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The human health effects of ozone depletion and interactions with climate change.

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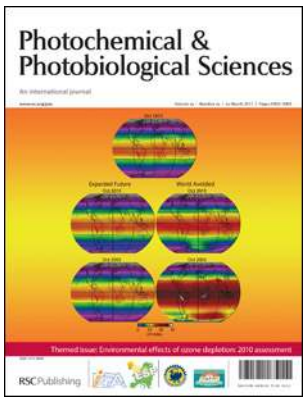

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PERSPECTIVE

The human health effects of ozone depletion and interactions with climate change†

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Depletion of the stratospheric ozone layer has led to increased solar UV-B radiation (280–315 nm) at the surface of the Earth. This change is likely to have had an impact on human exposure to UV-B radiation with consequential detrimental and beneficial effects on health, although behavioural changes in society over the past 60 years or so with regard to sun exposure are of considerable importance. The present report concentrates on information published since our previous report in 2007. The adverse effects of UV radiation are primarily on the eye and the skin. While solar UV radiation is a recognised risk factor for some types of cataract and for pterygium, the evidence is less strong, although increasing, for ocular melanoma, and is equivocal at present for age-related macular degeneration. For the skin, the most common harmful outcome is skin cancer, including melanoma and the non-melanoma skin cancers, basal cell carcinoma and squamous cell carcinoma. The incidence of all three of these tumours has risen significantly over the past five decades, particularly in people with fair skin, and is projected to continue to increase, thus posing a significant world-wide health burden. Overexposure to the sun is the major identified environmental risk factor in skin cancer, in association with various genetic risk factors and immune effects. Suppression of some aspects of immunity follows exposure to UV radiation and the consequences of this modulation for the immune control of infectious diseases, for vaccination and for tumours, are additional concerns. In a common sun allergy (polymorphic light eruption), there is an imbalance in the immune response to UV radiation, resulting in a sun-evoked rash. The major health benefit of exposure to solar UV-B radiation is the production of vitamin D. Vitamin D plays a crucial role in bone metabolism and is also implicated in protection against a wide range of diseases. Although there is some evidence supporting protective effects for a range of internal cancers, this is not yet conclusive, but strongest for colorectal cancer, at present. A role for vitamin D in protection against several autoimmune diseases has been studied, with the most convincing results to date for multiple sclerosis. Vitamin D is starting to be assessed for its protective properties against several infectious and coronary diseases. Current methods for protecting the eye and the skin from the adverse effects of solar UV radiation are evaluated, including seeking shade, wearing protective clothing and sunglasses, and using sunscreens. Newer possibilities are considered such as creams that repair UV-induced DNA damage, and substances applied topically to the skin or eaten in the diet that protect against some of the detrimental effects of sun exposure. It is difficult to provide easily understandable public health messages regarding "safe" sun exposure, so that the positive effects of vitamin D production are balanced against the negative effects of excessive exposure. The international response to ozone depletion has included the development and deployment of replacement technologies and chemicals. To date, limited evidence suggests that substitutes for the ozone-depleting substances do not have significant effects on human health. In addition to stratospheric ozone depletion, climate change is predicted to affect human health, and potential interactions between these two parameters are considered. These include altering the risk of developing skin tumours, infectious diseases and various skin diseases, in addition to altering the efficiency by which pathogenic microorganisms are inactivated in the environment.

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Introduction

Depletion of the ozone layer has led to an increase in solar UV-B radiation reaching the Earth's surface, with many consequences for human health. These can be beneficial, such as promoting the synthesis of vitamin D, or detrimental, such as inducing skin cancer and cataract. It should be noted here that changes in human behaviour with regard to sun exposure over the past 60 years or so have probably contributed much more significantly to alterations in health risks than ozone depletion. Such changes, leading to an increase in exposure to solar UV radiation, include the widespread perception that a tanned skin is desirable and an indicator of good health, the huge rise in the popularity of sunshine holidays (and thus exposures to different UV radiation environments) encouraged by inexpensive air travel, and the wearing of minimal clothing and swimwear when air temperatures rise. Other changes have led to a decrease in exposure to solar UV radiation, including fewer outdoor occupations and more urban living. Climate change may also increase the vulnerability of the population to UV radiation.

The present assessment focuses on the four year period from 2006 to the present, except where some background information is included for clarity. It follows a similar format to our previous report published in 2007.[1] First the harmful effects of solar UV radiation on the eye, the skin and the immune system are considered. Secondly the positive aspects of UV-mediated endogenous production of vitamin D in protecting against several diseases are discussed. A third section considers ways in which individuals can protect their eyes and skin from solar UV radiation, and provides some cost-benefit analyses. The impact of toxicity and air pollution resulting from new substitutes for the ozone-depleting substances is discussed (with detail presented in an online appendix (ESI†)). A final section assesses the sparse information available to date on the possible health effects of the interactions between climate change and ozone depletion. Changes in lower atmospheric air quality as a result of UV radiation and climate change may also have health consequences, and this is considered elsewhere.[2]

The effects of solar UV radiation on the eye

There is convincing evidence that UV radiation exposure is a risk factor for some types of cataract, pterygium, pinguecula (conjunctival degeneration) and squamous cell carcinoma of the cornea and conjunctiva. In addition, acute photokeratitis and photoconjunctivitis are clearly UV-induced, and retinal burns can result from high intensity exposure, such as looking directly at the sun. For other disorders, including ocular melanoma and age-related macular degeneration, the evidence of a role for UV radiation is scanty and/or contradictory. Previous reports have reviewed the mechanics of UV-B irradiation of target tissues in the eye,[1] and the two major effects of chronic UV radiation, pterygium and cataract,[1,3] as well as effects on the cornea and conjunctiva.[4]

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† Electronic supplementary information (ESI) available: Appendix: Health risks associated with the use of substitutes for ozone-depleting substances. See DOI: 10.1039/c0pp90044c

Here we update that evidence and focus further on diseases where there remains uncertainty for an association with exposure to UV radiation, particularly UV-B radiation.

Pterygium

Pterygium is an inflammatory, proliferative and invasive growth on the conjunctiva and cornea of the human eye that can impair vision.[1] Recent studies support an association between higher levels of sun exposure and development of both primary and recurrent (after surgery) pterygium,[5] but provide no information regarding the relative importance of UV-A or UV-B radiation.

Previous work has implicated both dust and UV radiation in the pathogenesis of pterygium.[6] Support for the latter is indicated by the high prevalence in fishermen and sailors, who are not exposed to dust, but to UV radiation that is scattered and highly reflected from the sea, which can be up to 20% of the incident UV radiation.[7] Furthermore, exposure to scattered, rather than direct, UV radiation is more likely to irradiate the region of the eye where pterygium is generally found. Indeed it has been suggested that scattered light may expose the basal stem cells at the junction of the white of the eye and the cornea to increased amounts of UV radiation, leading to mutations in tumour suppressor genes and the generation of damaging reactive oxygen radicals.[6] UV-B irradiation may also cause the release of pro-inflammatory cytokines into tears bathing the mucosal surface, with resulting chronic inflammation and fibrovascular proliferation leading to pterygium formation.[8]

Cataract

In the previous report,[1] we assessed the epidemiological evidence for an association between exposure to UV-B radiation and the three main types of age-related cataract: cortical, nuclear and posterior subcapsular. There is considerable evidence that UV irradiation is a risk factor for the development of cortical cataract, with less evidence to support a relationship with nuclear cataract, although the timing of exposure may be particularly important for the latter. The evidence for an association with posterior subcapsular cataract remains weak. There has been little progress in this area. One study established an action spectrum for cataractogenesis using cultured whole porcine crystalline lens,[9] which was in good agreement with previously published action spectra for isolated lens epithelial cells and *in vivo* models. The peak effectiveness for the production of lens anterior subcapsular lesions occurred in the UV-B waveband, around 290 nm (see McKenzie *et al.*,[10] Table 2). More recent research has focused largely on animal studies, examining mechanisms of UV-induced development of cataract. A wide range of animals has been used, including mice and rats,[11–13] rabbits[14,15] and guinea pigs,[16] but none provides an ideal model for the human lens, and whether UV-A or UV-B wavelengths are more important for cataract formation varies from species to species.

Ocular melanoma

Limited evidence indicates that there may be a link between solar UV-B radiation and the development of ocular melanoma. Such tumours include both external, involving the eyelid and conjunctiva, and intraocular tumours, involving the iris, ciliary

body and choroid (collectively known as the uvea). The latter comprise the majority of ocular melanomas and are the most common primary eye cancer in adults with a reported annual incidence per million of 6 in fair-skinned and 0.3 in dark-skinned individuals.[17] Examples are shown in Fig. 1.

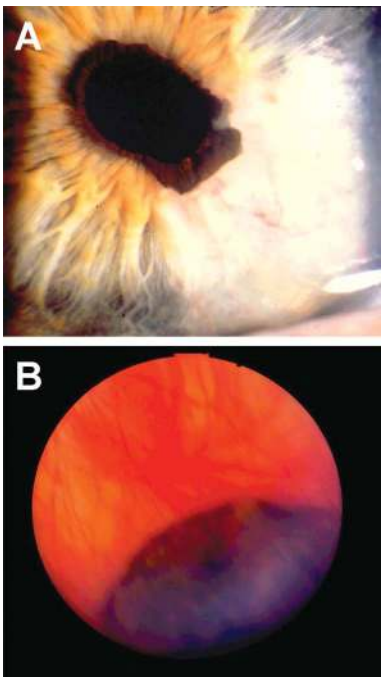

Fig. 1 Intraocular malignant melanoma: (a) an amelanotic iris melanoma with nutrient blood vessels, causing a rolling out (ectropion) of the pigment layer and distortion of the pupil, and (b) a dome-shaped choroidal melanoma with mottled appearance (photographs supplied by Dr A. Cullen, University of Waterloo, Canada).

Although there is substantial lenticular transmission of UV-B radiation in childhood, this decreases with age so that, in adulthood, uveal melanocytes are exposed to only a small amount of UV-B radiation.[1] This suggests that exposure of external and uveal melanocytes to UV-B radiation, at least in adulthood, is different. One study showed that higher exposure to UV radiation in the first 20 years of life is a risk factor for ocular melanoma,[18] while others have demonstrated an increased risk in relation to light-coloured irides, previous photokeratitis (due to welding or snow blindness), exposure to sunlamps, and wearing sunglasses or hats (interpreted as indicating photosensitivity).[19–22] Such evidence supports exposure to UV radiation as a causative factor in ocular melanomas, but epidemiological data suggest that the effects may be confined to external tumours.[23] For example, the age-standardised incidence of conjunctival melanoma increased more than 7-fold in Swedish men and women between 1960 and 2005, with the increase confined to tumours of UV-exposed conjunctiva (rather than the tarsal conjunctiva lining the eyelid). In contrast, the incidence of uveal melanoma is stable or even declining.[24,25] In the non-Hispanic white population in the USA (1992–2002), there was an inverse latitudinal gradient in the incidence of conjunctival melanoma (2.5-fold increase from 47–48° to 20–22° latitude, *i.e.* increasing incidence with higher ambient UV radiation), but decreasing risk of uveal melanoma with decreasing latitude (higher ambient UV radiation).[26]

Age-related macular degeneration

Age-related macular degeneration (AMD), also called age-related maculopathy, is the most frequent cause of loss of vision in humans living in developed countries. This retinal disease is most commonly the non-exudative (dry/atrophic) form, but the more severe exudative (wet/neovascular) form can also occur (see Fig. 2). The aetiology of AMD is unclear but is thought to involve both genetic and external factors, such as solar UV radiation. In animal studies, reactive oxygen species generated as a result of UV-induced changes can damage the retinal pigment epithelium, leading to degeneration of photoreceptors of the neural retina and the development of AMD.[27]

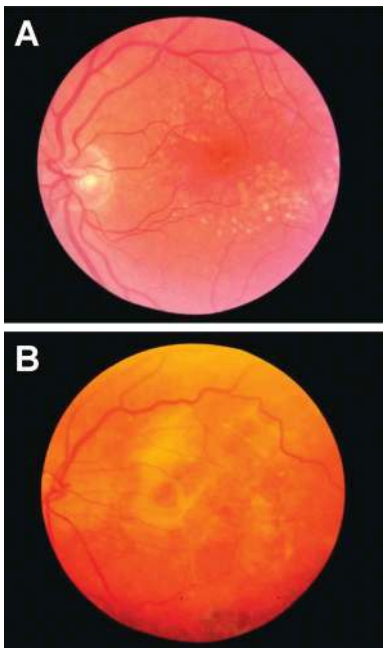

Fig. 2 Age-related macular degeneration: (a) early dry form showing discrete yellow spots (drusen) at the posterior pole and mild retinal pigment epithelial changes, and (b) sudden onset wet form with extensive macular oedema (fluid in and behind the retina), suggesting underlying abnormal blood vessels (photographs supplied by Dr A. Cullen, University of Waterloo, Canada).

AMD is significantly more common in higher ambient UV radiation settings or in population groups having greater exposure to UV radiation, such as farmers and fishermen.[28,29] Higher sun exposure, assessed either by questionnaire[29,30] or by facial wrinkling,[31] is associated with an increased risk of AMD, particularly the exudative form. Furthermore, in an Australian study, participants who had a history of sun-sensitive skin (burning rather than tanning) had a decreased risk of exudative AMD compared with subjects who had average sun-sensitivity,[32] an observation that could be explained by the former subjects having had lower lifetime sun exposure. These findings form a consistent picture of support for UV radiation being a risk factor, at least in exudative AMD. However, other studies reveal no association between ambient UV radiation or past sun exposure and AMD,[33] and no evidence to support dependence on a specific wavelength range. It is possible that any correlation between UV radiation and AMD may be confounded by other factors such as variable genetic

susceptibility or even blue light which is capable of generating reactive oxygen species.

The effects of solar UV radiation on the skin

Melanoma

Epidemiology of melanoma. The annual incidence of cutaneous malignant melanoma (CMM) varies geographically from between 5 and 24 per 100 000 in Europe and the USA[34–36] to over 70 per 100 000 in higher ambient UV radiation regions of Australia and New Zealand.[37–39] Even in locations with lower incidence, there are specific high-risk groups such as non-Hispanic white men older than 65 years in the USA, where the incidence is greater than 125 cases per 100 000.[36] In Australia, melanoma is currently the third most commonly reported cancer in men and women overall, and the commonest in women aged 17–33 years.[40] CMM is uncommon in individuals under the age of 20, although an increase of 2.9% per year between 1973 and 2003 in the USA has been reported in a recent review.[41]

Many studies in various countries indicate that the incidence of CMM has increased by 1–3% per year over the past half century.[42–46] In a few instances it has stabilised over recent years,[37,47] particularly in people younger than 40 years. For example, in Sweden the previously rapid increase in the incidence of CMM in teenagers from 1973 levelled off between 1983 and 1992, and since then has decreased.[48] This situation has been attributed to intensive public health campaigns over the past 30 years or so advocating avoidance of sunburn and seeking medical care promptly if pigmented skin lesions arise.[49–53] The increasing incidence pertains particularly to thin (early) melanomas, with the incidence of thick (late) melanomas relatively unchanged.[42,43,45,46] Whether this is real or an artefact of screening and diagnostic drift (*in situ* lesions not diagnosed previously as CMM now being included) remains controversial.

Mortality rates due to CMM, which increased in most European countries as well as in North America, Australia and New Zealand in the 1980s, peaked around 1990 and since then have tended to be stable, for example in the USA,[36] or to decrease, for example in women in Northern Ireland.[45] Any such reduction in the next few years will probably be due to early detection and treatment rather than to primary prevention and changes in ambient UV radiation.

The distribution of CMM varies by age and sex, probably related to different patterns of exposure to the sun. Head and neck tumours are found particularly in elderly populations,[34,54,55] and are thought to be correlated with chronic sun exposure, as indicated by their association with solar keratoses,[56,57] considered as a marker of repeated solar UV irradiation. In younger age groups, the highest rates of CMM occur on the trunk in males and on the extremities in females.[39,55] Intermittent sun exposure and sunburn[54,55,58] in childhood[59–61] and throughout adulthood[60,61] are major risk factors.

In high ambient UV radiation locations, the development of pigmented moles (acquired melanocytic nevi, AMN) in young children is very common,[62,63] particularly where there is a combination of fair skin type with higher sun exposure and episodes of sunburning. For example, only 8.3% of Brazilian children aged 2–8 years had no AMN.[62] Waterside vacations in the USA were associated with a 5% increase in the number of small moles in children examined at age 7 years, with a lag in the development of new moles of one year after the vacation.[64]

An important question for CMM in relation to stratospheric ozone depletion concerns the wavelength dependency of initiation and development. Although an early study in the *Xiphophorus* hybrid fish suggested a role for UV-A radiation,[65] this has not been supported by more recent work in the same model[66] or in mammalian models, including the South American opossum[67] and several genetically modified mouse strains (see, for example, ref. 68). The weight of evidence now supports UV-B radiation as critical to the initiation of melanoma, although a contributory role for chronic exposure to UV-A radiation in the progression of melanoma, through free radical formation or direct effects on DNA, is possible.[69]

Genetic damage and risk of melanoma. Cancer is thought to result from mutations in genes that control cell proliferation and migration/invasion into surrounding tissue. Mutations in key genes in CMM have been identified; but there is a lack of characteristic UV-related mutations in these genes and it is not clear whether and how they might be affected by UV radiation.

In human CMM, the pathway involving Ras proteins is frequently activated, with stimulation of cell growth, while the protein p16Ink4a, which acts as a tumour suppressor, is frequently down-regulated. In parallel with epidemiological findings on risk from early life exposures, and in contrast to an earlier study,[70] a single exposure to UV radiation of newborn mice deficient in *p16Ink4a* induced melanomas in the adult animals, and a defect in DNA repair (deficient XPC protein) further enhanced the formation of melanomas.[71]

Recently, the entire genetic sequences of a cell line from a CMM metastasis and a lymphoblast cell line derived from normal blood cells of the same person have been compared. There was an astonishingly large number of mutations in the CMM cells (33 345 somatic base substitutions), the majority of which were typical of changes that accompany exposure to UV radiation.[72] This titanic analysis unambiguously established that UV radiation was the major cause of the mutations, at least in this CMM.

Non-melanoma skin cancer

Epidemiology of non-melanoma skin cancer. Individuals in many countries continue to experience significant annual increases in the incidences of the non-melanoma skin cancers (NMSCs): basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[73,74] For example, the incidence of BCC increased by 3% per year from 1996–2003 in the UK,[75] and the incidence of SCC increased four-fold from 1960–2004 in Sweden.[54] The incidence of NMSC in Australia in 2002 was five times greater than the incidence of all other cancers combined.[76] In subtropical Australia, the incidence rate for people affected by a primary BCC was almost the same as for those with multiple lesions, indicating that the disease burden may be higher than is apparent from the usually cited incidence rates that rely on number of people affected rather than number of tumours.[77] In some regions or subpopulations, the increases in the incidence rates have slowed,[75,78] particularly in younger cohorts (<60 years for BCC and <50 years for SCC),[76] possibly related to the introduction of public health educational programmes. In some locations there is a change in the distribution

of NMSC on the body with an increase occurring on the trunk and upper arms. This has been attributed to the fashion for intentional body tanning in recent years.[54] One study in the Netherlands found that, between 1990 and 2004, an increasing proportion of BCC patients were in the high socioeconomic status group, as defined by income and value of housing (with a concomitant decrease in the proportion in the lower socioeconomic status group).[73]

In most populations, SCC is about 2.2-fold and BCC about 1.6-fold more common in men than women.[79] This is possibly due to higher sun exposure in males who tend to have more outdoor occupations and recreational activities, a larger area of skin exposed than women, and are less likely to use sunscreens.[80,81] However, recent animal studies also suggest that there may be a biological gender bias in risk, possibly through protective effects of local synthesis of estrogens that protect females against UV-induced photocarcinogenesis.[80–82]

Exposure to solar UV-B radiation is well-recognised as the predominant environmental risk factor for both SCC and BCC.[83,84] For SCC, cumulative life-time exposure, particularly occupational sun exposure, is key.[85] For BCC, the relationship is thought to be more complex: in one study the risk of BCC on the head was especially increased in sun-sensitive individuals, whereas BCCs on the trunk were more related to the number of reported sunburns rather than to general sun-sensitivity.[86] One common location for BCC is the inner canthus of the eye where the upper and lower eyelids meet. This is relatively sun-protected by the nose, eyebrow ridge, orbit and the cheek bone, but UV radiation may be reflected from the tear film, resulting in high dose exposure near the tear duct.[87]

Genetic damage and risk of non-melanoma skin cancer. Several UV-B-specific mutations are recognised in BCCs and SCCs,[1] such as in the *p53* gene and also in the *PTCH* gene of BCCs.[88] A number of other UV-related genetic factors may also be important in NMSC risk, but are less well-described. These include mutations in genes related to repair of DNA damage[89–94] and alterations in DNA methylation, where the latter is known to promote UV-induced DNA damage and affect genes involved in the regulation of the cell cycle and cell adhesion.[95–98] Variants of the melanocortin 1 receptor (*MC1R*) gene that determines skin pigmentation and phototype, and variants in other pigment genes, have been associated with BCC risk[99–101] and various polymorphisms in genes related to UV-induced immunosuppression and tolerance can affect the risk of BCC and SCC.[102–105] Finally, variants in the gene coding for the vitamin D receptor (see "Immune and other effects of vitamin D" section below) increase the risk of NMSC[106] and of solar keratosis,[107] the precursor lesion to NMSC.

Effects of solar UV radiation on the immune system

Mechanisms of UV-induced immunosuppression

Immune responses fall into two broad categories – innate and acquired/adaptive. The former responses are non-specific and act rapidly as the initial response to microbial challenge. The latter responses are specific to each microorganism, and require, in many cases, that the antigens are taken up by antigen-presenting cells (often dendritic cells), processed and then presented to the particular T lymphocytes that recognise the antigen fragments. As a consequence, these T cells are activated to proliferate and to secrete immune mediators. It was recognised many years ago that exposure of mice to UV radiation can suppress adaptive immune responses,[108] and that antigen-specific tolerance is induced, so that a further application of the same antigen at a later date still does not lead to the generation of an immune response.[109] More recently, it has been demonstrated that UV radiation can down-regulate already established (memory) immune responses.[110–112] Furthermore, exposure to multiple suberythemal doses of UV radiation from solar simulated lamps, to mimic what might occur during the summer months, does not lead to any protection against the immunosuppression developing, despite most people responding to such chronic irradiation by tanning and epidermal thickening.[113]

The mechanisms involved are complex and are summarised in Fig. 3. Details can be found in recent reviews.[114–117] The main points are that DNA and *trans*-urocanic acid in the epidermis act as important chromophores to initiate the immunosuppressive pathway and that a particular subset of T cells, called T regulatory cells, are induced at the end. On stimulation, these produce the immunosuppressive cytokine, interleukin (IL)-10, and develop and maintain immune tolerance. They also suppress the activation, cytokine production and proliferation of other types of T cells which are involved in immunostimulatory functions. Various aspects of UV-induced immunosuppression that affect human health are outlined below, starting with viral and bacterial infections and vaccination, followed by the skin cancers, and ending with the "sun-allergy" disease, polymorphic light eruption (PLE).

The effect of UV-induced immunosuppression on infectious diseases

Although there are about twenty models of infection in rodents that indicate a significant down-regulation in acquired immune responses to the microbe in question following UV radiation, robust evidence of such an outcome in human subjects is limited at present to two viruses, namely herpes simplex virus (HSV), which causes cold sores, and human papillomavirus (HPV), which commonly causes warts. It is possible that other human infections may be affected but have not been investigated as yet.

Viral infections. Aspects of the reactivation of HSV from latency following exposure to solar UV radiation were outlined in our previous report.[1] In brief, the viral genome is maintained in nerve tissue following the primary infection, and UV radiation is a common stimulus for its reactivation, release from the nerve tissue, and subsequent replication in the epidermis. There is probably a direct interaction between the latent HSV and UV radiation, possibly *via* damage to nerve endings, which leads to the activation of promoters within the viral genome. In addition, temporary UV-induced immunosuppression in the local skin site will occur, allowing replication of the virus and development of the 'cold sore' before immune control is regained.

For HPV, two interactions between solar UV-B radiation and the virus will be discussed here. First, the most common *de novo* malignancy arising in organ transplant recipients (OTR) is skin cancer: SCC occurs 65–250 times, BCC 10 times and CMM 6–8 times more frequently than in the general population. In OTR, persistent warts caused by HPV infection, cutaneous SCCs and their precursor lesions (actinic keratoses) arise mainly on sun-exposed body sites, leading to the conclusion that solar UV radiation is the major environmental risk factor for SCC in such

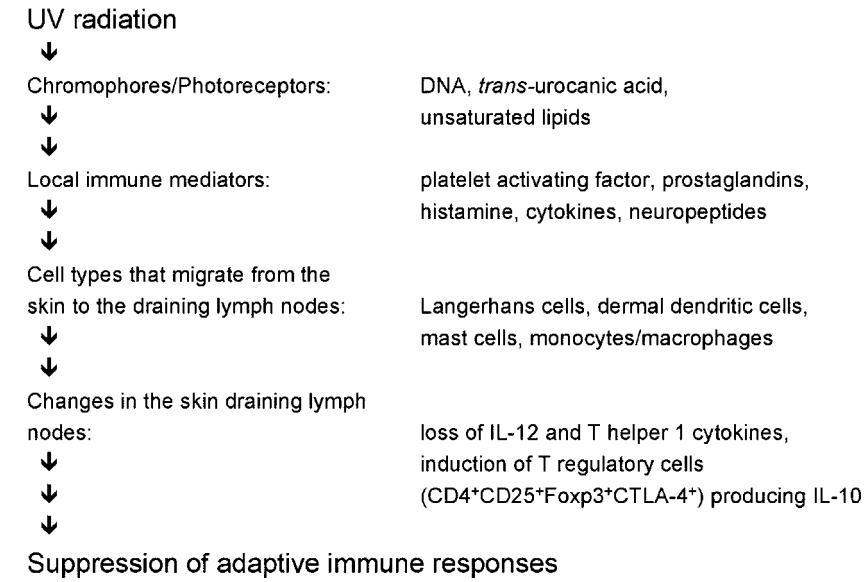

Fig. 3 Summary of steps leading to suppression of cell-mediated immunity following UV irradiation.

patients. Up to 90% of SCCs from OTR contain HPV DNA.[118,119] HPV, UV radiation and the immunosuppressive drugs interact to promote the tumourigenesis. For example, UV irradiation of the skin not only induces local immune suppression by the mechanisms outlined in Fig. 3, but certain HPV types can express proteins that interfere with the normal response of the cell to UV irradiation, such as the repair of DNA damage and the removal by apoptosis of cells with DNA damage.[120–123] Cyclosporin A, until recently the most commonly used immunosuppressive drug in OTR, also interferes with the mechanisms involved in the repair and removal by apoptosis of cells with UV-induced damage to DNA.[124] Hence, the end result is the selection and accumulation of cells with altered phenotype, leading to skin cancer. Conversely, other newer immunosuppressive drugs such as sirolimus may reduce the risk of skin cancer.[125]

Secondly, HPV infection appears to be involved in SCCs in healthy (immunocompetent) subjects. As in the OTR, the SCCs arise on areas of the body exposed most frequently to sunlight, such as the face and backs of the hands. A higher prevalence of DNA of certain HPV types (beta-HPV species 2) is found in SCCs than in uninvolved skin from the same subjects or in controls.[126] The same HPV types are associated with SCCs located on body sites most exposed to the sun.[127] A population survey of workers in Australia with and without a history of frequent sun exposure found that the prevalence of the DNA of cutaneous HPV was significantly higher in the forehead skin in individuals who spent more time outdoors and in those with a history of skin cancer.[128] Indeed, the risk of cutaneous HPV infection increased with the length of time spent working outdoors. Multiple HPV types were more common in individuals frequently exposed to the sun, a finding attributed to UV-induced immunosuppression. Possible interactions between the mutagenic and immunosuppressive activity of the UV radiation and the properties of the HPV types found in some SCCs are likely to be very diverse and are not elucidated at present, although, as outlined above, the viral proteins that are anti-apoptotic[121] and cause a delay in DNA repair may be important.

Finally for HPV, it should be noted that the suggestion[129] that some HPV types might play a role in the aetiology of squamous cell cancers in the conjunctiva of the eye in countries, such as Uganda, where exposure to sunlight is very high, has not been confirmed in more recent studies.[130,131]

Recently a polyomavirus has been identified in the tumour cells of Merkel cell carcinoma (a tumour of the dermis with neuroendocrine features and a very poor prognosis), which is not found in uninvolved tissue from the patients or in any other type of skin tumour.[132] These tumours arise predominantly on sun-exposed areas of the skin in elderly and immunosuppressed individuals.[133] Although rare, its incidence in the USA has increased 3-fold over the past 15 years, possibly due to the ageing of the population and extensive sun exposure. Currently, there is no information available regarding local or systemic immune responses to the polyomavirus antigens, particularly to evaluate whether there could be a role for UV-induced immunosuppression as a risk factor in the tumourigenesis.

Bacterial infections. In contrast to viruses where the acquired immune response, particularly the T cell component, is critical for the control of infection, innate defence mechanisms may be more important for bacteria, especially those infecting cutaneous or mucosal surfaces.[134] Glaser *et al.*[135] have shown that UV irradiation of healthy volunteers induced up-regulation in the expression of several antimicrobial peptides which form part of the innate immune response of skin. The enhanced expression continued for at least 6 days after the irradiation. Thus one reason for the lack of bacterial infections of human skin following solar UV radiation exposure could be the production of these antimicrobial peptides. They may be particularly relevant when burning of the skin has occurred and bacterial infections might be expected in blistered areas. The contrast between this result and the rodent models of bacterial infection, where microbial load and severity of symptoms increased due to UV-induced suppression of acquired immunity, may relate to the site of infection, the size of the inoculum, and differences in gene regulation and in

antimicrobial peptides between species. If the Glaser *et al.* results[135] are confirmed in other human studies, it may be necessary to consider whether innate immune responses, which tend to be up-regulated by UV radiation, or acquired immune responses which tend to be down-regulated by UV radiation, are most important in the control of specific infections, especially at early stages in the process.

The effect of UV-induced immunosuppression on vaccination

The immunosuppressive effects of UV radiation have been demonstrated in several animal models of vaccination, both if the exposure occurs prior to (see, for example, ref. 136) or after[110,137] the vaccine has been administered. Thus it is of much interest to consider whether exposure to solar UV radiation could adversely affect the immune response to vaccines in human subjects.

There has been only one published experimental human study in which volunteers were whole-body irradiated with solar simulated UV radiation before being vaccinated with hepatitis B surface antigen.[138] There was little effect of exposure on the T cell or antibody response to the vaccine except in irradiated subjects with a particular IL-1β polymorphism (which affects the production of this cytokine) who had lower levels of antibody to the hepatitis protein,[139] and in irradiated subjects with high cutaneous *cis*-urocanic acid (see Fig. 3) who had suppressed T cell responses to the hepatitis protein.[140] Thus UV radiation adversely affected the generation of immune responses to hepatitis B vaccine, but only in certain individuals.

Only a few studies to date have evaluated whether season or latitude have any effect on immune responses to vaccination. These factors are frequently used as crude measures of personal exposure to solar UV radiation. In a meta-analysis of 10 case-control studies and 13 prospective trials of BCG vaccination against tuberculosis, where the geographical latitude of the study site was recorded, it was found that the efficacy of protection increased with increasing distance from the equator, perhaps because of diminishing UV-induced immunosuppression.[141] Most recently, children living in northern Israel who had been injected with the measles-mumps-rubella vaccine at age 12 months were assessed for their antibody response to the rubella component at age 4–5 years.[142] In this area of the world, the UV Index in the summer reaches 10–12, while in the winter the peak values are 2–4. The children vaccinated in the winter months had significantly higher antibody levels compared with the children vaccinated in the summer months, and a bigger percentage had generated adequate levels. Thus the season when the subjects were vaccinated made a difference to the rubella antibody level 3–4 years later. These results require corroboration in more locations with marked differences in ambient solar UV radiation throughout the year, and using other viral vaccines. If it is true that, due to differences in solar UV radiation and hence effects on immune responses, vaccination in the summer leads to decreased immunity to the vaccine compared with vaccination in the winter, several practical implications follow. For example, it might be recommended to undertake vaccination only at times of the year when solar UV radiation is minimal, to ask individuals to limit their sun exposure for a few days before and after vaccination, and not to vaccinate an obviously sunburnt subject, especially on or through a site of erythema.

UV-induced immunosuppression and melanoma

Solar UV radiation is a risk factor for CMM and UV radiation is recognised to be immunosuppressive. It is not clear as yet if these two factors are linked. Muller *et al.*[143] have suggested that immune responses in newborn children, whose skin is immunologically immature, could determine melanoma outcomes in later life. Antigen applied at this time does not induce an immune response, but instead there is generation of antigen-specific T regulatory cells which then persist for life. Thus, if a melanoma antigen arises during this neonatal period, T regulatory cells specific for it will be produced, with the capacity to dampen effective anti-tumour immunity in adulthood. In addition, exposure of neonatal skin to UV radiation induces a poor inflammatory response compared with adult skin, thus limiting the development of an immune response. A micro-array study has identified several genes involved in enhanced immune responses in melanomas harbouring the BRAF mutations compared with non-mutated melanomas.[144] Another approach has centred on cytokine gene polymorphisms which might result in functional changes and influence susceptibility to CMM.[145,146]

UV-induced immunosuppression and non-melanoma skin cancer

The development of NMSC is controlled, at least in part, by the immune system, and by exposure to sunlight. For SCCs this is particularly apparent as the number of such tumours is greatly increased on sun-exposed areas of the body in organ transplant recipients (OTR) who are therapeutically immunosuppressed to prevent rejection of the transplant. These drugs suppress T cell activity predominantly and therefore T cell function is thought to play a major role in the immunological control of SCCs. UV radiation is known to suppress the production of the T helper 1 cytokines (see Fig. 3) which protect against SCCs in mice.[147] In addition, untreated human SCCs contain many infiltrating T cells of which about 50% are T regulatory cells.[148] Furthermore, blood vessels in the tumours do not express *E*-selectin, a molecule that skin-homing T cells require for their entry into the skin from blood. Thus SCCs exclude the skin-homing T cells that could destroy the tumour cells.

A histological study of human BCCs revealed T regulatory cells surrounding the tumour aggregates and immunosuppressive cytokines within the tumours.[149] Only immature dendritic cells were found intratumourally, implying poor antigen presentation to T cells. All these factors suggest a lack of immunity in BCCs, although an obvious inflammatory response is also seen,[149] together with an increase in the expression of pro-inflammatory cytokines.[150] Thus there is evidence for both an anti-tumour response and an attenuated state of immunity in BCCs.

UV-induced sun allergy

Polymorphic light eruption (PLE) is the most common of the disorders that are provoked by sunlight, occurring in about 5–20% of the population. It is most frequent in the spring or early summer, or during a sunny holiday, following the first exposure to an intense dose of sunlight, and is characterised by red, itchy skin eruptions (Fig. 4). After repeated exposures, the lesions are less likely to occur in most subjects – a process called hardening. The effectiveness with which various UV wavelengths induce PLE

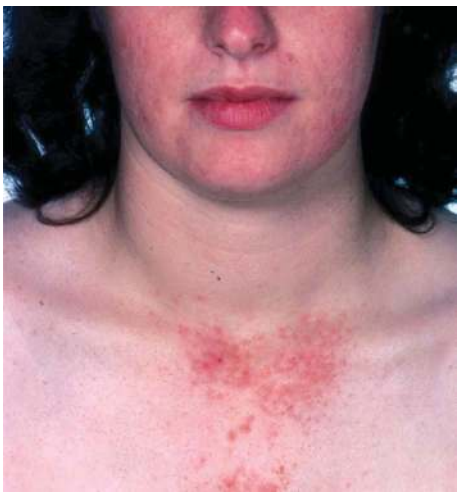

Fig. 4 Subject with polymorphic light eruption showing pruritic skin eruptions on sun-exposed body sites (photograph supplied by Dr S. Ibbotson, University of Dundee, Scotland).

is unclear and may depend on a complex mixture of factors such as dose, the genetic background of the individual and the cutaneous antigen provoked. Until recently it was thought that the prevalence of PLE increased with increasing distance from the equator, explained by the more marked change in seasonal ambient solar UV radiation at higher latitude. However, a recent large scale European survey found that latitude made no difference to the prevalence, suggesting that exposure to UV radiation could trigger the disease equally in countries with different patterns of solar UV irradiation throughout the year.[151]

PLE is immunologically-mediated, with increased immunosurveillance, and resistance to the immunosuppression that follows UV radiation. The subjects with PLE are thought to respond to photo-induced neoantigens in the skin by a form of delayed type hypersensitivity and the lack of immunosuppression may be due to reduced neutrophil and macrophage infiltration into the irradiated skin and possibly reduced numbers of T regulatory cells in the winter months.[152] The impact of these alterations from normal is illustrated by finding that the prevalence of PLE is 7.5% in people with skin cancer compared with 21.4% in gender and age-matched controls without skin cancer.[153] This implies that the immunological differences in the response of the PLE subjects to UV radiation may confer protection against skin cancer, and it also illustrates the evolutionary significance and potential advantages and disadvantages of UV-induced immunosuppression.

UV-induced vitamin D and its impact on health

For the majority of individuals, most of their vitamin D is derived from sun exposure. The additional sources of vitamin D are natural food stuffs, such as oily fish, supplemented foods, such as margarines and milk, and, in some cases, oral supplements. It has become clear recently that vitamin D status is also dependent on genetic differences in the metabolism of vitamin D.[154] A recent study in Denmark showed that the cumulative personal summer solar UV radiation dose correlated weakly with the vitamin D status of the individual in the summer and in the following winter.[155] Dietary intake of vitamin D appears to influence vitamin D status during the winter, at least at high latitudes, and this may provide an explanation for the observed weak correlation between the vitamin D status in the winter and summer, in these locations.[156,157] Recent simple model computations, based on UK data for ambient UV radiation, indicate that sun exposures in the summer may indeed be inefficient in maintaining a sufficiently high vitamin D status in the winter.[158]

The pathway to the formation of the active form of vitamin D, 1,25-dihyroxyvitamin D ($1,25(OH)_2D$), after skin exposure to UV radiation[159] is outlined in Fig. 5. Many cell types possess the enzymatic machinery to produce $1,25(OH)_2D$, (reviewed in ref. 160). The concentration of 25-hydroxyvitamin D (25(OH)D) in the serum is commonly used as a measure of a person's vitamin D status. Traditionally, the values considered as deficient, insufficient, sufficient and excessive are <25 (or <27.5), 25–50, 50–250 and >250 nmol L^{-1} respectively. More recently, it is suggested that the minimum level that provides the best health benefits should be increased from 50 to at least 75 nmol L^{-1}, with the optimum between 90–100 nmol L^{-1},[161–165] although it should be noted that not all agree with this opinion.[166] Any health benefit of maintaining a high serum 25(OH)D status has not been established,[167] and, indeed, may even be detrimental as has been shown recently for pancreatic cancer where a concentration of ≥100 nmol L^{-1} was associated with a 2-fold increase in risk.[168]

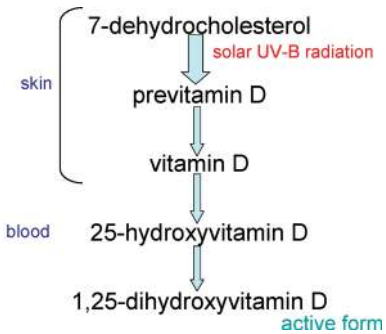

Fig. 5 Synthesis of the active form of vitamin D ($1,25(OH)_2D$) after solar UV-B irradiation of the skin.

By constructing an action spectrum for the conversion of 7-dehydrocholesterol to previtamin D_3 in human skin (see Table 6 in ref. 10), it was concluded that the most effective wavelength for the production of previtamin D_3 was between 295 and 300 nm with a maximum at 297 nm, and no production above 315 nm, *i.e.* UV-B wavelengths only.[169] Although the accuracy of the original data can be questioned (reviewed in ref. 170), this spectrum was standardised by the CIE in 2006[171] and extended mathematically to 330 nm. It has been used subsequently in several studies for weighting the solar spectra to obtain effective doses for potential vitamin D production at various latitudes throughout the year.[10,172–176] It is vital to obtain the best possible information in this regard so that accurate guidance can be given to the general public and to health agencies concerning personal exposure to sunlight in order to maximise vitamin D production while minimising any harmful effects of the UV radiation. Very few studies to date have measured the actual effect of known doses of UV radiation

on 25(OH)D levels. However, one study published very recently has shown that the concentration of 25(OH)D in the majority of fair-skinned subjects rises to sufficient levels (≥50 nmol L^{-1}) (although this may be sub-optimal) following simulated summer sun exposure (at latitude 53.5°N) of 13 min, three times weekly for 6 weeks, to 35% of the skin surface area.[177] Here it should be noted that the subjects were whole-body irradiated whereas, under natural conditions, people lying on their backs or fronts in the sun are irradiated either on the anterior or the posterior surface, rather than both at the same time. Thus the sunbathing time to achieve the equivalent magnitude of vitamin D synthesis would require an exposure of about 26 min. Other confounding factors include posture, orientation with respect to the sun and nearby shade, leading to the conclusion that considerably longer than 26 min would be required, typically greater than one hour.[178]

Based on the action spectrum for the production of previtamin D, the potential for synthesis of vitamin D is dependent on levels of ambient solar UV-B radiation. The amount of solar UV-B radiation that reaches the surface of the Earth varies greatly, depending on the solar zenith angle (highest in the summer and decreasing to as little as 5% of this value at mid-latitudes in the winter months) which also accounts for its strong diurnal variation (typically 50–60% of daily solar UV radiation is incident in the 4 h period around local noon) (see McKenzie *et al.*[10] for further details). It depends also on parameters such as ozone, cloud cover, air pollution and altitude. Furthermore, there are large interpersonal variations in the efficiency of previtamin D_3 production for a given dose of solar UV-B radiation. This may depend on skin colour (about 6-fold more UV-B radiation appears to be required if the skin is dark compared with fair skin[179]), age (about 50% less is made by the same dose of UV-B radiation in an 80-year-old compared with a 20-year-old[180]), obesity (leads to less bioavailability of vitamin D as it is sequestered in fat tissue[181]), baseline vitamin D status[182] and whether the irradiated skin site is one that has been repeatedly exposed, such as the face, as this affects the quantity of UV-B radiation reaching the deeper epidermal layers, rich in 7-dehydrocholesterol.[183] Hence it is very difficult to provide a single, simple message regarding the optimal sun exposure for vitamin D production that is appropriate for everyone in a particular location.

The vitamin D status of populations in different countries has been assessed and generally shows that many people of all ages are below what is considered sufficient. For example, the US National Health and Nutritional Examination Survey, 2000–2004, found the prevalence of vitamin D insufficiency (serum 25(OH)D <50 nmol L^{-1}) was 26% in men and 33% in women, and the overall deficiency (<27.5 nmol L^{-1}) was 5%.[184] A survey in 2005 of people aged 65 and above living in England demonstrated that 57% of women and 49% of men were vitamin D-insufficient (<50 nmol L^{-1}) with 13% of women and 8% of men being deficient (<25 nmol L^{-1}).[185] Data from a national survey of the US population indicated that the average concentration of 25(OH)D in the serum decreased by 20% over the past few decades.[186] It might be predicted that there would be a latitudinal gradient in vitamin D status at the overall population level, *i.e.*, a decrease with increasing distance from the Equator. Perhaps surprisingly, this was not found in a recent meta-regression analysis of world populations, although a small but statistically significant gradient was shown if the analysis was limited to those with fair skin (–0.7 ± 0.3 nmol L^{-1} 25(OH)D per higher degree latitude north or south).[187] Moreover, vitamin D levels in post-menopausal women in Europe showed the opposite gradient: low levels in the south and high levels in the north.[188] In a different multi-centre global study of post-menopausal women, 25(OH)D levels were assessed in a single laboratory, thus eliminating the considerable variability in measurements between centres.[189] A small, although statistically significant, overall negative gradient was found for 25(OH)D concentration and latitude between 15° and 65°; the gradient was three-fold steeper for readings in the winter than in the summer (about –0.6 *vs.* –0.2 nmol L^{-1} per degree). Factors such as diet, food fortification, taking sunshine holidays in the winter months and outdoor activities may account, at least in part, for the dampening in the anticipated negative gradient in vitamin D status with increasing latitude. Thus the latitude of residence is not strongly correlated with vitamin D status and latitude may not be an appropriate proxy for vitamin D levels in ecological studies. Rather the actual levels in individuals within study groups should be determined, if at all possible.

Vitamin D has been recognised for almost a hundred years as preventing rickets in children, osteomalacia (the rickets equivalent) in adults, osteoporosis and bone fractures. More recently the role of UV radiation and vitamin D in regulating immune responses has been revealed and evidence gathered to indicate that it might protect human subjects against a wide and increasing range of common diseases. These aspects are considered below.

Immune and other effects of vitamin D

The active form of vitamin D ($1,25(OH)_2D$) acts mainly through binding to, and activation of, the vitamin D receptor (VDR), which is present in many cells including those of the immune system. There are about 200 VDR variants (such as *FokI*, *TaqI*, *BsmI*, *ApaI*) which can affect susceptibility to infectious diseases and to skin tumours. The VDR-$1,25(OH)_2D$ complex alters the function and expression of more than 200 genes. $1,25(OH)_2D$ can inhibit the maturation of dendritic cells and hence reduce the presentation of antigens to the lymphocytes and can also act directly on T cells to inhibit their proliferation and to suppress the production of immunostimulatory cytokines. Recently, $1,25(OH)_2D$ was shown to directly induce the development of T regulatory cells which have the potential to suppress proinflammatory cytokines and to prevent the activation of autoreactive T cells.[190] Such activity is likely to be of importance in protection against autoimmunity (reviewed in ref. 191). In contrast, in vitamin D insufficiency, there is deregulation of the normal cytokine responses, leading to the overexpression of the immunostimulatory cytokines. Other non-immune targets for vitamin D may also play crucial roles in the prevention of autoimmunity.

$1,25(OH)_2D$ is also important in innate immunity by inducing a range of antimicrobial peptides.[191,192] Thus it has the potential to provide protection against a range of infectious diseases. Finally, as malignant cells express the VDR, $1,25(OH)_2D$ may protect against cancer by up-regulating the adherence of and signalling between cells, inhibiting proliferation, enhancing differentiation, stabilising the cell cycle, promoting apoptosis, and inhibiting neoangiogenesis (reviewed in ref. 193).

Cancer

In our 2007 assessment[1] we reviewed the evidence available at that time indicating that increasing exposure to the sun reduced the risk of several internal cancers. Vitamin D was suggested as the protective factor. A recent review summarises the ecological studies associating solar UV-B radiation, vitamin D, and cancer.[194] In many of these, latitude or ambient solar UV radiation was used as a proxy for exposure to UV radiation and hence of vitamin D status. As outlined above, vitamin D status cannot be assumed to decrease as the distance from the equator increases but is affected by many factors including skin colour, diet, outdoor activities, obesity, clothing habits and number of sunshine holidays, and VDR polymorphisms can also alter the risk of disease. While the ecological approach on its own has little power to prove the involvement of any potential causal factor, it has led to considerable and increasing interest in trying to evaluate the importance of solar UV radiation and of vitamin D in protection against internal cancers. In 2008 the International Agency for Research on Cancer (IARC), after a careful formal evaluation, concluded that there was some evidence for a link between sun exposure and a reduced risk of colorectal cancer and adenoma (polyps), limited evidence for such an association in breast cancer, and none in prostate cancer.[195] Other investigators disagree with the cautious approach of the IARC.[196] New information which will help to resolve this issue is becoming available. For example, in 2010, a remarkable set of pooled cohort studies conducted in Europe, the USA and Asia was published which revealed no inverse correlation between serum 25(OH)D levels and the later incidences of five types of "rarer" cancers (upper gastrointestinal, ovary, endometrial, kidney and non-Hodgkin lymphoma), but an increased risk of pancreatic cancer in the group with the highest 25(OH)D levels (reviewed in ref. 197). One difficulty in this area lies in distinguishing whether a low vitamin D status causes an increased risk of cancer, or whether the low vitamin D status is a consequence of poor general health. In addition it is possible, although not likely, that the assessment of cancer risk based on vitamin D status in adulthood may not reflect the cumulative effects of vitamin D through a whole lifetime. To illustrate recent advances in this area, a short overview of observational studies relating vitamin D to colorectal, breast and prostate cancer is given below.

Colorectal cancer. A recent meta-analysis of 7 epidemiological studies showed that the highest quintile (compared to the lowest) of circulating 25(OH)D concentration was associated with a 30% decrease in the risk of colorectal adenoma.[198] Adenomas are benign tumours developing from epithelial tissue and have cancerous potential. The IARC meta-analysis concluded that there was evidence that lower 25(OH)D levels were associated with an increased risk of colorectal cancer.[195] For example, in a pooled analysis of 5 studies, subjects with 25(OH)D levels greater than 95 nmol L^{-1} had a 55% lower risk of colorectal cancer compared with subjects with levels less than 40 nmol L^{-1}.[199] The inverse association of pre-diagnostic 25(OH)D levels and colorectal cancer has been demonstrated across a broad range of ethnicities – Japanese, Latino, African-American, White, and Native Hawaiian ancestry[200] – and in a study of over half a million participants in 10 western European countries.[201] The influence of vitamin D status on survival in patients with colorectal cancer was established retrospectively: a higher pre-diagnosis 25(OH)D level was associated with a significant improvement in overall survival and in colorectal cancer-specific mortality.[202] Also, Freedman and colleagues[203] showed that the risk of dying from colorectal cancer in individuals with serum 25(OH)D levels higher than 80 nmol L^{-1} was approximately one-quarter compared with those having levels less than 50 nmol L^{-1}. Thus there is good evidence to date that low 25(OH)D levels are associated with an increased incidence of colorectal cancer incidence and risk of death. One drawback of these studies is that vitamin D status is usually based on a single 25(OH)D level, although in cohort studies this is at least usually from blood taken prior to the diagnosis of adenoma or colorectal cancer. It is possible that lifetime exposure to UV radiation (and the resulting vitamin D status) is a better measure, but is often not available. It is not yet clear whether supplementation with vitamin D or increased exposure to solar UV-B radiation can modulate the risk in humans significantly, although experiments in mice with diets deficient in, and supplemented with, vitamin D indicate that this is the case.[204]

Breast cancer. The IARC review concluded that there was limited evidence for an association between vitamin D insufficiency and the risk of breast cancer.[195] In the USA[205] and other countries,[206] the incidence of breast cancer increases with distance from the equator and decreasing regional solar UV-B radiation, even after adjustment for possible confounding factors such as obesity and smoking. Data from two observational studies suggest that women with pre-diagnostic 25(OH)D levels of about 130 nmol L^{-1} have a 50% lower risk of breast cancer than those with levels less than 32 nmol L^{-1}.[207] However, in a recent nested case-control study in Sweden, there was only a weak, non-statistically significant decrease in the risk of breast cancer associated with higher pre-diagnostic 25(OH)D levels.[208] Furthermore, a recent meta-analysis of observational epidemiological studies, investigating the association between serum 25(OH)D levels (generally a single sample, taken before diagnosis) and risk of breast cancer incidence or mortality, showed no significant correlation.[209] A large clinical trial in post-menopausal women, randomised to receive either vitamin D (400 IU daily) and calcium daily or placebo and followed for an average of 7 years, revealed no difference in the incidence of breast cancer between the two groups.[210] It is possible that the vitamin D dose may have been insufficient to achieve protective levels, or some undetected premalignant breast lesions may have been present at the start of the study, or a longer follow-up period may have been required. Higher ambient levels of sunlight or outdoor occupations have also been inversely linked to mortality from breast cancer.[211] Further work is required to understand whether exposure to solar UV-B radiation (and vitamin D) is beneficial in reducing the risk of developing, and death from, breast cancer.

Prostate cancer. Initial studies indicated an inverse association between the risk of prostate cancer and sunlight exposure[212–214] or the level of 25(OH)D,[215–218] but subsequent reports have not substantiated these findings. Neither the IARC meta-analysis[195] nor a more recent meta-analysis of 10 longitudinal studies[219] found an association between 25(OH)D level and the risk of prostate cancer. Recent observational analyses also demonstrated either no statistically significant association[220,221] or even a possible

increased risk of aggressive disease with the highest 25(OH)D levels.[221] Any associations between particular polymorphisms in the VDR and the risk of prostate cancer remain inconclusive,[222] and there is no evidence that dietary or supplemental vitamin D offer significant protection (for example[223]).

Skin cancers. There is mounting evidence that vitamin D and its receptor are involved in protection against NMSC; for example, vitamin D can regulate the differentiation of normal skin cells and reduce the proliferation of murine BCC cell lines.[224] Also, topical vitamin D_3 applied daily reduced the number and size of BCCs in BCC-susceptible mice,[225] while mice lacking the gene that codes for the VDR were more susceptible to UV-induced skin tumours than the wild type mice.[226] However, a nested case-control study of subjects, where vitamin D status was assessed prior to the diagnosis of BCC (up to 11 years prediagnosis),[227] demonstrated that the risk of BCC increased linearly with increasing serum 25(OH)D level. Thus, in the context of BCC, vitamin D is not protective, although the carcinogenic effect of high UV radiation, particularly as experienced in acute intermittent doses, may overwhelm any positive effects of vitamin D production in the skin.

Autoimmune diseases

Ecological and observational studies suggest that lower solar UV radiation and/or vitamin D status may be important risk factors for several autoimmune diseases. Two examples, multiple sclerosis (MS) and type 1 diabetes mellitus (T1DM), are described below.

Multiple sclerosis. MS, the result of an immune-mediated destruction of myelin-producing cells in the central nervous system, is the most common disabling neurological disorder of young adults. Its incidence has increased over the past 20 years and this does not appear to be an artefact of better diagnosis. The underlying aetiology of MS is unknown, but one of the most striking characteristics is the strong positive latitudinal gradient in occurrence so that the further from the equator, the higher the prevalence.[228,229] While there is a clear genetic susceptibility, geographic and temporal patterns have led to the hypothesis that an important risk factor for MS may be low exposure to UV radiation, possibly working through inadequate synthesis of vitamin D.[230] This suggestion is supported by results using a variety of approaches, as summarised below, but it should be noted that a new study using a mouse model of MS (experimental autoimmune encephalomyelitis) has revealed that chronic exposure to UV radiation can suppress the clinical symptoms of the disease and that this occurs independent of vitamin D production.[231] Thus the ability of the UV radiation to suppress the immune response may be of critical importance in reducing susceptibility to MS, acting through the mechanisms outlined in Fig. 3, rather than through vitamin D.

Although the latitudinal gradient in prevalence of MS may have weakened in recent years in the USA,[232] in other countries there is persistence of a gradient in incidence,[233] or prevalence.[234,235] Evidence from several studies suggests that low ambient UV radiation[234,236,237] or low exposure to the sun prenatally or in childhood[238] may represent a particularly significant risk for MS.

Observational studies have largely supported the suggested link between vitamin D and protection from the onset or progression of MS. In two cohort studies in the USA, higher vitamin D intake or serum 25(OH)D levels were associated with a decreased risk of developing MS; higher 25(OH)D levels when aged less than 20 years were especially important.[239,240] In Tasmania the relapse rates for MS were inversely correlated with ambient erythemal UV radiation and serum 25(OH)D levels.[241] Variants in genes of the vitamin D pathway[242,243] have been shown to be important in risk of MS, although there are conflicting findings in relation to variants in the VDR,[244–246] possibly because the role of environmental risk factors was not taken into account.[247]

Type 1 diabetes mellitus. T1DM is a T-cell mediated autoimmune disease with environmental and genetic risk factors. As is the case for MS, the incidence of T1DM has increased worldwide over the last two decades[248,249] and the age of onset has decreased in some regions.[250–253] The incidence or prevalence of T1DM increases with distance from the equator, or is inversely correlated with ambient UV radiation in several countries,[254–256] although the magnitude of the effect is generally less than that for MS. For example, in the Diabetes Mondial Project Group (DiaMOND) Study, the incidence of T1DM varied from less than 5 per 100 000 at the equator to 37 per 100 000 in Finland, at 60°N.[256] In a recent Australian study, there was a strong inverse correlation between the incidence of T1DM (ages 0–14 years) and ambient erythemal UV radiation, but this relationship reversed in high population density (urban) areas,[257] possibly related to greater sun avoidance with increasing ambient UV radiation in urban areas, compared with rural areas.

Many studies (but not all) note a seasonal variation in the birth of people who later develop T1DM, with summer and autumn births being more common.[258–260] One hypothesis to explain this finding is that low vitamin D levels in the mother during the winter preceding birth modulate the developing immune system in the foetus so that the risk of later development of autoimmunity is increased.[251,261–263] Individual-level studies have shown that higher intake of vitamin D (usually as supplements) by the mother or infant may be protective against the later development of islet cell antibodies[264,265] or T1DM.[266–268] In addition, several reports have revealed that T1DM is more commonly diagnosed in the winter than in the other seasons.[251,261,263,269–271] Late winter is the time when vitamin D levels are generally at their lowest. This finding is consistent with the loss of a proposed protective effect of a higher dose of UV radiation or higher vitamin D status. In a recent study of US military personnel, the incidence of T1DM was more than twice as high in African Americans compared with non-African Americans,[269] a finding possibly explained by deeply pigmented individuals being more likely to be vitamin D-insufficient.[272] Dietary and genetic factors may also be involved.

There have been conflicting findings regarding a relationship between VDR polymorphisms and T1DM risk, but a recent meta-regression analysis of 16 studies from 19 regions found that two VDR variants were associated with an increase in T1DM risk with increasing ambient winter UV radiation (long-term average midwinter-month noontime erythemal UV irradiance for the years 1997–2004, based on satellite data), while another VDR variant was associated with a decrease in T1DM risk with increasing ambient winter UV radiation.[247] These results suggest that ambient UV radiation may modulate the association between the VDR

genotype and T1DM risk, and further implicate a role for vitamin D in T1DM.

Infectious diseases

Many infectious diseases, especially those caused by viruses affecting the respiratory system, have a seasonal incidence with a peak in the winter months. Although this pattern could be explained by the smaller likelihood of viral inactivation during transmission in the winter compared with the summer, it has also been attributed to reducing levels of vitamin D as the dose of ambient solar UV-B radiation decreases. Lower vitamin D status could diminish innate immunity, particularly the expression of antimicrobial peptides in the airways, thus increasing susceptibility to infection. Definitive evidence to support such a suggestion is lacking currently, although preliminary observations are consistent with vitamin D being protective.[273,274] In a clinical trial, supplementation with vitamin D correlated with decreased incidence of symptoms of the common cold and influenza in African-American postmenopausal women, although this endpoint was not one of the original aims of the study and was not rigorously assessed.[275] More convincingly, in a recent small randomised, double-blind, placebo-controlled trial in children in Japan, the treatment group received a vitamin D_3 supplement (1200 IU daily) and the incidence of laboratory-confirmed influenza A infections was the primary outcome: the incidence of influenza A (but not influenza B) was reduced in the supplemented group compared with the placebo group and, in addition, there was significant protection against asthma attacks.[276] In observational studies, low concentrations of 25(OH)D in the serum were associated with an increased risk of acute respiratory infection in Indian children under 5 years old,[277] in young Finnish men serving in the military,[278] and in newborns in Istanbul.[279] In addition, in a study of almost 19 000 participants in the American Third National Health and Nutrition Examination Survey, those subjects with serum 25(OH)D levels of less than 25 nmol L^{-1} had a 55% higher odds of a self-reported recent upper respiratory tract infection than those with levels greater than 75 nmol L^{-1}[280] It has also been suggested that vitamin D insufficiency may increase the risk of exacerbations of asthma through an association with poorer lung function and an increased chance of contracting viral respiratory infections.[281,282] However, whether increasing vitamin D levels by sunlight exposure helps to prevent asthma or to reduce the chance of an exacerbation has not yet been tested, as far as we are aware.

Tuberculosis is caused by infection with *Mycobacterium tuberculosis*. As early as the 19th century, it was recognised that open air sunbaths were beneficial in the treatment of patients with tuberculosis. By the 1920s, heliotherapy was a widely accepted treatment for tuberculosis, although it was not advised by most specialists for acute tuberculosis of all types, including pulmonary, as it could cause death. As a result of this therapeutic approach, susceptibility to tuberculosis or disease progression and vitamin D deficiency have been linked, (reviewed in ref. 283), possibly through impaired immunity to *M. tuberculosis* as a result of vitamin D deficiency.[284] Although early work suggested that treatment of tuberculosis patients with oral vitamin D improved the recovery rate and enhanced the acquired immune response against the bacilli, recent clinical trials of vitamin D supplementation,[285] or UV-B irradiation[286] did not lead to any improvement in clinical outcome or mortality[285] or the immune response to the mycobacteria.[286]

Further clinical trials are urgently required to assess whether exposure to solar UV-B radiation and sufficient vitamin D status can prevent *M. tuberculosis* infection or reactivation from the latent state, and also reduce the risk of developing other respiratory infections.[283,287,288] VDR polymorphisms need to be taken into account as some are known to confer enhanced susceptibility to particular infections.[192]

Cardiovascular diseases

The prevalence of coronary heart disease and hypertension increases with increasing distance from the equator.[289] In one study, irradiating hypertensive patients with UV-B radiation reduced their blood pressure into the normal range, while UV-A radiation had no effect.[290] These findings are suggestive of a possible protective effect of UV-B radiation acting through enhanced synthesis of vitamin D. Vitamin D has been shown to regulate blood pressure through the renin-angiotensin system, and to decrease the proliferation of myocardial and vascular smooth muscle cells. A meta-analysis of 18 randomised controlled trials involving more than 57 000 participants demonstrated that a daily intake of vitamin D_3, averaging 520 IU, improved all-cause mortality, partly by decreasing deaths due to cardiovascular disease.[291] Later studies have also shown that lower levels of 25(OH)D and 1,25$(OH)_2$D were independently associated with higher all-cause and cardiovascular mortality,[292] including in older adults (aged 65 and above),[293,294] and a higher risk of myocardial infarction.[295] More trials involving solar exposure or vitamin D supplementation are required to confirm a role for vitamin D in reducing the risk of these cardiovascular outcomes.

Personal protection

Effective personal protection can mitigate the adverse health effects from increases in ambient UV radiation, resulting from thinning of the stratospheric ozone layer and/or from climate change and UV-exposure related factors in some regions, *e.g.*, where cloud cover is projected to decrease. Health campaigns in several countries such as the USA, Australia, New Zealand, Canada and the UK (for example: www.cdc.gov/cancer/skin/basic_info/prevention.htm; www.sunsmart.com.au; www.cancernz.org.nz/reducing-your-cancer-risk/sunsmart/; www.msc-smc.ec.gc.ca/education/uvindex/index_e) have tried to increase the public's awareness regarding the inherent dangers of overexposure to the sun. Such messages contain the information that sun exposure increases the risk of skin cancer and that precautions can be taken to reduce this risk. However, understanding in general remains low, one reason being that a single, simple message is not appropriate for all due to variations in place, season and skin phototype.[296,297] One potentially useful parameter is the UV Index (discussed in ref. 10 and 298) which is published daily in many countries. Greater efforts are required to make this a useful tool in the management of sun exposure as it is not generally understood by individuals.[299]

Current advice centres on avoiding sunburn by seeking shade when the sun is most intense, wearing clothing that protects against

the penetration of UV radiation, the use of topical sunscreens, and protecting the eyes. Each of these will be discussed briefly in turn.

Shade

The most effective way to reduce exposure to the sun is avoidance, particularly in the middle of the day. Staying indoors is best as most of the sky is blocked and glass transmits less than 10% of solar UV radiation. In one study, dense foliage offered the best outdoor protection and a beach umbrella the least.[300] The species of tree makes a difference, and the shade varies according to the season and sun angles, with highest protection usually in the summer months.[301] Careful consideration must be given to the construction of proper shade, especially the material used and the design of the shading structure to minimise diffuse and scattered UV-B radiation. Adolescents in particular are known to be reluctant to use many protective measures, such as wearing hats, and are frequently sunburnt in countries with high levels of solar irradiation. One successful strategy to reduce exposure to solar UV radiation during school hours, especially at lunch-time, is to erect special sails that provide shade in school playgrounds and which reduce levels of ambient UV-B radiation by at least 94%.[302]

Clothing

Textiles can be a reliable method of personal photoprotection for covered areas of the body, although by no means all are effective. At present there is no uniform standard for labelling such clothing as some tests are performed *in vivo* in a similar fashion to sunscreens, while others are assessed by *in vitro* transmittance giving a UV protection factor (UPF) (reviewed in ref. 303). Many variables affect the transmission of UV radiation through textiles, such as the porosity, colour, weight and thickness of the fabric. No information is given currently to indicate how the material responds to stretching, wetness, washing, humidity and ambient temperature.

Despite these limitations, there is increasing use of clothing and hats for the sun protection of children (see Fig. 6) and such a method may also be useful for the protection of outdoor workers and others during recreational activities, particularly outdoor sports.[304] The main aim here is to lessen the risk of sunburn and the development of moles in children.[305] In Australia an occupational standard for exposure to UV radiation has been introduced[303] which states that outdoor workers should be provided with appropriate clothing (rated UPF50+) plus other items for their protection from solar UV radiation. Further developments in the manufacture of UV-protective textiles are expected.

Sunscreens

Sunscreens can be inorganic – reflecting, scattering and absorbing UV radiation, such as zinc oxide and titanium dioxide – or organic – absorbing UV radiation, such as cinnamate and salicylate (reviewed in ref. 306). They give different levels of protection against sunburn ranging from sun protection factors (SPFs) of 6 to more than 50. Sunscreens of SPF 30 are recommended for use in some official health guidelines.[307] They were designed originally to protect against sunburn but also protect against other acute effects of solar UV radiation such as sunburn cell formation in the skin,

Fig. 6 Children wearing sun-protective hats and clothing (photograph supplied by Dr A. Lesiak, Medical University of Lodz, Poland).

cutaneous DNA damage, immunosuppression and reactivation of latent HSV. With regard to the more chronic effects of solar UV radiation, the regular use of sunscreens reduces the incidence of actinic keratoses[308] and SCCs, with a tendency (although not statistically significant) towards decreasing the incidence of BCCs.[309] The beneficial effect of sunscreens in preventing SCCs was revealed to be long-lasting, up to at least 8 years after the end of a trial in which they had been applied daily to the head, neck, hands and forearms.[310] Furthermore, sunscreen use attenuates the development of new moles in children on body sites that are intermittently sun-exposed.[311] Such protection may reduce their risk of CMM later in life, although the efficacy of sunscreens in preventing melanoma remains controversial.[312–315] Although research in yeasts has indicated that UV-B irradiated titanium dioxide may be mutagenic,[316] other work shows no skin absorption of such sunscreen components and no evidence of toxicity in humans exposed *via* this route.[317]

One concern expressed about the widespread and increasing use of sunscreens is that a vitamin D-insufficient or deficient state could result, with reduced protection against a range of diseases. Although such an outcome has been demonstrated under very strictly controlled conditions, in real life it is unlikely to occur for a variety of reasons (reviewed in ref. 318). First, a fraction of the incident UV photons is transmitted through the sunscreen; for example for a product with SPF 30, 3.3% of the erythemal UV irradiation will be transmitted. Secondly, and probably most importantly, sunscreens are rarely applied at the concentration that is used to give the tested level of protection, 2 mg cm^{-2}.

Most commonly, subjects use only about 0.5 mg cm^{-2}. Apart from ignorance about the correct level to use, 2 mg cm^{-2} feels excessive, is often visually unattractive and is costly. The relationship between the quantity of sunscreen applied and the SPF is uncertain as one study finds a linear relationship[319] while another finds a non-linear relationship with, for example, a sunscreen of SPF16 being reduced to SPF2 when used at 0.5 mg cm^{-2}.[320] Because almost all sunscreens are under-applied, calls have been made for the labelling to be changed.[321–324] Thirdly, the coverage of the sunscreen is inevitably uneven and the frequency of re-application is often inadequate. Fourthly, sunscreens are rarely applied to all areas of the exposed body surface. Finally, it has been demonstrated in several recent surveys that sunscreen users often expose themselves to more sun than non-sunscreen users and therefore are less likely to develop vitamin D insufficiency.[155,325,326]

A "sensible" approach is advocated for the use of sunscreens. The SunSmart programme in the United Kingdom stresses the need to avoid sunburn and emphasises the fact that the amount of sun exposure required to ensure production of sufficient vitamin D is less than the amount that causes sunburn.[327] In Europe, Diffey recommends that sunscreens with high SPF values are not applied all day every day but are reserved for times of exposure to intense solar UV radiation, during a sunshine holiday and during recreational activities in the middle of a summer day.[328] This contrasts with the position statement issued in 2007 in Australia and New Zealand that considered the risks and benefits of sun exposure.[329] In both countries, the local UV Index throughout the day is used as the Sunsmart UV Alert: use of sunscreen is recommended if the value is 3 or higher. Media reports in several countries have begun to highlight the suggested health benefits of vitamin D and have tended to emphasise the negative aspects of sun protection while promoting sun exposure (see, for example, ref. 330). Changing attitudes towards sun behaviour have been studied in Queensland: evidence of a recent reduction in sun protection practices in this high solar UV radiation environment was found which could lead to a significant increase in the incidence of skin cancer in future years.[297]

Other topical or oral agents that protect against UV-induced skin damage

In most individuals, it is likely that some DNA photodamage will occur due to solar UV radiation, even if various methods of photoprotection are used. Thus, alternatives are being sought which function beyond absorption or avoidance of UV radiation,[331] some of the most promising of which are described below.

Skin creams have been developed containing DNA repair enzymes (Advanced Night Repair Concentrate) with the aim of minimising skin cancer risk in susceptible individuals especially if they are unavoidably exposed to the sun.[332,333] When applied topically, they protect against the immunosuppression that follows solar UV radiation. In addition, RNA fragments (UV-C-irradiated rabbit globulin mRNAs which decrease sunburn cell formation and DNA damage), applied topically to human skin at the time of irradiation, minimise UV-induced immunosuppression.[333]

An approach creating considerable interest at present concentrates on substances that are applied topically or taken orally, and that could be used alongside the sunscreens to provide additional protection. Compounds that activate the tanning pathway, such as melanocyte-stimulating hormone, reduce inflammation and promote DNA repair when applied topically.[334] Both oral[335] and topical[336,337] nicotinamide (vitamin B3) protect against UV-induced immunosuppression of the tuberculosis skin test (Mantoux reaction), and a topical mixture of vitamin C, ferulic acid and α-tocopherol also provides substantial photoprotection.[338] Over a three year study period, subjects taking angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers by the oral route had a lower incidence of skin cancer than non-users.[339] Supplementation of the diet with the probiotic bacterium *Lactobacillus johnonii* for several weeks prior to exposure to solar UV radiation accelerated the recovery of immune function in the irradiated skin.[340] Green tea polyphenols have long been known to protect against many of the damaging effects of UV radiation in human skin, acting by a variety of cellular, molecular, and biochemical mechanisms (reviewed in ref. 341). Most recently a green tea extract applied topically to the skin of subjects before UV radiation reduced the epithelial damage,[342] and, in another study, both green and white tea extracts also applied topically to human skin after UV radiation protected against several of the effects of UV radiation on cutaneous immunity.[343]

Cost-effectiveness of sun protection education and sunscreens

The SunWise programme which runs in schools in the USA teaches children how to protect themselves from overexposure to the sun. It has been evaluated to determine its cost-effectiveness.[344] Assuming that the programme continues until 2015 at the current funding levels, it is estimated to avert more than 50 premature deaths, 11 000 skin cancer cases and loss of 960 quality-adjusted life-years amongst the subjects taking part. In addition to the morbidity and mortality benefits, for every dollar invested in SunWise, between 2–4 dollars in medical care costs and productivity losses would be saved. Thus SunWise is considered a successful and worthwhile investment. A similar exercise has been undertaken in Australia where the equivalent programme, SunSmart, was started in the early 1980s.[345] Only the incidence of melanoma was included in the calculation as there is lack of coverage of BCC and SCC incidences in cancer registries. On a national scale, the programme is estimated to avert the loss of 120 000 disability-adjusted life-years over the next 20 years, with associated reductions in health care costs. Every dollar invested in SunSmart will return AU$2.30 in terms of health costs, although further returns are likely if societal perspectives are included. Therefore SunSmart is considered excellent value for money.

There is interest also in determining the cost-effectiveness of public education campaigns promoting the use of sunscreens for the prevention of actinic keratoses and NMSC. Gordon *et al.*[346] have published the first such study in which the cost effectiveness of advising a cohort of Australians living in sub-tropical Queensland to apply sunscreen daily *versus ad hoc* use over a 5 year period was calculated. The cost of the programme was US$0.74 per person and the saving to the government was US$109 per person, providing much better value for the expenditure. It was concluded that community-based interventions that promote regular sunscreen use in fair-skinned subjects living in sub-tropical or tropical environments are cost-effective in protecting against skin cancer. Such analyses for other public health advice regarding personal protection from the detrimental effects of solar UV

radiation would be beneficial. Any savings in the costs for human health from protecting the ozone layer are unknown at the present time.

Eye protection

The eye is naturally protected from overhead solar irradiation by its location within the bony orbit of the skull and by the brow, lids and eyelashes. Hence, the structures of the eye are only infrequently exposed to direct solar UV radiation, although exposure *via* scattering can be considerable. In Norval *et al.*,[1] the interaction of solar UV-B radiation with target tissues in the eye was discussed and the importance of peripheral light focusing when considering ocular protection.

Sunglasses are the most practical and effective method of protecting the eye. The International Organization for Standardization continuously modifies its standards for sunglasses and related eyewear (ISO 12312-2, 2009). Although most sunglasses manufactured currently provide protection from axially incident ambient UV radiation, they may permit UV irradiation from above, from ground reflections and laterally if they are poorly fitting. One study in India found that all branded and most unbranded sunglasses provided good protection against penetration of UV-A radiation but satisfactory protection against UV-B radiation was not provided by all sunglasses, whether branded or unbranded.[347] In another study, excellent protection from UV radiation was achieved by some inexpensive sunglasses, that was superior in some cases to branded products.[348] In general, apart from absorption of UV radiation, the more expensive sunglasses have lenses of better quality but much of the increased cost is accounted for by the designer frames and logos. Ideally sunglasses should meet international standards, and be wrap-around in design or have side shields in the case of prescription lenses. Goggles are recommended at high altitudes and for snow sports.

It has been confirmed recently that UV-blocking contact lenses are capable of protecting the cornea, aqueous humour, and crystalline lens from UV-induced pathologic changes.[349] The conjunctiva and lids are not protected by such lenses and they should not be considered as substitutes for sunglasses. The UV radiation absorber is incorporated into the polymer of the contact lens and the absorption properties vary with thickness across the lens.[350] For example a minus (negative) contact lens to correct myopia is thicker at the edge than the centre and would provide more protection to the periphery of the cornea and from peripheral rays than the centre of the lens.

Risks associated with the use of substitutes for ozone-depleting substances

As a part of the Montreal Protocol, signatories are committed to the development and use of acceptable alternatives or replacements for ozone-depleting substances (ODSs). The introduction of new chemicals, or old chemicals for new uses, may result in increases in human exposures to these chemicals; thus the substitutes need to be evaluated not only for their ability to replace ODSs *per se* but also for their ability to do so within a framework of acceptable risk. From a regulatory standpoint, at least within the USA, such evaluation is being undertaken by the Significant New Alternative Policy (SNAP) programme of the Environmental Protection Agency, details of which are provided in an online appendix to this paper (ESI†). However, much of the information to which the SNAP programme has access is not publicly available. As a consequence, while the SNAP programme is discussed in detail in the appendix, the focus of this section is the information in published research papers.

While there are probably several hundred chemicals and chemical mixtures being used as replacements for ODSs in various applications, there is little recent information on their toxicity. However, a number of reviews have summarized the limited older data available on the toxicity of a number of the classes of the chemicals that serve as ODS substitutes and their degradation products.[351–356] Of the substitutes discussed, probably the most toxic is sulfuryl fluoride, a fumigant proposed to replace methyl bromide. Fatalities have been reported from acute occupational exposures and the occupational exposure limit has been set very low (5 ppmv).[354] For the hydrofluoroethers (HFEs), carcinogenicity, mutagenicity, reproductive toxicity or systemic chronic toxicity are thought unlikely. Overexposure under occupational conditions is possible, although the levels needed for severe effects, *e.g.* cardiac sensitization are extremely high (>100 000 ppmv).[351] There are little or no specific data for the hydrofluoropolyethers (HFPEs), but by analogy, the expectation is that the HFPEs will not pose any risks to humans from carcinogenicity, mutagenicity or reproductive toxicity. The information on perfluoro-n-alkanes is similar to that of the HFPEs, that is, they have low toxicity, low flammability, and low corrosiveness. Degradation products from these classes of chemicals include a variety of toxic compounds such as carbonyl fluoride, hydrogen fluoride, hydrogen chloride, formaldehyde, formic acid, and acetic acid but there are little if any data on the atmospheric concentrations of these compounds.[351–353] The findings for hydrofluorocarbons (HFCs) with regard to reproductive toxicity indicate little reason for concern. Exposure to degradation products, such as carbonyl fluoride and, by analogy, sodium fluoride, have shown some developmental effects in animals. There are insufficient data on the reproductive effects of other degradation products, including trifluoroacetic acid and formic acid, to draw any conclusions about safety.[355,356]

Possible health effects of the interactions between climate change and ozone depletion

The World Health Organisation has stated that human health should be at the centre of concerns about climate change and is working to ensure that the issue of health has prominence at various international conferences, including the United Nations Framework Convention on Climate Change in Copenhagen, 2009. At a meeting of the Commonwealth Health Ministers in May 2009, the view was expressed that local adverse health effects due to climate change were actually occurring already, and require urgent public health management.[357] When considering possible interactions between stratospheric ozone depletion and climate change, it is not possible at present to come to any firm general conclusions regarding their impact on human health as so little research has been published in this area, perhaps due to the lack of interdisciplinary approaches.

Many assessments predict the effect of climate change on increasing the incidence of allergic diseases and several infectious

diseases, such as malaria, Lyme disease (a bacterial infection spread by ticks) and leishmaniasis (a protozoal infection spread by sand-fly bites) in different parts of the world, but do not include changes in solar UV-B radiation.[358–360] Climate factors suggested to affect infectious and other human diseases include increased water temperature leading to increased survival of waterborne agents, increased rainfall leading to increased breeding sites for insect vectors, increased humidity leading to enhanced microbial survival in the environment, decreased seasonal exposure to solar UV-B radiation leading to lower vitamin D levels with diminished protective effects, increased atmospheric pollutants leading to less efficient mucociliary action, and changing rainfall patterns and ocean temperatures that result from long-term natural variabilities such as the El Niño Southern Oscillation events.[361] One obvious uncertainty for solar UV radiation is whether people will spend more or less time outdoors in sunlight in the future as temperatures rise but as humidity, storms, floods and drought also increase.

The following summarises the present sparse knowledge regarding interactions between climate change and ozone depletion with respect to human health.

Skin cancer

On the basis of previous results obtained from photocarcinogenic experiments in mice housed at different temperatures, van der Leun and de Gruijl[362] suggested several years ago that rising temperatures due to global warming might enhance the induction of skin cancer by solar UV radiation. This has been tested by correlating the incidence of skin cancer in fair-skinned people in 10 regions of the USA with measured annual UV irradiance and temperature (average daily maximum temperature in the summer months) in each of the regions. The analysis showed a predominant influence of the UV radiation but also a statistically significant influence of temperature.[363] For the same UV irradiance, each one degree Celsius increase in temperature resulted in an estimated 3% increase in the incidence of BCC, and 6% of SCC. This consequence may therefore represent a significant hazard in terms of global health. Furthermore, high temperatures and humidity, as experienced in the tropics and as predicted for some areas for the future, may increase the deleterious effects of UV-B radiation on human health, including suppression of immunity to infectious diseases and skin cancers.[364]

Infectious diseases

One study of illness in children aged less than six years, presenting as emergency cases in Sydney, found that the maximum daily temperature was a risk factor for both fever and gastroenteritis, while increasing UV Index was inversely correlated with gastroenteritis incidence; air quality was not a significant risk factor.[365]

A group in Philadelphia has assessed the seasonality of both invasive pneumonia, caused by *Streptococcus pneumoniae*, and invasive meningococcal disease and tested associations with acute (day-to-day) environmental factors. For pneumonia, the weekly incidence in Philadelphia County was greatest in the winter months. This pattern correlated with extended periods of lowest solar UV radiation and, to a much lesser extent, with temperature.[366] The limited solar UV radiation available at higher latitudes,[10] could aid the survival of the bacterium or could adversely affect innate immunity, possibly through the lack of vitamin D. As temperature is not a major factor in the seasonality of invasive pneumonia, global warming is unlikely to affect the incidence of the disease significantly, although increased cloud cover could reduce ambient UV radiation and hence lower the vitamin D status. For invasive meningitis, the number of cases in Philadelphia was highest in the late winter and early spring.[367] A one-unit increase in the UV Index 1–4 days prior to the onset of symptoms was associated with a 46% decrease in the odds of disease. The dose of solar UV-B radiation could affect transmission from a colonised subject or the infectivity of the bacteria.

Thus, although the evidence to date is sparse, ozone depletion leading to increased solar UV-B radiation, or decreases in UV radiation projected for the future,[10] in combination with other environmental factors, could impact significantly on the incidence of particular infectious diseases.

Dermatoses

Chronic actinic dermatitis (CAD) is an uncommon eczematous photosensitivity disease affecting mainly sun-exposed sites on the body. The provoking wavelengths are within the UV-B waveband in almost all patients.[368] As more cases have been diagnosed since 1991 in the Pusan region of South Korea than in previous years, the relationship between various climate factors and the incidence of CAD was investigated.[369] Recent changes in the climate of Pusan include increased air temperature all year round, expanding desertification with Asian dust and a year-by-year increase in sunshine duration. A close correlation was found between the number of cases of CAD and increased ambient sunshine. This emphasises the relationship between solar UV radiation and photosensitivity disorders and how climate change can affect their incidence.

Environmental effects

UV radiation in sunlight is a major factor in causing the death of microorganisms in the environment that are pathogenic for humans. It acts by direct effects on genomic DNA or by the generation of reactive oxygen species. UV radiation can inactivate human pathogens present in drinking water. For example, natural sunlight was tested recently for its ability to reduce the infectivity in drinking water of bacteria, viruses and protozoa that can cause disease in human subjects.[370] Other reports demonstrated that insolation rapidly inactivated the protozoan *Cryptosporidium parvum* in environmental waters, with UV-B radiation identified as the most effective waveband.[371,372] Interactions between temperature, pH and water transparency will affect the UV-induced reduction in infectivity of this microorganism.[372] Sagripanti *et al.*[373] examined the inactivation of the virulent bacterium *Burkholderia pseudomallei* by sunlight under different environmental conditions such as in rain water and in seawater, and showed that an increase in exposure to solar UV-B radiation led to increased microbiocidal activity. Sunlight exposure is an important mechanism for inactivating certain microorganisms in sewage in shallow sea water, provided the water is clear.[374] One study has revealed that inactivation of some bacterial species in fresh water occurred more rapidly in the summer than in the winter, and that inactivation by sunlight increased with increasing salinity of the water.[375] The efficiency

Table 1 Suggested gaps in current knowledge regarding solar UV-B radiation and human health

Subject	Key questions
The eye	• What are the wavelength dependencies for cataract development? • Does solar UV-B radiation play a role in age-related macular degeneration? • What role does solar UV-B radiation play in uveal melanoma?
The skin	• What is the UV wavelength dependency for melanoma induction? • What is the interaction between solar UV radiation and the human papillomaviruses that are involved in squamous cell carcinoma? • Does vaccination in the summer months or in a sun-exposed individual lead to a suppressed immune response against some vaccines? • What is the mechanism for the induction of T regulatory cells following UV radiation? • Does solar UV radiation induce innate defence mechanisms in human skin that can control bacterial and other infections? • Is there a balance between the positive and negative effects of UV-induced immunosuppression? • What is the optimal vitamin D status for all its health benefits, and how much solar UV-B radiation is required to attain it in people of different skin colour living at different latitudes at different times of the year? • Is exposure to UV-B radiation and/or vitamin D status linked directly with protection against certain internal cancers, autoimmune diseases and infectious diseases? • Can all the potential benefits of vitamin D adequacy be met from supplementation?
Protection measures	• What is the most effective health message to give the general public regarding "safe" sun exposure? • How can public understanding and use of the UV Index be improved? • Can components of our diet or substances applied topically provide protection for the eye and skin against the harmful effects of UV radiation? • Is additional photoprotection required after cataract surgery? • Should the SPF of sunscreens be modified to reflect the actual concentration commonly used by the public? • Is it important to measure and publicise the immune protection factor of sunscreens?
Effects from climate change/ozone depletion interactions	• Does an increase in temperature combined with increased solar UV-B radiation cause enhanced adverse effects in the eye and/or skin? • Will sun exposure behaviour alter with climate change conditions? • What effect does climate change have on lifestyle factors which influence personal sun exposure such as sunshine holidays, clothing, diet and tanning? • Does climate change alter the daily solar UV-B radiation reaching the Earth's surface? • Does climate change affect the efficacy of solar UV radiation to inactivate pathogenic microorganisms in water supplies? • Will populations migrate to environments that have more favourable climates (cooler, better water supplies, *etc.*), but increase/decrease the risks of harmful effects of solar UV-B radiation or vitamin D insufficiency?

of inactivation of microorganisms by exposure to sunlight in the environment is determined by a complex mixture of factors including the amount and type of photoproducts produced, the ability to repair the damage, the ambient temperature,[376] the pH and salinity of the water, and the solar spectrum. At least 60–94% of the killing of bacteria by solar exposure is suggested to be due to the UV-B component of sunlight.[377]

Further work is required to assess possible interactions between changes in climate, such as global warming, and solar UV-B radiation on the viability of pathogenic microorganisms in the environment.

Gaps in knowledge

Stratospheric ozone depletion leading to increased solar UV-B radiation has had adverse health effects on human populations, the most serious and widespread being skin cancer and cortical cataract. Such an increase in solar UV-B radiation can be beneficial in increasing vitamin D status and thus lowering the risk of developing a range of diseases. Although the ozone layer is projected to recover slowly in the coming decades, continuing vigilance is required regarding exposure to the sun: for ageing populations who are more susceptible to a number of serious diseases in which UV radiation plays a part but also for young people, as risk for at least some UV-related diseases may be largely determined by early-life exposures. Personal protection to prevent sunburn is recommended whilst ensuring enough sun exposure to provide sufficient vitamin D. When climate change is considered together with ozone depletion, any health effects, either advantageous or disadvantageous, are hard to assess currently as the impact of such a change on societies and behaviour is not clear. However, it may be more difficult to maintain adequate vitamin D status from exposure to the sun at mid to high latitudes. Many gaps in our knowledge remain, some of which are summarised in Table 1.

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