Links between exposure to ultraviolet radiation and skin cancer.

A REPORT OF THE ROYAL COLLEGE OF PHYSICIANS

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The general public and the media are showing an increasing interest in the hazards of exposing the skin to sunlight. This interest has in part been stimulated by reports of public awareness campaigns organised in Australia [1], in certain parts of the USA [2] and, most recently, in Scotland [3]. All these campaigns have given information on recognition of skin cancer at an early stage, and the first two have discouraged fair skinned individuals from excessive sun exposure in areas of high sunlight intensity. Excessive, in this context, means significant exposure to strong midday sun, and any sun exposure that results in prolonged redness of the skin, and discomfort, scaling or peeling.

This Report gives information currently available on the association between excessive exposure of the skin to ultraviolet radiation and skin damage, in particular skin cancer.

The spectrum of ultraviolet radiation

Ultraviolet (UV) radiation is divided according to wavelength in the UV spectrum. Thus, UV-A, or long wavelength UV, is the 315–400 nanometer (nm) range. UV-B is 280–315 nm and UV-C is 100–280 nm.

Sources of ultraviolet radiation

Natural sunlight is the commonest source of ultraviolet radiation in everyday life, with UV-B being the most active component affecting the skin in natural terrestrial sunlight. Artificial sources of ultraviolet radiation include UV-A and UV-B sources used diagnostically and therapeutically in dermatology departments, sunbeds, some lasers, and some fluorescent and other lighting sources. Fluorescent tubes emit UV of various wavelengths, the most commonly used ‘daylight’ fluorescent strip lighting emitting mainly UV-A, and minimal UV-B.

UV-A lamps, used in dermatology departments for psoralen photochemotherapy (PUVA), also emit a small percentage of UV-B as do UV-A tubes used in commercially available sunbeds. The old fashioned ‘health lamp’, now generally withdrawn from sale, emitted mainly UV-B radiation.

UV-C is emitted by germicidal lamps, and it is in extraterrestrial sunlight, but is completely screened out in the atmosphere. It is therefore a wavelength to which human skin is very rarely exposed and will not be considered further.

Although this Report deals with the relationship between ultraviolet radiation and skin problems, it should be remembered that ultraviolet radiation is also damaging to the eye and that patients who use ultraviolet sources for therapeutic or recreational purposes must be warned of this and instructed to wear appropriate protective glasses. Current evidence suggests that the most appropriate glasses for this purpose are the wrap-around style with Polaroid (trademark) polarising lenses [4].

Exposure to ultraviolet radiation and skin damage

Exposure to UV-B radiation causes acute and chronic effects on human skin. The acute effects of excessive exposure to natural sunlight are well recognised as sunburn, with erythema and sometimes swelling, blistering and subsequent peeling of the skin, commencing within hours of exposure, and taking several days to resolve. The severity of the reaction depends on both the individual’s skin type and on the intensity of radiation.

Dermatologists divide skin type with regard to reaction to sun exposure into six types [5]:

Type 1—Never tans, always burns.
Type 2—Tans with difficulty, burns frequently.
Type 3—Tans easily, burns rarely.
Type 4—Always tans, never burns.
Type 5—Genetically brown skin (Asian or Mongoloid).

Type 6—Genetically black skin (Negroid).

Skin types 1 and 2 usually burn easily, after 20–40 minutes exposure to midday summer sun in temperate areas.

The intensity of UV reaching the earth’s surface varies with altitude, latitude, time of day, time of year, cloud cover, and shade; so variations are very large. Cloud cover and moderate shade do not greatly attenuate UV, but UV scatter from blue sky and UV reflection from rippling water or snow may greatly increase radiation intensity.

The chronic effects of UV exposure are initially seen as dryness, wrinkles, laxity and patchy variation in skin pigmentation. These changes are traditionally associated with ageing, and have recently been studied in some detail. Comparison of habitually exposed facial skin and habitually covered buttock skin in an elderly person shows clearly that exposure to the elements is more important than age per se in causing these changes.

Skin cancer and exposure to ultraviolet radiation

There are three well-recognised types of skin cancer: basal cell cancer (Fig. 1), squamous cell cancer (Fig. 2) and malignant melanoma (Figs. 3–6). The hairless (but not athymic) mouse is used as an animal model for ultraviolet-induced carcinogenesis studies in many laboratories. It is well established that exposure of these animals to UV-B may cause both benign skin papillomas and squamous cell carcinomas.

There is considerable evidence to suggest that the aetiology of both basal and squamous cell carcinomas in man is associated with long-term cumulative exposure to natural sunlight, as in the occupational exposure of farmers, fishermen and other outdoor workers [6]. This correlates well with the commonest sites of these lesions on the face (Fig. 1), the backs of the hands (Fig. 2) and the forearms. The higher incidence of these two types of tumours in fair skinned Caucasians in areas with high natural sunlight intensity, such as Australia, is strong supporting evidence [7].

Malignant melanoma of the skin is less common than basal cell carcinoma but is the cutaneous malignancy which accounts for the great majority of deaths from skin cancer. Four clinical types of malignant melanoma are currently recognised [8]. These are lentigo maligna melanoma, superficial spreading malignant melanoma, nodular malignant melanoma, and acral melanoma.

Lentigo maligna melanoma has many clinical features which suggest that its aetiology may be similar to that of basal and squamous cell carcinoma. It affects older individuals who may have spent many years outdoors and almost always involves exposed sites such as the face and back of hands [9]. These facts would suggest that cumulative long-term sun exposure is important in this type of melanoma.

The clinical appearance of lentigo maligna melanoma is initially that of a slowly expanding flat brown stain on the face, usually the cheek. This lesion may grow very slowly for a number of years, but in time will develop a raised nodular central area (Fig. 3) which indicates that the lesion is now an invasive lentigo maligna melanoma. In the flat or radial growth phase, the lesion may be called a pre-invasive lentigo maligna.

Superficial spreading, nodular, and acral malignant melanomas affect individuals two or three decades younger than those suffering from lentigo maligna melanoma and other types of skin cancer. Superficial spreading melanoma accounts for approximately 50 per cent of all cutaneous melanomas in the UK [10], and the commonest sites affected are the female lower leg and the male back. Superficial spreading melanomas are recognised as black or brown lesions with an irregular or geographical lateral margin (Fig. 4). They are usually over 1 cm in diameter by the time they are diagnosed, and may have striking variation of pigmentation within the lesion, with shades of black and brown admixed with red, and sometimes also a bluish tinge (deep melanin pigment) and areas of depigmentation (partial healing or regression). Many are crusted and, in later lesions, there may be frank bleeding.

Nodular melanoma is the most rapidly growing type of melanoma, commonly found on the trunk (Fig. 5). It is the type most difficult to diagnose on clinical grounds, and is a raised red or brown lesion on the skin.

Acral melanoma is a relatively rare clinicopathological type of melanoma on white skin, although it represents almost 50 per cent of melanomas in Japan. It is recognised as an extensive macular irregular brown area on the skin, with some roughening or nodule development, and loss of the normal skin lines. The great majority of acral melanomas are on the sole of the foot (Fig. 6).

Some epidemiological features of melanoma are similar to those of squamous and basal cell carcinomas. All these skin tumours, for example, are much less common in non-white peoples, whether of Asian or African origin. Studies in the USA and Canada, Australia, the UK, and Norway, have shown that the frequency of all these types of skin cancer is more common in people living nearer the equator within that country [11]. Individuals with lighter hair and skin colour are at higher risk, and, therefore, within Europe the frequencies of these conditions are higher in Scandinavia than they are in southern Europe.

However, malignant melanoma is quite different from other types of skin cancer in a number of important respects. The average age at onset is considerably younger, being around 50 years in the UK compared with 70 years for non-melanoma skin cancer. The socio-economic distribution is quite different, with melanoma being commoner in professional and managerial groups [12], whereas other skin cancers are more common in those with unskilled occupations. Studies comparing occupational groups of similar socio-economic status show that melanoma is in fact more common in indoor than in outdoor workers [13], in contrast to other types of skin cancer.

There are several studies in progress to determine the exact aetiological relationship between malignant melanoma and exposure to natural sunlight. In Australia, which has the world’s highest incidence of melanoma,
Fig. 1. Basal cell carcinoma on the face of a farmer, showing the classical raised ‘pearly’ border with central ulceration.

Fig. 2. Squamous carcinoma on the hand of an agricultural worker, showing an irregular ulcer arising on a background of scaling, sun-damaged skin.

Fig. 3. Lentigo maligna melanoma on the cheek of a 72-year-old female. The flat brown stain-like area has been present for many years and is seen in old family photographs. The central black nodule has only appeared in the past 3 months.

Fig. 4. Superficial spreading melanoma on the leg of a 38-year-old female. The size, irregular outline, irregular pigmentation and central inflammation are all indications that this is a melanoma.

Fig. 5. Nodular melanoma on the back of a 42-year-old male, showing a densely pigmented lesion with an irregular outline.

Fig. 6. Acral lentiginous melanoma on the heel of a 56-year-old male, showing extensive irregular pigmentation and a central densely black ulcerated area.
European immigrants arriving before the age of 10 years have risks similar to those of native-born Australians, while arrival at any age after 15 results in a lower rate, suggesting that childhood sun exposure is of critical importance [14]. Canadian work, distinguishing between different types of sun exposure, has shown that the risk of melanoma is increased in individuals who have had high levels of intermittent intense exposure to the sun from holiday or recreational activities, while there is no parallel increase in individuals whose excess exposure has been the constant, everyday, occupational type of sun exposure. This suggests that the increasing incidence of melanoma may be specifically related to increases in intermittent exposure through holidays and similar activities in individuals who have low levels of sun exposure for the bulk of the year [15].

Both these and other studies show consistently that individuals who tend to burn easily, have difficulty in tanning, have light coloured hair, skin and eyes, and who have increased numbers of benign pigmented naevi (moles) have a greater risk of melanoma than darker skinned Caucasians [16].

Scottish and North American studies also show a relationship between increased risk of melanoma and a history of severe sunburn, a further indication of the role of unaccustomed intense exposure [29].

There is considerable interest in an entity described in the USA in 1980 as the ‘dysplastic naevus syndrome’ (DNS). This entity appears to exist in both a sporadic and a familial form, and has recently been the subject of an NIH Consensus Conference [17]. Affected individuals have large numbers of pigmented naevi which are usually large, may have an irregular edge, and may look inflamed. The majority of these are acquired at around puberty, but a few may appear in childhood. Histologically, there may be evidence of both architectural and cytological atypia [18]. Work is in progress to determine accurately the prevalence of this condition in the population, and the true risk of melanoma in affected individuals in both the familial and the sporadic forms of the disease. Preliminary results suggest that patients with multiple unusual naevi, who have one or more relatives who have already had melanoma, are at increased risk of developing melanoma themselves, and require careful supervision.

The exact role of excessive ultraviolet exposure in the development of so-called dysplastic naevi is not yet fully established, but in one series of 12 patients who had both malignant melanoma and dysplastic naevi nine had a history of excessive sun exposure [19].

Prognosis for skin cancer

The prognosis for basal cell carcinoma after local excision or radiotherapy is excellent, and the prognosis for squamous cell carcinoma, if recognised and excised early, is also very good. For malignant melanoma the prognosis is directly related to the tumour thickness of the primary lesion. This is measured by a very simple technique developed by the late Alexander Breslow [20]. An optical micrometer in the microscope is used to measure in millimetres the distance between the overlying epidermal granular layer and the deepest invasive tumour cell of the primary melanoma.

In Scotland at present, the five-year survival rates for melanomas under 1.5 mm, 1.5–3.5 mm, and over 3.5 mm thick are 91, 67 and 38 per cent, respectively [10]. A recent public education campaign in the west of Scotland, designed to make patients aware of the clinical features of malignant melanoma in its early growth stages, was followed by an increase in the presentation of both the numbers and proportion of patients with tumours in the ‘thin’ good prognosis group, and a decrease in the number of patients with ‘thick’ poor prognosis tumours [3].

A useful component of this campaign was the development of a 7-point checklist (Table 1) which included features commonly seen in malignant melanoma. One point is scored for each feature seen, and any lesion scoring 5 or more has a 95 per cent chance of being a melanoma. Conversely, any lesion scoring 3 or less has a 90 per cent chance of being a non-melanoma pigmented lesion. We recommend that any pigmented lesion with a score of 3 or more is referred for specialist opinion, as well as any other which is in any way disturbing or unusual.

| Table 1. The 7-point checklist. |
|--------------------------------|
| 1. Presence of itch or altered sensation. |
| 2. Diameter of 1 cm or greater. |
| 3. Increasing size. |
| 4. Presence of an irregular or geographic lateral border. |
| 5. Variation in density of black and brown pigment within the lesion. |
| 6. Inflammation. |
| 7. Bleeding or crusting. |

Immunosuppression, sun exposure, and cutaneous malignancy

Patients who receive therapeutic immunosuppression following a renal transplant have now been carefully followed up for several years to establish whether they have an increased incidence of malignancy. Studies from the UK and Australia, mainly on renal transplant patients who received azathioprine as their major immunosuppressant, suggest that there is an increase in the number of both basal and squamous cell carcinomas in both areas, but a greater increase in areas with high natural sunlight intensity. Evidence of an increase in malignant melanoma and dysplastic naevi comes at present from only one group, and requires further study.

Currently available topical sunscreens

In the past decade there have been worthwhile improvements in the effectiveness and spectral range of protection of topical sunscreens. The majority of these are now marketed by both pharmaceutical firms and producers of cosmetics with a number called the sun protection factor (SPF). A cream with an SPF of 6 indicates that human skin protected by this preparation used prior to and
during sun exposure can be exposed to a six times higher dose of sunlight than unprotected skin before the first signs of sunburn become visible. SPF numerical values on currently available preparations are a reasonable guide to sunscreen efficacy, provided the preparation is applied both before and during exposure.

Currently available preparations carry SPF figures from about 2 to 20, figures of 6 or more suggesting significant sun protection. These preparations do protect well against immediate sun damage, and, almost certainly, against chronic damage, although they have not been used long enough for this to be stated definitively.

Cutaneous malignancy and exposure to sources of ultraviolet radiation other than natural sunlight

A case control study published in 1982 suggested that a higher proportion of melanoma patients had a history of working underneath an unshielded fluorescent light source than age- and sex-matched healthy control subjects. This caused considerable interest, and stimulated further studies which have given inconsistent results. The amount of ultraviolet radiation emitted by fluorescent fixtures is small, and is completely blocked by plastic diffusers used in most modern light fittings.

There are a small number of patients who have developed cutaneous malignant melanoma after using commercial UV-A sunbeds. Without information on other exposure of such individuals to UV radiation, one cannot state that sunbed use led to subsequent development of malignant melanoma. Experiments on laboratory animals and man using only UV-A as a light source have, however, suggested early development of cutaneous ageing, and one recent study has reported the development of squamous carcinoma in mice [32]. It thus seems likely that prolonged exposure to UV-A in man may be associated with an increased incidence of various types of skin malignancy, either alone or by augmenting the effect of other UV exposure. Fair skinned subjects who burn easily and tan with difficulty cannot therefore be reassured that sunbeds are ‘safe’, and they should be warned that as UV-A irradiation leads to very little visible inflammation, damage may be done to the skin without the customary redness and peeling seen with natural sunlight.

Therapeutic exposure of patients with dermatological disorders, such as psoriasis and cutaneous lymphoma, to UV-A after ingestion of an oral photosensitising drug, psoralen (PUVA therapy), has been in use in European dermatological departments for the past 10 to 15 years. Patients are carefully selected for this therapy, usually after prolonged use of topical therapy has failed to clear their skin condition. Treatment is undertaken in centres with specialised equipment and careful records are kept, both of response of their skin disease to PUVA and also of the development of possible side-effects, either systemic or cutaneous. To date, experience in Europe suggests that there is no overall increase in incidence of any type of cutaneous malignancy in patients receiving PUVA therapy, although there is one report of a patient treated in London with photochemistry who developed cutaneous malignant melanoma [21]. In North America experience is different, with an increased incidence of squamous cell and basal cell carcinomas and a reversal of the normal ratio of basal cell to squamous cell carcinomas in PUVA-treated patients [22]. Again, there is one report of malignant melanoma developing in a patient receiving PUVA. Differences in the reports between North America and Europe may be explained by differing PUVA dosage regimes, and to some extent by differing treatment of patients prior to commencing PUVA treatment, as a high proportion of USA patients appear to have been treated with recognised carcinogens, such as X-ray therapy in addition to receiving UV therapy [22-23].

Summary and recommendations

1. There is strong epidemiological evidence that natural sunlight is the main factor in the aetiology of cutaneous basal cell carcinoma and squamous cell carcinoma in man [24]. This evidence relates to long-term exposure to sunlight in an occupational setting.

2. Natural sunlight includes wavelengths of ultraviolet radiation which cause squamous cell carcinoma in animal models [25].

3. For malignant melanoma of the lentigo maligna melanoma variety, found mainly on the face, there is also strong evidence that long-term cumulative sun exposure is a major aetiological factor.

4. For the other three main types of malignant melanoma (superficial spreading, nodular and acral melanoma), there is evidence that sun exposure is also a major aetiological factor, but the precise relationship between the risk and the type of sun exposure is more complex [26]. Current evidence would suggest that short-term exposure to intense sunlight of skin which is not normally exposed to sunlight may be the type of sun exposure which is most important in this group of malignancies.

5. The risks of all types of skin cancer are increased in subjects with light brown or blond hair, blue eyes, and fair skin [27]. The risk of melanoma is increased in subjects who have large numbers of naevi [28] who burn easily and tan poorly with exposure to unaccustomed sunlight [29].

6. Patients on long-term immunosuppression, such as renal transplant recipients, are at increased risk of developing non-melanoma skin cancer [30,31]. They are, therefore, a group who particularly need advice about sun exposure and sunscreens.

7. Exposure to ultraviolet radiation other than natural sunlight requires further long-term study to determine the associated risks of skin ageing and malignancy in man. Squamous cell carcinomas in animals have been reported following UV-A exposure [32].

8. The regular use of topical sunscreens in preparations with a sun protection factor (SPF) of at least 6, and
previously higher, is an effective method of preventing sunburn [33]. It is probable that these preparations also prevent or delay the development of premature ageing changes and pre-malignant and malignant skin damage.

9. In the light of our present knowledge, it is reasonable to warn white subjects, particularly those who burn easily and tan poorly that excessive long-term exposure of their skin to strong sunlight, either occupational or recreational, will cause accelerated wrinkling, scaling, and pigmentary irregularities traditionally recognised as skin ageing [34], and may predispose to future skin cancer. They should be counselled to avoid lengthy persistent exposure to summer sun, especially between 11 am and 4 pm, at low latitudes, and near snow or water. They should be advised to wear appropriate long-sleeved clothing and a hat, and to use a topical sunscreen with a SPF of at least 6, and preferably higher, when out of doors in strong sunshine, both in the UK and overseas. This advice applies to children as well as adults. The sunscreen should be applied before sun exposure, and renewed every two hours and also after swimming.

References
1. McLeod, G. R., Davis, N. C., Little, J. H. et al. (1985) Melanoma in Queensland, Australia. Experience of the Queensland melanoma Project in cutaneous melanoma (eds C. M. Balch and G. W. Milton). Philadelphia: Lippincott.
2. Riegel, D. S., Friedman, R. J., Kopf, A. W. et al. (1986) Journal of the American Academy of Dermatology, 14, 857.
3. Doherty, V. R. and MacKie, Rona M. (1986) British Medical Journal, 292, 967.
4. Cox, N. H., Jones, S. K., MacKie, R. M. et al. (1986) British Journal of Dermatology, 116, 145.
5. Melski, J. W., Tannenbaum, L., Parrish, J. A. et al. (1978) Journal of Investigative Dermatology, 68, 328.
6. Hueper, W. C. (1942) Occupational tumours and allied diseases. Illinois: Thomas Springfield.

7. Marks, R. (1985) European Journal of Epidemiology, 1, 319.
8. Clark, W. H., Ainsworth, A. M., Bernardino, E. A. et al. (1975) Seminars in Oncology, 2, 83.
9. McGovern, V. J., Shaw, H. M., Milton, G. W. et al. (1980) Histopathology, 4, 235.
10. MacKie, R. M., Smythe, J. F., Soutar, D. S. et al. (1985) Lancet, 1, 899.
11. Magnus, K. (1973) Cancer, 32, 1275.
12. Lee, J. A. H. and Strickland, D. (1980) Cancer, 41, 757.
13. Cooke, K. R., Skegg, D. C. G. and Fraser, J. (1984) International Journal of Cancer, 34, 57.
14. Holman, C. D. J. and Armstrong, B. K. (1984) Journal of the National Cancer Institute, 76, 403.
15. Elwood, J. M., Gallagher, R. P., Davison, J. et al. (1985) British Journal of Cancer, 53, 543.
16. Beral, V., Evans, S., Shaw, H. et al. (1983) British Journal of Dermatology, 109, 165.
17. National Institutes of Health Consensus Development Conference (1984) Journal of the American Academy of Dermatology, 10, 683.
18. Seywright, M. M., Doherty, V. R. and MacKie, R. M. (1986) Journal of Clinical Pathology, 39, 189.
19. MacKie, R. M. (1982) British Journal of Dermatology, 107, 621.
20. Breslow, A. (1970) Annals of Surgery, 172, 902.
21. Kemmet, D., Reshad, H. and Baker, H. (1984) British Medical Journal, 289, 1498.
22. Gibbs, N. K., Honigsmann, H. and Young, A. R. (1986) Lancet, 1, 150.
23. Stern, R. S., Laird, N., Melski, J. et al. (1984) New England Journal of Medicine, 310, 1156.
24. Scotto, J., Kopf, A. and Urbach, F. (1974) Cancer, 34, 1333.
25. Emmet, E. A. (1973) Critical Reviews in Toxicology, 2, 211.
26. Lee, J. A. H. (1983) In Pigment Cell, Vol. 6, pp 1-21 (ed Rona M. MacKie). Basel: Karger.
27. Emmett, A. and O’Rourke, M. (1982) (eds) Malignant skin tumours. Edinburgh: Churchill Livingstone.
28. Svedlow, A. J., English, J. S. C., MacKie, Rona M. et al. (1986) British Medical Journal, 292, 1555.
29. MacKie, R. M. and Aitchison, T. C. (1982) British Journal of Cancer, 46, 955.
30. Penn, I. (1987) Transplantation Proceedings, 16, 492.
31. Shell, A. G. R., Mahoney, J. F., Horvath, J. S. et al. (1979) Australia and New Zealand Journal of Surgery, 49, 617.
32. Strickland, P. T. (1986) Journal of Investigative Dermatology, 87, 272.
33. Sayre, R. M. et al. (1979) Archives of Dermatology, 115, 46.
34. Gilchrist, B. A. and Szabo, G. (1983) Journal of Investigative Dermatology, 80, 81.