Public Health Classics

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. This month Mary Norval reviews the 1977 paper by Michael Fisher and Margaret Kripke on ultraviolet light irradiation and its relationship to ultraviolet carcinogenesis. The original paper is reproduced by permission of Margaret Kripke.

Immunosuppression induced by ultraviolet radiation: relevance to public health

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The article by Fisher & Kripke (*1*), published 25 years ago, is a seminal one as it represents the first occasion on which ultraviolet radiation (UVR) was demonstrated to have systemic suppressive effects on the immune system. It marked the initiation of an exciting and fast-moving area known as "photoimmunology" and has led to important advances in understanding how the immune system of the skin operates. The findings have had far-reaching implications for diverse issues including skin cancers, infectious diseases, sunscreens and phototherapy.

Experiments in mice in the early 1970s had shown that chronic UVR over a period of several months led to the induction of skin cancers. These tumours, unlike most other tumours, were highly antigenic, as shown by their rejection on transplantation to recipient mice of the same genetic background. So, how could they arise and grow progressively in the original animals? Fisher & Kripke had found previously that, if mice were ultraviolet (UV) irradiated for a period insufficiently long to induce primary skin tumours and then received the transplants, the tumours were not rejected (*2*). In the paper discussed here, the alteration induced by the short-term UV exposure in the recipient mice was shown to be immunological in nature and was systemic. This was revealed by three types of experiments described in the article. On the basis of the results of these experiments the authors concluded that UVR can prevent an immunological mechanism that normally eliminates nascent tumour cells in the skin.

The sequence of steps leading to UV-induced systemic immunosuppression was not established and, indeed, has not been fully explained, even today. Fisher & Kripke speculated that the production of soluble "antigens" in response to the skin damage caused by UVR could lead to the generation of suppressor cells, rather than effector cells. It is now known that various photoreceptors located in the upper layers of the skin, of which DNA and urocanic acid are probably the most important, absorb UVR, alter their structure as a result, and then initiate the production of a series of immunological mediators, both locally and systemically, as well as phenotypic changes in the skin and lymph nodes. The end result is the induction of particular subsets of T regulatory cells which down-regulate cell-mediated immunity (*3*). The evolutionary explanation of such a response to UVR may be to prevent the altered molecules being recognized as "non-self" neoantigens. If immune responses were generated routinely to these molecules or to the cells in which they were located, this might result in chronically inflamed skin. Thus the immunomodulation which follows UVR may be desirable under many circumstances. Where it might not be desirable is in the case of a skin tumour or infection.

The most serious adverse health effect of UVR is the development of skin cancers. Excess sun exposure increases the risk of both non-melanoma (squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)) and melanoma skin cancers. It has been estimated by the United Nations Environment Panel that, in the past few years, over 2 million cases of non-melanoma and 200 000 cases of malignant melanoma have occurred annually in the world. The incidence of both BCCs and SCCs in white-skinned people living in temperate countries and places nearer the equator has increased in the past 30 years, in many surveys by two- or threefold. Similarly the incidence of malignant melanomas and mortality rates have risen sharply in recent decades in whites, although not in blacks. This tumour is less common than BCCs or SCCs but causes 80% of the deaths associated with skin cancer.

The critical role of the normal host defence mechanism in preventing skin cancer is shown dramatically in immunocompromised individals, such as patients with kidney transplants, who are at significantly increased risk of developing cutaneous malignancies, especially SCCs, on sun-exposed parts of their bodies, such as the face and the back of the hands (*4*). Skin phototype may be an important variable here as it was revealed recently that the people who burn easily and tan with difficulty are more susceptible to UV-induced immunosuppression compared with people who burn rarely and tan relatively easily (*5*). This factor may help to explain why the former individuals are at higher risk of developing skin cancer than the latter. In brief, UVR can be considered as a "complete" carcinogen as it not only causes mutations in the DNA of skin cells but it also down-regulates immunity.

The case for UV exposure affecting immunity to pathogens to the extent that the severity of symptoms or the risk of death is affected is not clear for most human infections. However, a link has been established between sun exposure and the reappearance of cold sores caused by herpes simplex virus infection in a proportion of latently infected subjects. Also there is a high risk of conversion of benign papillomas

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caused by various human papillomavirus types to SCCs in areas of the body frequently exposed to sunlight, particularly in immunosuppressed individuals. While the information from studies in human subjects is limited, at least 15 rodent models of infection with a wide range of microbes have been developed where UVR has been reported, in almost all instances, to induce down-regulation of immunity to the agent (*6*). In some models, a decreased ability to clear the infection and increased severity of symptoms, or even death, occurred. Calculations have been made to relate the results obtained in the animal models to humans and it was concluded that people could receive sufficient solar UV in about 100 minutes at mid-latitudes around noon to suppress their immune responses to microbes by 50% (*7*). This amount of UV exposure is experienced frequently by many individuals and therefore the effectiveness of the immune system against pathogens may be compromised as a result. Questions arise from this conclusion concerning several infectious diseases, particularly the persistent infections where the microbial agents are not cleared from the body following the primary infection. These organisms are sometimes associated with particular cancers or severe neurological symptoms. In addition, vaccination policies require to be examined to determine whether it might be inadvisable to vaccinate in the summer months as exposure to solar UVR is likely to be considerably higher than in the winter months, or to vaccinate just before or after a sunshine holiday.

Sunscreens have been developed as part of the campaign to promote "safe sun exposure". Their efficacy is measured routinely by the sun protection factor (SPF) which indicates how well they prevent burning of the skin. While this endpoint provides a simple and non-invasive test, the SPF does not necessarily indicate whether a sunscreen will protect against immune suppression. One difficulty here is in deciding what immune parameter or parameters should be used to assess the effectiveness of a sunscreen. In addition the wavelengths which induce immunomodulation are likely to be rather different from those inducing burning, and the type of artificial UV light source used in the testing requires to be considered (*8*). At the moment the best immune protection seems to be offered by sunscreens which include filters for both the UVB (290–320 nm) and the UVA (320–400 nm) wavebands and have a relatively high SPF. On a very positive note, the daily use of sunscreens in a community-based randomized trial in Queensland, Australia, led to a reduction in the incidence of SCC (1115 in the sunscreen group vs 1832 in the placebo group per 100 000) after a follow-up period of only 4.5 years (*9*). In addition, daily sunscreen application has been reported to decrease the incidence of further solar keratoses, the precursor of SCCs, in people who already had keratoses (*10*).

One final repercussion from the paper of Fisher & Kripke lies in the development of a range of therapies based on the immunosuppressive consequences of UVR. The successful use of these techniques has led to the new sub-speciality of photomedicine. One example is the treatment of psoriasis where long-lasting clinical remission frequently results from UVB phototherapy. Within the last decade, narrow-band UVR (311–313 nm) has been introduced to replace the broad-band UVB used up until then. The narrow-band exposure depletes T cells from the epidermis and the dermis of the lesions, probably by direct cytotoxicity, and lessens the risk of burning the skin as a side-effect. Another example of a recently developed therapy is the use of UVA-I (340–400 nm) irradiation for patients with acute atopic dermatitis, early stage cutaneous T cell lymphomas and cutaneous mastocytosis. Here the major effect of the UV is likely to be the induction of apoptosis in the immune cells that infiltrate the skin (*11*). Further therapeutic advances involving UVR can be expected.

Finally it should be noted that there are considerable concerns currently regarding UV exposure and human health. Changes in lifestyles in recent years have led to an increased environmental exposure to UV due to factors such as the fashion of tanning, more frequent sunshine holidays, the wearing of less clothing and no hats, and the use of tanning parlours and sunbeds. On top of this, the atmospheric ozone concentration has declined over some regions of our planet because of the emission of greenhouse gases, giving rise to significant increases in solar UVR at ground level. Although the adoption of the Montreal Protocol has largely halted the process of ozone depletion, its repair has been estimated to take at least 50 years and may be compromised by non-compliance with the Protocol, emission of other gases or by climate change. Public health policies require to take into account the adverse effects of UV exposure, and to raise awareness, particularly amongst children and young adults, of its considerable hazards, one of which is immunosuppression.

Therefore the findings of Fisher & Kripke, reported in 1977, have made an astonishing impact not only in establishing how our skin immune system operates but also in several areas of importance to public health today. ■

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