eyes, damage to the light sensitive retina may result without any feeling of pain. The extent of visual loss may not be immediately apparent, and progressively increase for up to several hours after the exposure.
- 4** The safest and most inexpensive method of observing the eclipse is indirectly, by standing with your back to the sun and projecting an image through a pinhole made in a large sheet of card onto a second white card placed in shadow about a metre from the opening (see the figure).
- 5** The only way that the sun might be viewed directly is when wearing eyewear specially designed for the purpose. Even then, however, great care is needed. Ensure the eyewear is in perfect condition without any sign of scratches, scuffs or other damage and that instructions for use are supplied, are adequate and are properly followed. It is important to realise that 'sunglasses' are **not** designed for this purpose.
- 6** Other materials used as filters, such as photographic film or smoked glass may **not** give adequate protection. The fact that the sun appears dim, or that you feel no discomfort when looking at it, does not mean that your eyes are safe.
- 7** Avoid taking any risks with your eyesight.

* This Statement by the Advisory Group was first published on the NRPB website (www.nrpb.org) on 21 June 1999 and was also distributed to the media and other interested bodies.

Indirect viewing of
the solar eclipse



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Statement by the Advisory Group on Non-ionising Radiation

CHAIRMAN: SIR RICHARD DOLL

USE OF SUNBEDS AND COSMETIC TANNING

Supplementary Report by the Advisory Group on Non-ionising Radiation (prepared by a Subgroup on Ultraviolet Radiation)*

- 1** In 1990 the Director of NRPB established an Advisory Group on Non-ionising Radiation, chaired by Sir Richard Doll, to review work on the biological effects of non-ionising radiation relevant to human health and advise on research priorities. The Advisory Group has produced reports on:
 - exposure to electromagnetic fields and the risk of cancer¹⁻³,
 - health effects related to the use of visual display units⁴,
 - health effects from exposure to ultraviolet radiation⁵.
- 2** This Statement follows from the previous advice on exposure to ultraviolet radiation by the Advisory Group and was prepared by its Subgroup on Ultraviolet Radiation.
- 3** Sunbeds and sunlamps, which emit ultraviolet radiation (UVR), are widely used in the UK for cosmetic tanning, particularly by young people⁶. The International Agency for Research on Cancer (IARC) considers that their use entails exposures that are classified as probably carcinogenic to humans⁷. Exposures to UVR also pose other potential risks to health⁵. The Advisory Group considers that the use of sunbeds and sunlamps for cosmetic tanning should be discouraged and that information about their potential adverse health effects should be made available to users and the general public.
- 4** This advice does not apply to the use of UVR as part of a medical treatment, where the benefits and potential risks need to be assessed in a clinical context.
- 5** People at particular risk of adverse effects include:
 - people with a large number of moles, a tendency to freckle or a family history of skin cancer,
 - people with a susceptibility to sunburn,
 - children,
 - people with existing, sun-damaged skin or certain skin diseases,
 - people taking medication that changes the skin's response to UVR.
- 6** Scientific knowledge of the health effects from exposure to UVR is summarised below. Further details and background can be found in publications of the National

* This Statement by the Advisory Group was published in the *Radiological Protection Bulletin* (No. 218, December 1999) and was also put on the NRPB website (www.nrpb.org) in January 2000.

Radiological Protection Board⁵, the British Photodermatology Group⁸, the International Commission on Non-Ionizing Radiation Protection⁹, and the World Health Organization¹⁰.

Health effects of UVR

- 7 Sunlight, which contains both UVA and UVB radiation*, is the major source of human exposure to UVR. Tanning, which results from the increased production and distribution of the pigment melanin within the epidermis of those people who are able to tan, is considered to represent a protective response to UVR-induced damage to the skin¹¹. However, this tanning gives incomplete protection. There is considerable evidence that high levels of cumulative exposure to solar UVR cause premature ageing of the skin, which then looks mottled, coarse, leathery and wrinkled, and that high cumulative levels of exposure of the eye may cause an increased risk of cataracts later in life⁵. A reduction in the immune response has been observed after UVR exposure although the consequences for health are not known⁵.
- 8 There is also a variety of circumstances in which people can exhibit abnormal, hypersensitivity responses to solar UVR, mostly confined to exposed areas of the body, following contact with certain chemicals such as coal tar extracts, plant extracts or treatment with certain drugs. Such responses include phototoxic reactions, characterised by redness, swelling and blistering often after a delay of 3–4 days, and photoallergic reactions, which result in an eczematous dermatitis similar to ordinary contact dermatitis. Common photosensitising drugs include amiodarone, nalidixic acid, non-steroidal anti-inflammatories, phenothiazines, psoralens, sulphonamides, tetracyclines, and thiazide diuretics.
- 9 The most serious health effects attributed to UVR exposure of the skin are skin cancers⁵. Squamous and basal cell carcinomas (non-melanoma skin cancers) are relatively common but are rarely fatal. There is strong evidence that solar UVR causes these cancers in humans^{5,7} and experimental studies have shown that solar-simulated radiation can cause squamous cell carcinomas in mice^{5,7}. Cutaneous malignant melanoma occurs much less frequently than non-melanoma skin cancers, but is more serious and accounts for the majority of skin cancer deaths. There has been an increase in the incidence of melanoma in white populations over recent decades which is thought to be due primarily to changes in people's behaviour with regard to exposure to the sun⁵. The epidemiological data indicate that the pattern of exposure to UVR is an important influence on the risk of skin melanoma: short-term intermittent exposure of usually unexposed skin to high levels of solar UVR is believed to be particularly important in this respect^{5,7}. In addition, the risk of malignant melanoma is higher in people who have a large number of naevi (moles), and in those who sunburn readily and tan poorly^{5,7}. There is evidence that exposure to solar UVR in childhood may be especially important in melanoma aetiology^{5,7}.

Sunbeds and sunlamps

- 10 Sunbeds and sunlamps emit predominantly UVA radiation with small amounts of UVB radiation compared with the ratio in solar radiation, although there has been an increase in UVB levels in some newer models. The lamps generally produce a tan only in people who tan well in sunlight. Those who tan poorly or not at all or who sunburn

* UVR is divided by wavelength into UVA 315–400 nm, UVB 280–315 nm and UVC 100–280 nm.

easily are likely to be disappointed with the cosmetic results. Short-term damaging effects include:

- sunburnt skin, which becomes painful, red and may blister and peel,
- skin dryness and itching,
- eye irritation if suitable protective eyewear is not worn⁸.

11 It is likely that sunbed exposure may also contribute to premature skin ageing and, if suitable protective eyewear is not worn, possibly to cataract formation⁸. In addition, people taking certain drugs or applying some cosmetics and who then use a sunbed may develop a UVR-sensitive reaction which appears as an itchy or painful rash, sometimes followed by pronounced pigmentation⁸. Sunbed use may also provoke transient skin reactions such as polymorphic light eruption (non-scarring, red lesions appearing on light-exposed skin) or exacerbate pre-existing diseases such as lupus erythematosus (a chronic multi-system inflammatory disease)⁸.

12 IARC considers that both UVA and UVB radiation are probably carcinogenic to humans⁷. Whilst the direct epidemiological evidence about the risk of non-melanoma skin cancers with sunbed use is inconclusive, laboratory studies have demonstrated unequivocally that radiation in the UVA range as well as in the UVB range can damage genetic material in cells^{5,7}, including human skin cells. This can lead to mutation, a critical step in the carcinogenic process. In addition, both UVA and UVB radiation will induce squamous cell carcinomas in mice^{5,7}. Certain epidemiological investigations have found a positive relationship between tanning lamp use and melanoma but the scientific evidence is as yet insufficient to permit a firm conclusion regarding a causal relationship¹². However, their use involves intermittent periods of intense exposure of the skin to UVR, including exposure of skin sites that are usually covered in everyday life. This is the pattern of exposure that is believed to be important to the risk of melanoma from solar UVR exposure, and there is no reason to believe that sunbed exposure would not likewise contribute to risk.

Conclusions and recommendations

13 There is strong evidence that exposure to solar UVR can have adverse effects on health, notably an increased risk of potentially fatal cancers of the skin and probably, with high exposures, to an increased risk of cataract. It is likely that UVR exposure from sunbeds will contribute to the risk of adverse health effects, particularly skin cancers (and cataracts, if protective eyewear is not worn) and that certain groups of people will be at an increased level of risk. The Advisory Group therefore recommends that the use of sunbeds and sunlamps for cosmetic tanning should be discouraged and that information about their potential adverse health effects should be made available to users and the general public.

14 This statement applies to cosmetic tanning. It does not apply to the use of UVR as part of a medical treatment, where the benefits and potential risks need to be assessed in a clinical context.

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Documents of the NRPB

Further information on these and other NRPB publications is available on the NRPB website (www.nrpb.org).

VOLUME 1 (1990)

- No. 1 Radiological Protection Act 1970
Directions by the Health Ministers under the Radiological Protection Act 1970
Statement by NRPB: limitation of human exposure to radon in homes
Human exposure to radon in homes: recommendations for the practical application of the Board's Statement
- No. 2 Gut transfer factors: values proposed by a Nuclear Energy Agency Expert Group for radionuclides ingested by members of the public
Gut transfer factors: values for plutonium and americium in shellfish and best estimates for actinides in food
- No. 3 Patient dose reduction in diagnostic radiology (Joint report with the Royal College of Radiologists)
- No. 4 Statement by NRPB: principles for the protection of the public and workers in the event of accidental releases of radioactive materials into the environment and other radiological emergencies
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Radon affected areas: Cornwall and Devon

VOLUME 2 (1991)

- No. 1 Statement by NRPB: principles for the protection of patients and volunteers during clinical magnetic resonance diagnostic procedures
Limits on patient and volunteer exposure during clinical magnetic resonance diagnostic procedures: recommendations for the practical application of the Board's Statement

VOLUME 3 (1992)

- No. 1 Electromagnetic fields and the risk of cancer (Report of an Advisory Group on Non-ionising Radiation)
- No. 2 Statement by NRPB: approval of consumer goods containing radioactive substances
Criteria of acceptability relating to the approval of consumer goods containing radioactive substances
Radiological protection standards: ionisation chamber smoke detectors; radiological time measurements instruments; tritium light sources; compasses containing gaseous tritium light sources; thoriated gas mantles
- No. 3 Statement by NRPB: radiological protection objectives for the land-based disposal of solid radioactive wastes
Radiological protection objectives for the land-based disposal of solid radioactive wastes: recommendations for the practical application of the Board's Statement
- No. 4 Protection of the patient in x-ray computed tomography
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VOLUME 4 (1993)

- No. 1 Statement by NRPB: 1990 recommendations of ICRP
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- No. 2 Occupational exposure: guidance on the 1990 recommendations of ICRP
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