For Debate . . .

Psoriasis and cancer

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Summary and conclusions

The incidence of skin cancer in patients with psoriasis seems to be low, despite repeated use of known carcinogens in treating the disorder. This may be due to a reduced capacity of psoriatic skin to metabolise pre-carcinogens because of impaired arylhydrocarbon hydroxylase (AHH) activity. If this hypothesis is correct, and impaired AHH activity in psoriatic skin is shared by other tissues, the incidence of cancers associated with environmental carcinogens may also be reduced in patients with psoriasis. Since the disease is probably genetically transmitted as a dominant trait, it may have persisted because it confers genetic advantage.

This hypothesis, though speculative, provides a basis for further study.

Introduction

We suggest that the incidence of skin cancer may be low in patients with psoriasis because of a lowered capacity of psoriatic skin to metabolise carcinogens. This hypothesis arises from the fortuitous association of two separate ideas.

Psoriasis and skin cancer

Psoriasis is a disorder in which the rate of epidermal cell replication is greatly increased and, by analogy with other organs and tissues, this might be thought to predispose to skin cancer. Furthermore, psoriasis is treated by the topical application of tars, which are carcinogenic,¹ and with ultraviolet B (UVB) radiation, which is a major cause of skin cancer in healthy people. Yet although the effects of these treatments have been followed over many years—by physicians who are good observers and who, if anything, exaggerate the relation of skin disease to medicaments—no increase in the incidence of skin cancer has been reported in chronic psoriasis. Thus it has been suggested² that there is a cancer-protective mechanism in psoriasis, but few attempts have been made to confirm or refute this.

Kocsard reported a much lower prevalence of solar keratoses (pre-malignant skin lesions) among Australians with a history of psoriasis.³ He observed solar keratoses in 721 out of 819 men aged 45 or over with normal skin (88%), but in only two out of 51 patients with psoriasis (4%) in the same age group. Although these findings support our hypothesis, more detailed studies are required: because of the social stigma of skin disease and its effect on self-image,⁴⁻⁶

patients with psoriasis might be less inclined to expose themselves to solar irradiation, though therapeutic use of UVB might more than compensate for this.

Mono-oxygenases and chemical carcinogenesis

Many chemical carcinogens require metabolic "activation" before carcinogenesis.⁷⁻⁹ Microsomal mono-oxygenases can convert polycyclic hydrocarbons into carcinogenic metabolites which are mainly epoxides and di-epoxides. Arylhydrocarbon hydroxylase (AHH) activity (a measure of mono-oxygenase activity) is present in most tissues,⁹ including skin.¹⁰ Skin cancer produced in animal studies after topical application of common carcinogens such as benzo[a]pyrene¹¹ and dimethylbenzanthracene¹² may depend on the formation by mono-oxygenases of toxic metabolites that bind to DNA.¹¹⁻¹³ Moreover, the carcinogenic effect of UVB in hairless mice is enhanced by chemical carcinogens such as benzo[a]pyrene.¹⁴

Normal human skin contains AHH, which is virtually confined to the endoplasmic reticulum of the epidermis.¹⁰ The enzyme (or enzymes) appears to have biochemical properties similar to those found in other human tissues and in epidermis from animals. Epidermal AHH activity may be induced after incubation with substances such as benzo[a]anthracene.¹⁰ Nevertheless, epidermis from patients with psoriasis shows reduced "basal" and "induced" AHH activity, both in the lesions and in the lesion-free skin.¹⁵ Many biochemical changes have been found in the lesions of psoriasis, but most are secondary and not important aetiologically. Indeed, only those abnormalities that are present in the normal-looking, lesion-free skin are likely to be fundamental to the pathogenesis of the disorder. Since the defect in AHH activity is far greater than any other abnormality found in normal-looking psoriatic skin, we suspect that it may be close to the fundamental aetiological mechanisms of psoriasis.¹⁵

Thus, the reduced capacity of psoriatic skin to metabolise known precarcinogens couples logically, if fortuitously, with our earlier views on the need to find out why patients with psoriasis do not seem to develop skin cancer, despite repeated use of carcinogens in treating the disorder.

Comment

If our hypothesis is correct, it would provide strong support for the idea that epidermal AHH activity is a major determinant of the development of skin cancer. Our hypothesis also has two further general consequences. Firstly, it raises the possibility that the incidence of systemic cancer may be less in patients with psoriasis. We do not yet know to what extent the impaired activity of AHH, which we find to be a characteristic of psoriatic skin, is specific to the skin or shared by other tissues. For example, if AHH activity in lung is important in determining bronchial carcinomas among smokers, it would be worth investigating whether the incidence of lung cancer is lower among patients with psoriasis who have a comparable history of smoking. The incidence of other cancers associated with environmental carcinogens in patients with psoriasis requires study.

The second consequence concerns the reason for the persistence of psoriasis. Psoriasis is probably transmitted as a simple dominant trait (although several other genetic variants have been

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proposed). Rashes are socially unacceptable, have an adverse effect on self-image,^{5 6} and might therefore be expected to have a similarly adverse effect on evolutionary selection.⁴ We must therefore consider the possibility that psoriasis has persisted because it offers a genetic advantage—namely, the decreased AHH activity of psoriatic skin—which reduces the incidence of cancer of the skin and perhaps of other organs.

A hypothesis which explains known facts is good, but one which suggests further experiments is better. Our proposal that the incidence of skin tumours is likely to be low in psoriasis because of a reduced activity of skin AHH in that disease, opens the question rather than closes it.

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Reading for Pleasure

From lecture to reference

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I once had the pleasure of treating a direct descendant in the male line of Sir Thomas Gresham, to whom was imputed the "law" which declares that bad money drives out good. I think this principle can be applied more widely than to coin of the realm—for example, in many matters of administration the short-term inescapable drives out the long-term planning, which, in the end, is more important. And when it comes to reading, there is a certain tendency for the turgid essential to encroach on what might otherwise be read for pleasure.

I might well be asked at this point, "Why, then, are you writing this article?" I have two rationalisations to offer. I do, in fact, make time for leisure reading, basing myself on Voltaire's maxim, "Le superflu, chose si necessaire." And also, thank goodness, the dividing line between what one has to read and what one wants to read is far from absolute. If, for example, it is assumed that we ought to read letters sent to us, then many of those which I receive are a pleasure to read, though I am getting a little tired of fluoride (especially when the same letter appears half-a-dozen times from different directions). And again, it would surely be admitted that the editor of a book should read the chapters in it, even though they appear successively as manuscript, as galleys, and finally on pages (and "finally" may be a long time); but I must be an addict, because I still extract pleasure even at the page-proof stage. Finally, the books which come in the way of business often give pleasure as well; indeed, the first two books which I am going to mention both fall in this category.

In the way of business

By a curious coincidence, they were reviewed in successive issues of the *British Medical Journal* (20 and 27 January), so I may be absolved from attempting to summarise their contents. As Tony Smith points out in his review of Colin Dollery's Rock Carling Lecture on *The End of an Age of Optimism; Medical science in retrospect, and prospect*, the two books adopt the same device, that of a mock trial with medical science (and to a large extent in John Bradshaw's book, medicine in general) in the dock. In *Doctor on Trial* the judge (whom I presume to be in sound physical health) declares "I find Western doctors today are certainly more productive, directly or indirectly, of ill health, in every sense, than of health; and therefore in the terms of the brief of this court I have no hesitation at all in finding doctors 'Guilty.'" Of course, a considerable part of John Bradshaw's case is directed against "high-technology society" in general. But he blames doctors, as responsible members of society, for failing to protest against the ills, as he sees them, of life as we lead it today. He allows that the generality of doctors are "conscientious, hard-working, kind and competent by their standards"; and that, in mitigation, doctors may be "unwittingly guilty." But he clearly thinks that medicine is on the wrong track.

I had the pleasure of hearing the Rock Carling Lecture delivered, as well as of reading the monograph later. Unlike John Bradshaw's book, but like Archie Cochrane's earlier Rock Carling Lecture, the monograph can be read at an enjoyable sitting—it might even be on a train journey, with a bonus of extra time such as is not unknown these days. It would be strange indeed if I did not find the Dollery analysis more appealing than the Bradshaw one; but I have a puritan background which drives me to read books with whose thesis I tend to disagree. Sometimes, I amuse myself by picking out the contention that I find most unacceptable. With Ivan Illich in *Medical Nemesis*, my crux came with his easy, and no doubt