
Premalignant Disease of the Epidermis

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Premalignant disease provokes questions and provides social challenges. Its occurrence on the skin gives unrivalled opportunities for study of the neoplastic process *in vivo*. In the past 50 years, many of the aetiological factors responsible for pre-neoplastic and neoplastic disease of the epidermis (non-melanoma skin cancer) have been identified and studied extensively. The most important of these is ultraviolet radiation (UVR) but the carcinogenic potential of X-irradiation, chronic heat injury, exposure to soot, pitch and other chemical carcinogens, as well as papilloma virus infection, should not be forgotten. With this information and with the accessibility of the target tissue, it should be possible to characterise accurately the stimulus-response relationship and determine factors that modulate this relationship.

Because the skin is easy to sample it should also be possible to track the biochemical and immunological alterations that take place during the progression from normal to premalignancy and from there to frank malignancy. Why do some premalignant lesions remain in *status quo* for long periods? Why do others regress? What determines their onward progression? Such questions have implications for neoplasia in general and explain the fascination of this group of disorders.

Prevalence

Non-melanoma skin cancer is essentially a preventable disease yet its frequency in Caucasian populations is increasing to a frightening degree. It has, for example, been computed that in 1985 there will be 0.5 million new patients with non-melanoma skin cancer in the USA. Robin Marks (a friend but not a relative of mine), surveying a small town in Victoria, Australia, found that 56.9 per cent of the adult population had at least one solar keratosis and 2.32 per cent had at least one squamous cell carcinoma[1]. In another study by the same group it was estimated that at least 1,000 patients with non-melanoma skin cancer presented per week in the State of Victoria[2]. There appears to have been no similar study in the UK and it may be thought that in our comparatively sunless climate it would be a rather unproductive exercise. However, I do not believe this to be the case. Cardiff can hardly be considered to be exceptionally favoured by the climate, yet solar keratoses, squamous cell carcinoma and

other forms of skin cancer occupy a not inconsiderable proportion of our clinic practice. In 1984, 4,540 new patients were seen in our clinic, of whom 187 (4.1 per cent) had solar keratoses or Bowen's disease, 29 (0.6 per cent) had squamous cell carcinoma, and 176 (3.9 per cent) had basal cell carcinoma. That is, 8.5 per cent of all new patients had the commoner types of non-melanoma skin cancer.

Interestingly, this relatively high prevalence in Cardiff does not seem to be mirrored in all areas. For example, at St John's Hospital for Diseases of the Skin, London, the comparable figures for non-melanoma skin cancer in 1981, 1982 and 1983 were 1.1, 0.9 and 1.2 per cent respectively (Griffiths, personal communication). Of course, it is difficult to draw firm conclusions on the basis of these figures, as referral patterns differ between centres. Nonetheless, the dissimilarity between the incidence in the two centres seems so large that there may well be genuine differences in the experience of non-melanoma skin cancer in the two populations served. The differences may well be due to the comparatively large number of individuals of Celtic origin in the South Wales area and the predisposition of this group may not be entirely due to their light complexions. There is some evidence that they have a fault in DNA repair after UVR injury, similar in type but less in degree, to that seen in xeroderma pigmentosum[3,4]. It is of interest in this respect to find a higher 'Celticity index' in patients with malignant melanoma in Massachusetts and Australia[5,6].

Clinico-pathological Considerations

The keratosis is the archetypal premalignant epidermal lesion. It is often termed solar or actinic keratosis to denote the usual cause. Solar keratoses are usually scaly or warty, pink or gray patches on a light-exposed area of skin. Histologically the keratosis may be identified as an area in the epidermis in which the basal epidermal cells show irregular staining, shape and size, particularly as far as their nuclei are concerned (dysplasia). In addition, the affected epidermis often demonstrates abnormal differentiation resulting in individual cell keratinization (dyskeratosis) or parakeratosis. We have demonstrated that these lesions have a high rate of epidermal cell production, as

does the epidermis on which these arise[7]. Bowen's disease represents one further step towards frank malignancy. Bowen's disease often presents clinically as a psoriasiform scaling plaque but may also be a warty nodule. In this condition the abnormal cells are bizarre in their heterogeneity of size, shape and staining properties and are present throughout the entire thickness of the epidermis. When these lesions become frankly malignant they enlarge and ulcerate. The histological hallmark of the resulting squamous cell carcinoma is dermal invasion by the abnormal epithelial cells.

Not all solar keratoses transform to a more 'malignant' phase but there are only scanty data to characterise the frequency with which this occurs. Early estimates suggested that some 20 per cent of keratoses transform to squamous cell carcinoma[8] but the fact that the former lesions are so much more common than the latter[1] suggests that this is not the case. Nonetheless, the disparity in numbers could be a reflection of the different rates of growth of the two sorts of lesion and it could be that all solar keratoses are committed to develop into frankly neoplastic lesions at some point. To determine whether this is the case or whether an additional stimulus is necessary, good long-term studies are required. However, providing a convincing answer will not be easy because of the need to remove and examine lesions to establish the diagnosis. Without good non-invasive diagnostic techniques it cannot be certain that any lesion followed is indeed a solar keratosis, and if it is excised there is no knowing how it might have behaved.

It may be that some solar keratoses regress and I will discuss one possible example of this later. Regression of bronchial metaplasia after stopping smoking has been described[9] and we are currently involved in determining whether regular use of a sunscreen to prevent further damage from ultraviolet radiation can reduce the degree of dysplasia present.

The Role of Solar Ultraviolet Irradiation

There can be little doubt that solar irradiation is the major stimulus to the development of non-melanoma skin cancer. The evidence has been summarised on several occasions in recent years[10-13] but it is worthwhile reiterating the main points before proceeding to document our own involvement. The most persuasive evidence concerns clinical experience. Black-skinned individuals are protected from the damage caused by ultraviolet by the melanin pigment produced by melanocytes and subsequently donated to epidermal cells. Non-melanoma skin cancer is extremely uncommon in this group of individuals. The converse is also true in that the lighter the complexion, the higher the incidence of solar keratoses, squamous cell carcinoma and basal cell carcinoma. There is also evidence of a dose-effect relationship as those individuals with outdoor jobs which involve considerable exposure to the sun are much more likely to develop lesions than those who are mostly indoors. Recently the matter has been highlighted by the widespread use of a form of ultraviolet irradiation in the treatment of psoriasis (photochemotherapy with long

wave ultraviolet radiation—PUVA). Individuals treated in this way appear to have a much higher prevalence of squamous cell carcinoma[14]. Another plank in the argument is that patients with the rare genodermatoses xeroderma pigmentosum, who often die from some form of skin cancer, have a defect in a DNA repair mechanism after damage by UVR[15]. As well as the clinical evidence cited above, there is strong experimental evidence, mostly deriving from the irradiation of mice with ultraviolet[16].

A Human Model for Photocarcinogenesis

Human skin differs markedly from that of small mammals in its response to UVR. Because of this we felt that to answer questions relating to solar protection and the wavelength dependency of photocarcinogenesis it would be more useful to study man. We noted reports suggesting that enhanced glucose-6-phosphate dehydrogenase (G6PDH) activity was characteristic of premalignant and malignant epithelial lesions; in particular, changes were noted in bronchial mucosal and gastrointestinal lesions and in a model—the hamster cheek pouch[17-19]. We wondered whether this activity could form the basis of a marker for premalignant change in human epidermis. Therefore we decided to study the distribution of this pentose shunt enzyme activity as well as citric acid cycle enzyme activities in solar keratoses and squamous cell carcinoma, and exposed but non-involved skin near the lesions (paralesional skin), as well as in normally non-exposed skin. In order to compare the results of our tests in the different samples examined we used a carefully standardised sectioning and incubation technique. We also measured the densities of the formazan reaction products in the tissues by a densitometric method[20] using a scanning and integrating microdensitometer. The results demonstrated a considerable increase in G6PDH activity in the lesions examined throughout the epidermis but particularly in the granular cell layer. Paralesional skin also showed enhanced G6PDH activity in the epidermis compared with normally non-exposed skin of the buttock.

Studies of the succinic dehydrogenase (SDH) activities also presented us with some interesting results. The SDH activity was only slightly decreased overall in the epidermis but when the various parts of the epidermis were investigated separately for SDH activity the granular layer showed a significant decrease in both lesions and paralesional areas.

As the cytochemical changes (increased G6PDH and decreased SDH activities) were also present in exposed but non-involved skin it seemed quite likely that chronic exposure to ultraviolet radiation was responsible. In order to confirm this we irradiated 3 cm² areas on the buttock skin of five normal healthy volunteer subjects with broad spectrum ultraviolet (290-400 nm) radiation 10 times in a 14 day period. The dose given was sufficient to keep the colour of the areas slightly pink and was one to two 'minimal erythema doses'. At the end of the experiment the treated sites and non-irradiated control sites in the same, normally non-exposed, area were biopsied. The

biopsies were studied for G6PDH and SDH activities in the same standardised manner as outlined above. The results of this experiment were quite similar to the findings in patients[21]. After irradiation, the SDH activity dropped to 50 per cent of the control value in the granular cell layer but did not change much overall in the epidermis. The G6PDH activity increased by about 30 per cent overall in the epidermis and was markedly increased in the basal and granular cell layers. These findings suggested to us that we did have the basis of a model for UVR-induced epidermal change of the type associated with neoplasia.

The first question that we wanted to ask of the model concerned the relationship between sunburn and the cytochemical alterations discussed. Are individuals who are 'protected' from sunburn by sunscreen agents similarly protected from the epidermal damage caused by UVR? As the sun-worship cult gains strength, outdoor activities increase in popularity and holidays in the Mediterranean sun become ever cheaper, it is important to know how to reduce the risk of sun-induced skin cancer. The experiment we designed to obtain this information was again in normal human volunteer subjects and we studied two sunscreen products—one containing 2.5 per cent isoamyl-p-N.N-dimethylaminobenzoate and the other containing 4 per cent Mexenone[22]. The first is effective at absorbing UV of wavelengths in the medium UV wavelength band (UVB), around 290 nm—the wavelengths well known to be responsible for causing sunburn—and the preparation in which it was formulated had a sun protection factor of 7 (i.e. a seven times greater dose of UV is necessary to cause erythema when it is used than when it is not used). The second preparation has a broader absorption spectrum and is weakly absorbent in part of the long wave UV range though it is mainly effective in the UVB band. The protection factor of this preparation was approximately 6. Small areas on the buttocks were irradiated with different doses of UV from fluorescent tubes. Some areas were 'protected' by one or other of the sunscreens and others were not. Irradiation was performed 10 times in a 14 day period and the irradiated sites, and non-irradiated control sites, were biopsied 24 hours after the last irradiation. The biopsies were assayed cytochemically as described previously and, in addition, portions were incubated in tritiated thymidine for subsequent autoradiography and epidermal labelling index determination[23]. Measurements of epidermal and stratum corneum thickness were also made.

The preparations were certainly effective in preventing sunburn erythema, but were less effective in preventing the objective consequences of UV exposure on the epidermis. At the higher doses of UVR (still less than needed to produce erythema) there was a marked increase in G6PDH throughout the epidermis and some decrease in SDH activity. The same was true for the epidermal thickening and increased thymidine autoradiographic labelling index usually noted after UVR stimulation of normal skin in that, despite the absence of clinical 'burning', there were significant UVR induced alterations. Although these changes were most prominent with

the higher doses—there seemed to be a regular dose-effect relationship—they were also evident with less irradiation. This dissociation between the clinical sunburn effect and the objective responses of the epidermis to UVR is a cause for concern. It suggests that individuals can expose themselves covered in these sunscreens and not burn, but nonetheless sustain significant injury to the skin.

One possible explanation for the dissociation between clinical burning and epidermal damage is that the latter is at least in part caused by wavelengths not absorbed out by the sunscreens used. Both sunscreens used absorb maximally in the 290 nm wave band (the 'erythema' wave band) and allow through most of the longer wavelengths of the fluorescent lamps used. Solar radiation certainly contains the longer UVA wavelengths but this form of UV radiation has always appeared much less biologically effective and less attention has been devoted to it in relation to solar neoplasia. Because of the practical importance of knowing whether UVA was indeed responsible for the changes in our model, we mounted an experiment employing a monochromator to irradiate the skin instead of 'broad spectrum' fluorescent lamps. We chose UVA at approximately 360 nm and used a similar schedule of treatments on volunteer subjects as described previously. The energy employed was sufficient to produce slight tanning at the sites irradiated by the second week of irradiation. The results demonstrated that similar cytochemical and cell kinetic alterations take place after exposure to UVA as take place after irradiation with 290 nm[24]. Manufacturers have now started to include UVA absorbing chemicals in their sunscreen products. Unfortunately, in most cases their presence is ineffectual, as they are not as efficient UVA absorbers as the other substances are UVB absorbers. This suggests that damaging radiation may still reach skin protected from burning. We do not know the precise relationship of the cytochemical changes described to the development of epidermal neoplasia. Indeed, the relationship may be indirect, their presence only indicating epidermal damage of the type that eventually leads to skin cancer. We believe, nonetheless, that the human model we have described can be used to answer questions concerning the effects of repeated UVR exposure and attempts to minimise the damage caused by such radiation.

The Antigenic Profile of Non-Melanoma Skin Cancer

Solar keratoses are much more common than squamous cell carcinomata. A suppressive effect by host immunological defences could explain the apparent lack of vigour of keratoses, and researchers have made special efforts to identify antigenic differences between normal and neoplastic epidermal tissue. The loss of various cell surface markers and other cytological components of normal epidermal differentiation as detected by immunolocalisation procedures has been reported by several groups, including ourselves.

Abnormalities in the distribution of the intercellular pemphigus antigen was probably the first such change recorded[25]. Moragas *et al.*[26] claimed that there was a progressive loss of pemphigus antigen with increasing

dysplasia. Others have also found that solar keratoses retained this intercellular component, often with reduced intensity of staining, but that squamous cell carcinomas showed a marked reduction in the presence of pemphigus antigen[27]. We demonstrated that short-term incubation of lesions before examination made the demonstration of antigen loss very much more obvious[28]. The antigenic profile of the skin tissues on which neoplastic epidermal lesions rest has also been studied. The bullous pemphigoid antigen of the basement membrane region is also deficient in squamous cell carcinoma but we found accentuation of staining in the sub-epidermal region due to antibodies raised to procollagen[29]. The latter has led Mitrani and Marks[29] to suggest that the dermal connective tissue synthesis plays a central role in the genesis of epidermal neoplasia.

Dabelsteen *et al.*[30] found that oral premalignant lesions demonstrated loss of blood group substances A and B but that benign leukoplakic lesions did not. Other studies have shown that $\beta 2$ microglobulin is deficient in epidermal cell surfaces in some lesions, particularly basal cell carcinoma[31, 32]. Binding experiments with the lectin concanavallin A reflect the changes registered with pemphigus antibody—which is not surprising as it seems that pemphigus antibody and concanavallin A share binding sites. Beta 2 microglobulin, however, appears differently distributed over the cell surface. Class 2 mixed histocompatibility (MHC) antigens are expressed on all normal epidermal cells but there are relatively few studies of MHC antigen expression in premalignant and malignant tissue[33]. Our own studies indicate a not dissimilar picture, as seen with other cell surface markers. There is a patchy loss of these antigens which is more marked the more dysplastic the tissue appears. Clearly this group of cell surface components may be of particular importance, as they appear to be involved in regulating T-lymphocyte responses.

Differences in the distribution of keratins between normal and neoplastic epidermal tissue have also been documented. Winter *et al.*[34], using both polyacrylamide gel electrophoresis and two-dimensional electrophoretic methods, have demonstrated that the larger molecular weight keratin peptides are absent from both experimentally-induced rodent and spontaneously-occurring human squamous cell cancers. A not dissimilar finding was that of Klein-Szanto *et al.*[35] who determined that the keratin fibril organising basic protein (filaggrin) present in the keratohyalin granules of normal epidermis was absent from squamous cell carcinoma but present in keratoacanthomas.

Apart from the potential diagnostic significance of these various findings, do they yield any biologically important messages that inform on the nature of the neoplastic process or can be utilised therapeutically? For the most part they appear to indicate faulty epidermal differentiation and faulty membrane synthesis. From the functional standpoint the loss of cell recognition markers and cell contacts at the surface has several implications. It may allow cells to invade and metastasise rather than stay attached to other cells. It could explain the curious phenomenon of carcinoma segregans in which groups of

dysplastic epidermal cells appear to grow around other epidermal structures. Failure of recognition by the immune system of the abnormal cells as 'self' may also permit an immune response and explain spontaneous regression. Most of the reported studies have detected an alteration that is evident in frankly malignant lesions but only partially expressed in the premalignant lesions examined. They indicate a stepwise progression and not a fundamental alteration.

No tumour-specific antigens have yet been detected in solar keratoses or squamous cell carcinoma.

Evidence of 'Immune Surveillance'

A dense lymphocytic infiltrate beneath a solar keratosis is a commonly observed histological feature and could be interpreted as indicating an immune response to the lesion. In a few lesions the pathological picture simulates lichen planus in that there is basal cell liquefactive degeneration and 'colloid body' formation as well as a heavy infiltrate of lymphocytes sub-epidermally. These lichenoid keratoses may be examples of the immune response succeeding in checking the neoplastic process. We found that 6.1 per cent of 212 solar keratoses examined retrospectively and 10.7 per cent of 28 keratoses examined prospectively demonstrated the distinctive changes of lichenoid keratosis[36]. Basal cell liquefactive degenerative change occurred without full-blown 'lichenoid change' in some 27.8 per cent of keratoses. Colloid body formation and apparently apoptotic cells are often seen in keratoses and may represent a similar type of individual cell death. We could not identify a specific pattern of immunoglobulin or complement deposition in lichenoid keratoses, neither could we identify a particular morphological feature with which the phenomenon was associated. Similarly, Tosca *et al.*[37] could not identify a particular immunological mechanism for the regression of keratoacanthoma.

Patients who have had renal transplants and who have been immunosuppressed for several years to prevent rejection of the transplanted kidney have a higher prevalence of solar keratoses and squamous cell carcinoma than control populations. Although this is clinically evident in the UK, it is more of a problem in sunnier climates where there is already a high prevalence of non-melanoma skin cancer[38, 39]. A likely explanation for this phenomenon is that the normal immune 'check mechanisms' are prevented from acting to suppress UVR-induced neoplasia and the onward progression of pre-neoplastic lesions.

A corollary of this hypothesis is that if solar keratoses could be transplanted to immunologically privileged sites away from immune influences they would transform and become more malignant. In order to test this idea we have transplanted solar keratoses to athymic nude mice and have been successful in maintaining these lesions for periods of up to nine months[40]. We removed solar keratoses from patients, split them in two and examined half by routine histological methods and transplanted the other half. The transplanted tissue seemed to retain most of its own characteristics during its sojourn in the host site, free of the influence of delayed hypersensitivity. The

cell kinetic characteristics and the overall morphology of the transplanted tissue were similar to those of the original lesion although there was a tendency for the grafted tissue to be thinner than the original lesion from which it derived. It was quite obvious that the grafted lesion retained its human identity. The dysplastic nature of the epidermis was obvious, as was the solar elastotic degenerative change in the dermis. Even more convincing, however, were the antigenic similarities of the grafts to human epidermis. Involucrin is a component of the tough protein membrane just inside the plasma membrane of mature human epidermal cells[41]. Antibodies to this substance reacted with the grafted tissue but not with neighbouring mouse epidermis. Similarly, antibodies to the mixed histocompatibility complex (anti-HLA, A, B and C) reacted patchily with the original lesions and with the grafted lesions early on, but not at all with older grafts. Interestingly, we have found that there is an analogy with this state of affairs in cultured epidermal cells. After the first days of a subculture the HLA positivity is lost—to be regained for a short time immediately after subculturing, but then lost again as the culture ages (Thomas, Dykes and Marks, in preparation).

We were surprised that there was so little change overall in the grafted lesions even after periods of nearly nine months. Not a single transplanted keratosis became frankly malignant. We have no complete explanation for this lack of progression but two possibilities should be considered. The first is that the athymic mouse does retain some capacity for mounting an immunological reaction and that this is sufficient to keep the lesions in check. The second possibility is that solar keratoses require further UVR stimulation for any frankly neoplastic change to occur.

The epidermal dendritic Langerhans cell, for so long an annoying puzzle to dermatologists, anatomists and electron-microscopists, has now been identified as a sort of macrophage. It has the function of presenting antigen to T-lymphocytes and is of central importance in the development of delayed hypersensitivity. In recent years it has been found that irradiation of the skin with UV causes the Langerhans cells to disappear[42] and inhibits the development of delayed hypersensitivity. Whether this is of importance in allowing the development of neoplastic epidermal cells in chronically sun damaged skin is uncertain but clearly it is a possibility. Other work by Margaret Kripke[43] may also be important. When UVR-induced tumours in mice are transplanted to other irradiated mice the tumours are not rejected even though other types of tumour are. It has been suggested that the UVR induces a specific immune tolerance to tumours caused by UVR by inducing suppressor T cells that interfere with the rejection of the tumours.

It will be evident from the above that the events leading up to the establishment of a premalignant lesion after long-continued sun exposure and the subsequent further development of a squamous cell carcinoma in some cases are extremely complex. There can be little doubt that the immune system is involved in several ways but the relative contribution of each mechanism to the process is as yet uncertain.

Measurement of the Degree of Epidermal Dysplasia

Methods have been devised for measuring dysplastic change in bronchial mucosa[9] and have assisted in detecting an improvement after stopping smoking. If we possessed a 'dysplasia index' it would be much easier to assess the effects of drugs and prophylactic measures than with the present subjective qualitative methods. We have used two ways of deriving such a dysplasia index[44]. The first is in reality a semi-quantitative method which employs 10 cm visual analogue scales. A mark is made on a 10 cm line indicating the severity of the epidermal change, the left hand end of the line representing no dysplasia, the right hand end representing the severest possible dysplastic change. The accuracy of this procedure is totally dependent on the experience and consistency of the observer, but in our hands can be shown to be reproducible.

The second method that we have devised utilises image analysis techniques. Nuclear area and its variability, cell size, epidermal thickness and irregularity, the degree of parakeratosis and the number of dyskeratotic cells are all assessed. The values are weighted arbitrarily and a dysplastic index is obtained with a complex formula. Unfortunately, this method is extremely time-consuming, as at present it takes four man hours per sample. We believe that some modification of one or other of these assessment techniques will be helpful in exploring dose-effect relationships as far as epidermal neoplasia is concerned.

The Social Significance

In countries such as the USA, Australia and South Africa, non-melanoma skin cancer is now a major public health problem. Although the various lesions induced by chronic sun exposure do not often kill, they cause considerable morbidity. Campaigns have been mounted through the various popular media in those countries to make the public more aware of the danger of sunbathing and we must hope that these will be successful. Our problem in the UK is smaller but rapidly growing in size because of the increased opportunities for travel and the growing emphasis on outdoor activities. It would be prudent to alert the British public to the potential hazards now.

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