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The melanoma epidemic: reality and artefact

Warrants a reappraisal of the relation between histology and clinical behaviour

Skin watchers have their own equivalent of the Heisenberg uncertainty principle. Just as you can't know exactly both the momentum and the position of a single electron, once you excise a pigmented lesion and know its histology you forfeit the chance of knowing what would have happened if you had left it in situ; progression, metastasis, or even involution are all possible. Removal of pigmented lesions is now one of the commonest surgical procedures and has radically changed the pattern of referrals to dermatologists. Epidemiological studies show a dramatic increase in histologically confirmed melanomas[1] and raise the important questions of whether the increase is real or a diagnostic artefact and whether we should reconsider the relation between sun exposure and melanoma.

The incidence of melanoma has increased by 3-7% per year from the mid-1950s to the early 1980s.[1-3] These changes have been seen in both sexes and in a large number of different caucasian communities in both the northern and southern hemispheres.[1-5] A smaller rise has also been seen in mortality, with a reduction in case fatality from an estimated level of over 85% in 1925[3] to under 20% today. Cohort analyses show, perhaps surprisingly, that mortality from melanoma rose from the 1890s to the 1950s and then started to decline, with forecasts that the overall mortality from malignant melanoma will peak early in the next century.[1-3 5] These cohort effects are not easily explained by changes in leisure activity. However, more recently (from the early 1980s onwards) several studies have shown steep rises in the incidence of melanoma, of 15-43% per year; in parts of New South Wales a doubling of histologically confirmed melanomas has been reported over a two year period.[1 4 6]

Armstrong suggests that these recent steep increases cannot be solely attributed to earlier diagnosis, changes in histopathological criteria for melanoma, or an increase in the proportion of excised lesions being referred for histological opinion.[1 4 6 7] In the case of New South Wales, he argues that since the increase in detection and removal of thin lesions has not been followed by a reduction in incidence of thicker lesions (which one might expect if the increase was due to earlier case ascertainment), this apparent epidemic of melanoma represents in part an increasing recognition of a pre-existing non-metastasising but invasive form of melanoma. The presence of such a lesion should not be surprising. In many, if not most, cancer systems the majority of dysplastic lesions do not progress to clinically relevant malignancy. Perhaps the clearest example is squamous cell cancer of the skin, where careful epidemiological studies have shown that, despite the presence of multiple genetic changes,[8] over 99·9% of actinic keratoses fail to progress to invasive tumours in any one year and as many as 25% may regress.[2]

Understanding the relation between melanocytes, naevi, and melanoma is considerably more confusing: some argue that melanomas are nearly always derived from pre-existing naevi,[9] while others argue that this is a rare event[10]; some believe that melanomas in the radial growth phase are incapable of metastasis (although what percentage of radial growth phase proceeds to vertical growth phase is unclear)[9]; and the never ending change in terminology for atypical or dysplastic naevi betrays the difficulty in relating histology to clinical behaviour.

Does questioning the relation between histopathological description and clinical behaviour have implications for those seeking to persuade people to change their attitude to sun exposure? The answer is surely "yes." The arguments relating melanoma to sun exposure are well rehearsed,[2] but the relation is not nearly as clear cut as it is between sun exposure and squamous cell malignancy. Most melanomas occur on skin that is only intermittently exposed; individuals with higher continuous sun exposure have lower rates than those exposed intermittently; and there seems an important interaction between skin type and incidence of melanoma. There is much else that is unclear[11]: we do not understand which part of the sun's spectrum is responsible for melanoma, nor the relative importance of ultraviolet radiation to mutagenesis, tumour promotion, or impairment of cutaneous immunity in the pathogenesis of melanoma.

The need for such understanding is underlined by models that predict that changes in the pattern of leisure exposure to the sun or that the use of sunscreens may actually increase rather than decrease melanoma risk.[12] There is after all no robust empirical evidence to defend most health promotion in this area. It has been suggested that the antithesis of science is not art but politics[13]; melanoma is perhaps an example of the two having become mistakenly intertwined. An amicable separation is required. The certainties of Health of the Nation and "slip-slap-slop" already look a little shaded: molecules care little for consensus.

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Minocycline for acne

First line antibacterial treatment of acne should be with tetracycline or oxytetracycline

See p 169

Acne is sometimes severe enough to cause psychological and physical scars, but for the most part it is a physiological inconvenience and few would risk their lives to be free from it. The drugs generally used to treat it should not, therefore, cause serious adverse effects. Minocycline has been promoted as a useful drug for treating acne because it is well absorbed, even when taken with food, and it need be taken only once or twice a day. However, there is increasing evidence that it can sometimes produce severe adverse effects.

The series of seven patients reported by Gough *et al* (p 169) provides more evidence that minocycline causes an unusual form of drug induced liver disease, in which hepatitis, sometimes with the histological features of chronic active hepatitis, is associated with polyarthralgia and positive antinuclear antibodies.[1] As would be expected with drug induced systemic lupus erythematosus, tests for antibodies to DNA were negative or only weakly positive, and the patients recovered within three months of stopping treatment with minocycline. Drug induced chronic active hepatitis is rare. It has been reported with the laxative oxyphenisatin (which is no longer widely used) and with nitrofurantoin, methyldopa, and diclofenac.[2] Most cases described in the literature have been in women.

The current series is augmented by data from spontaneous reports to Britain's Committee on Safety of Medicines of adverse reactions to minocycline, describing eight patients with systemic lupus erythematosus, 15 with hepatitis, and one suffering both reactions. Some of the adverse hepatic effects may have been due to fatty infiltration of the liver, similar histologically to that seen in Reye's syndrome and known to occur with high dosages of tetracyclines, especially in pregnancy. This reaction has previously been considered rare with minocycline.[2] One case report incriminated intravenous minocycline,[3] but cases have also been reported in association with oral minocycline.[4]

Minocycline has been implicated in another rare adverse reaction that is likely to have an immunological basis, eosinophilic pneumonitis. Patients develop dyspnoea, cough, and fever, and there is radiological evidence of pulmonary infiltrates, with eosinophilia in bronchoalveolar lavage fluid or peripheral blood.[5-7] This reaction seems to resolve within a few weeks of stopping minocycline.

Cases with mixed features have been reported. One patient suffered a febrile illness with pneumonitis, hepatitis, and a positive test for antinuclear antibody with each course of minocycline.[8] In another patient hepatitis was accompanied by eosinophilia.[4] A patient with pneumonitis and arthralgia, positive for antinuclear antibody, has also been described.[9]

Reports of immunological adverse effects with tetracycline and oxytetracycline are sparse or absent, though there is a suspicion that tetracycline can aggravate pre-existing systemic lupus erythematosus. Patients who have suffered immunological reactions to minocycline can nevertheless be treated successfully with tetracycline[8] or oxytetracycline (unpublished observations). Other adverse effects specific to minocycline are blue-black hyperpigmentation affecting the skin, mucus membranes, nails, adult teeth, and internal organs, which is due to the deposition of black metabolites of the drug,[10] and dose dependent vestibular disturbance.[11]

All tetracyclines are contraindicated in pregnancy because they are deposited in the teeth and bones of the fetus. Benign intercranial hypertension is another potentially serious adverse effect of this class of antibacterial drug, and treatment should be withdrawn promptly if patients develop headache and signs of raised intracranial pressure.

Minocycline is widely used, and serious reactions are rare. However, its unusual propensity for causing immunologically mediated reactions may make it less safe than other tetracyclines, and this should be taken into account when treating essentially benign conditions such as acne. It is also very expensive, as Gough *et al* point out.[1] Tetracycline (or oxytetracycline) in a single or divided dose of 1 gram daily is effective and tolerable for most patients who require a systemic antibacterial agent to treat acne.[12] Absorption will be best if the tablets are taken with a glass of water at least half an hour before food. Prescribers should explain that the benefits will be seen only gradually, and treatment for several months is necessary. Tetracycline or oxytetracycline will be cheaper, and perhaps safer, than minocycline, which can be reserved for those patients who do not improve with one of the first line drugs.

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