severe melanosis and melanocytic tumours [10, 11]. *Ret* is found activated by rearrangement in a consistent number of papillary thyroid carcinomas [12], and, although not fully explored in melanomas, its expression has been detected in tumours originating from the neural crest [13, 14].

(d) Tumour suppressor gene. Loss of heterozygosity (LOH) analysis of melanoma cells has indicated a high frequency of LOH at many loci on different chromosomes, again including chromosomes 1, 3, 6 and 9, but in general has also indicated a significant high chromosomal instability of these tumour cells (reviewed in [4]).

With another approach, using cell fusion techniques, Trent *et al.* [15] showed that the introduction of a normal chromosome 6 in two different human melanoma cell lines (one with a detectable 6q15 deletion) resulted in altered cell morphology and diminished cloning efficiency in soft agar, and the *in vivo* growth in nude mice correlated with the loss of the introduced chromosome 6. Unfortunately, no progress has been reported subsequently for the identification of the locus on chromosome 6 responsible for the suppression of malignant phenotype in melanoma. Finally, two recent papers have reported a very high frequency of positivity (85%) by immunostaining with p53 antibodies in two series of 83 specimens of primary and metastatic melanomas.

These findings represent one of the highest incidences of p53 mutation yet registered in a human malignancy and support the concept that alterations of this gene may be an early event in melanoma development [16, 17]. So far, a similar analysis also employing molecular techniques has not been reported.

In conclusion, although in recent years several investigations have dealt with the issue of genetics and molecular biology of melanomas, perhaps with the exception of p53, we are still far from the identification of relevant genes significantly involved in its development and progression. However, the success of the molecular approach in identifying the genes of other inherited cancer syndromes, such as retinoblastoma or adenomatous polyposis (for review see [18]), leaves us with the hope that future investigations on the molecular aspect of melanoma will provide the clue for a more successful management of this increasingly important neoplastic disease.

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VI. What Has Been Achieved by Primary and Secondary Prevention Campaigns?

R. Mackie

THE THREE main types of skin cancer are basal cell cancer, squamous cell carcinoma and malignant melanoma. In the past, basal and squamous cell carcinomas have tended to be grouped together as non-melanoma skin cancer, but there are good reasons for separating these two entities out. The exact pattern of incidence in relation to sun exposure is different between the two malignancies, and it is becoming clear that squamous cell carcinoma is a greater risk in those who are immunosuppressed.

A further problem that arises regarding basal cell and squamous cell carcinomas is incomplete cancer registration. This is because there is a continuing tendency to diagnose a proportion of these lesions clinically, and to then treat with non-excisional

techniques such as liquid nitrogen, diathermy, interferon or 5-fluorouracil. Thus, cancer registration dependant on a pathological diagnosis for registration will miss a varying proportion of these malignancies.

All three types of skin cancer are associated aetiologically with excessive exposure to ultraviolet radiation (UVR). The exact nature of the link between UVR exposure and the induction of melanoma, basal cell carcinoma and squamous cell carcinoma is not entirely clear. However, animal models and site distribution of squamous cell carcinoma both suggest that cumulative life-time exposure to ultraviolet radiation is the major risk factor for squamous cell carcinoma, and that this can be accelerated by therapeutic immunosuppression. As far as basal cell carcinoma is concerned, the great majority of lesions are on the head and neck area, but the subsites in this area are not those sites at which sun exposure is maximal. Basal cell carcinoma tends to affect the areas of the face which, in fetal life, were the sites of embryonic fusion planes, and there may, therefore, be an interesting association between UVR exposure and incomplete maturation.

The study of the aetiology of malignant melanoma again strongly implicates excessive exposure of Caucasian skin to UVR. However, in the case of the melanoma patient, cumulative life-time sun exposure appears to also interact with intense burning exposure, often experienced earlier in life. Studies of immigrants from climates with few hours of natural sunshine to intensely sunny environments, such as Australia and California, suggest that intense sun exposure prior to the age of 10 years is a risk factor for developing malignant melanoma, often three to four decades later. Thus, it must be assumed that childhood sun exposure acts as an initiation factor, and that other factors, possibly further UV exposure, are promoting factors in the stepwise progression to malignancy. The observation that patients who have melanoma have a higher than expected incidence of severe blistering sunburns has given rise to what is termed the intermittent sun exposure hypothesis, in association with the aetiology of malignant melanoma. This hypothesis has been promoted mainly by Elwood, but it has been vigorously challenged by Green and others in Australia, who demonstrate convincingly that cumulative life-time sun exposure is again an important risk factor for melanoma in that continent.

The cell type giving rise to malignant melanoma is the melanocyte, for squamous cell carcinoma it is the keratinocyte, and for basal cell carcinoma it has not been fully established. Extensive cell biological studies do not suggest that it is the basal cell of the epidermis, and at present there is intense interest in studying the hair follicle keratinocytes, particularly those in the bulge region of the hair follicle adjacent to the arrector pili muscle, which may well be an important site of differentiation, and therefore also possibly of development of basal cell carcinoma.

UVA radiation is a newer hazard, with regard to risk of developing any type of cutaneous malignancy. Tubes emitting relatively pure UVA or long wave UVR (320–360 nm) have only been available for approximately the last 15 years. Initially they were introduced for the therapeutic management of certain severe dermatological disorders, such as psoriasis and cutaneous lymphoma. Long wave UVA tubes are used in conjunction with an oral photosensitising agent or psoralen. Two hours after ingestion of the psoralen the patient is exposed to a measured dose of UVA in a specially designed cabinet. An off-shoot of these medically recommended UVA cabinets, however, has been the widespread availability of the long tube UVA sunbeds, available both for home purchase and for use in beauticians' or hairdressers' salons, etc.

The exact relationship between UVA and cutaneous malignancy has not yet been totally quantitated. Long-term follow-up studies of patients on photochemotherapy (PUVA) have clearly demonstrated an increasing incidence of squamous cell carcinoma in patients who have received over 1000 joules of UVA in combination with oral psoralens. To date, there are no convincing reports of an excess of either basal cell carcinoma or malignant melanoma.

The use of sunbeds and subsequent risk of malignancy is at present under study in a number of centres. There are two published case–control studies, one by Walters *et al.* in Canada [1] and one by MacKie *et al.* [2] in Scotland, which both demonstrate a statistically significant increased relative risk of developing malignant melanoma for males but not for females after relatively short-term use of UVA sunbeds. More data are needed in this field, and it is essential that the exact characteristics of the sunbeds used are reported in subsequent studies.

A recent publication from the U.S.A. emphasises the potential hazards of so-called tanning salons and give a disquieting account of lack of operator knowledge of the output and hazards of the machines [3].

To date, there have been no convincing primary or secondary prevention campaigns addressing the problem of basal and squamous cell carcinoma. In Australia, primary prevention campaigns aimed mainly at reducing both the mortality and, in time, the incidence of malignant melanoma should, if successful, also have an effect in reducing the incidence of non-melanoma skin cancer, possibly squamous cell carcinoma.

Secondary prevention campaigns or educational activities carried out in the U.S.A. and published by the American Academy of Dermatology [4] have reported on screening over a quarter of a million individuals for malignant melanoma. This has been done at skin cancer fairs and other occasions, when the public has been offered a free skin examination and advice. Of 279 000 individuals screened, 2496 suspected melanomas were identified. However, only 176 of this number were pathologically confirmed as malignant melanoma. This is a rate of one melanoma for every 1588 individuals screened. Data on the incidence and thickness patterns of malignant melanoma in the geographical areas in which these screenings have been carried out, prior to and after introduction of the screening, are not available, but data of this type are currently being collected in the U.S.A.

In Scotland, an intensive public education campaign, aimed at secondary prevention of malignant melanoma was commenced in 1985. Results were published in the *British Medical Journal* in June of this year [5], and show clearly that an approach based on television, newspapers and other appropriate use of the media has had an effect in reducing the average thickness of melanoma lesions excised in the entire country with an encouraging trend towards reduction in mortality in females but not yet in males. This study utilises the primary care physicians as an initial screening group and is highly successful, with a ratio of suspected to confirmed melanomas of 1:25.

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FUTURE RESEARCH

FUTURE RESEARCH on the aetiology of melanoma and non-melanoma skin cancer should be planned on a multicentric and multidisciplinary basis in order to investigate, in a homogeneous way, the relationship between sun exposure and skin cancers in different ethnic groups.

There is evidence from epidemiological studies that those at greatest risk of skin cancer (including melanoma) are individuals of light complexion (who burn easily, tan with difficulty) with a large number of banal or clinically atypical melanocytic naevi.

It is important to plan studies in different populations aimed at:

(1) identifying objective criteria to define the UVR susceptibility trait with regard to (a) the amount and type of melanins (eumelanin, pheomelanin, oxymelanin), (b) the redox state of the glutathione system, (c) *in vivo* measurement of DNA repair capacity in different epidermal cells, (d) immunosuppression;
(2) assessing how these criteria correlate with each other;
(3) studying how these criteria correlate to skin cancer;
(4) assessing the role of photoprotection of melanins and sunscreens in respect of cancer skin.

Although molecular biology has not provided specific examples of genes significantly involved in the development and progression of human melanoma, two recent reports have identified p53 by immunocytochemistry as a significant marker in human melanoma [1, 2]. Investigations at the molecular level to define specific mutations of this gene may be informative DNA samples for all subjects entering into these studies should be collected for both tumour and normal tissue.

Hopefully, these will be useful in future screening programmes and in developing objective methods of measuring sun exposure and its consequences.

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MESSAGE TO THE PUBLIC

CAMPAIGNS THAT could generate anxiety should be discouraged. It was unanimously agreed that general messages to the public, stating that excessive sun exposure (and exposure to UVA lamps) are dangerous are not likely to be effective and could be counterproductive. Instead, information should be targeted.

It was decided that the following messages seem reasonable:

(1) the need to protect children's skin from sunburn,
(2) excessive sun exposure and exposure to UVA lamps could be dangerous for individuals with pale skin who tan poorly, burn easily and have a large number of naevi on their skin,
(3) there is no evidence that sunscreens can protect from long-term risks.

Campaigns aimed at alerting the public to the features of early melanoma should be encouraged, provided that elements for evaluating the outcome of the campaign are present.

Guidelines to promote primary and secondary prevention of melanoma (and skin cancer) have been recently published by the WHO Melanoma Programme [1].

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