shown to produce excess IgA.³ The abnormal production seems, then, to affect both the mucosal and non-mucosal compartments. The IgA in the serum of patients also differs qualitatively from that in normal subjects, and these differences are reflected in the IgA deposited in the kidneys⁴: it has an increased negative charge and an increased ratio of λ to κ light chains, and its carbohydrate content is abnormal—a portion is galactose deficient. IgA eluted from glomeruli and in the circulating complexes is polymeric and of the IgA₁ subclass; the other subclass, IgA₂, which is mainly produced in mucosae, is not found. The meaning of these findings is not clear.

The failure to detect IgA₂ suggests that the main source of glomerular IgA is not mucosal. It may be the physical changes in the IgA molecule that increase its deposition in and reduce its clearance from the glomeruli, which have receptors that bind to the heavy chain of IgA. The differences in the charge and class of IgA in IgA nephropathy might be explained by a particular antigen or antigens driving the selection of B cells that produce IgA, or some dysregulation of production of IgA producing excess IgA, with these characteristics.

How might this dysregulation occur? Again, two possibilities can be considered. The first is through T cell activity, which influences the production of IgA by B cells in various ways. Several interleukins (produced by T cells) regulate production of immunoglobulin, and among these is interleukin 6, which increases production of IgA. Increased concentrations of interleukin 6 have been found in the blood and urine of patients with IgA nephropathy. A second possibility is that the dysregulation of production of IgA is genetic. Research studies have given conflicting results. Genetic dysregulation would fit with the familial incidence of IgA nephropathy and the abnormalities of production of IgA in healthy relatives of patients.

One way forward in understanding a human disease is to study an animal model. Several models of glomerular deposition of IgA have been developed, but the animals mostly do not develop glomerulonephritis, and the results are not yet answering fundamental questions.

With all these uncertainties about the aetiology and pathogenesis of this disease, can it be treated? Neither prevention nor cure is yet possible, but rigorous treatment of hypertension will slow progression of the disease, as it will for any chronic renal disease. The therapeutic reflex to treat any

"immune" disease with immunosuppressive drugs has largely been unfruitful: the two exceptions are the uncommon acute crescentic variety of IgA nephropathy and some recent evidence that alternate day treatment with prednisone may slow progression.⁵ Phenytoin has the curious property of diminishing serum concentrations of IgA. A trial of this drug in 1980 showed no benefit,⁶ but recent long term follow up of the cohorts has suggested that progression of IgA nephropathy may have been slowed.

Tonsillectomy has been recommended with the aim of removing a source of increased production of IgA or a portal of entry of antigen driving production of IgA, or possibly both, and this might stabilise the renal disease. Certainly the serum concentration of IgA does indeed fall postoperatively.⁷ Prospective trials to evaluate these measures are now needed. Secondary IgA nephropathy—which is associated with such conditions as ankylosing spondylitis, coeliac disease, dermatitis herpetiformis, and, most recently, AIDS—does not seem to respond to treatment available for the underlying disorder.

Possibly the immunohistological diagnosis of idiopathic IgA nephropathy is simply a renal phenotype that represents several different disorders. Let us hope, then, that when the time comes for the 50th anniversary of IgA nephropathy the idiopathic form will have disappeared from our terminology and that specific treatments—for example, to eliminate particular B cell clones that produce IgA—will be available.

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Sunburn and melanoma: how strong is the evidence?

A history of frequent sunburn modestly increases the risk of melanoma

Melanoma—both its incidence and its mortality—has been increasing in many populations around the world recently.¹ Even higher rates have been predicted as a result of the depletion of stratospheric ozone.² Many agencies around the world are now developing programmes to prevent melanoma in the future. For example, the control of skin cancer (including melanoma) is included as one of the targets in the *Health of the Nation*.³

Preventing disease relies on knowing both its cause and practical and cheap ways of either avoiding the cause or blocking its effect. Most people attribute the rising incidence of melanoma to social and behavioural changes this century that have resulted in increased exposure to sunlight.⁴ The

fashion for a suntan, associated with increasing public acceptance of decreasing proportions of the body being covered while outdoors, has led to large numbers of people being exposed to sufficient sunlight to cause sunburn during leisure hours.⁵

Exposures sufficient to cause sunburn, particularly in childhood, have been targeted by most educational programmes as the main changeable component in the process that leads to melanoma in people who are constitutionally predisposed to develop it.⁶ But just how strong is the evidence that exposure that is sufficient to cause sunburn is a risk factor for melanoma?

The epidemiological evidence linking sunburn with

melanoma is complex. During the past decade more than a dozen studies have compared the histories of sunburn of patients with melanoma and controls. Because of considerable variations in design and method and differences in the definition of sunburn it is difficult to quantify a single estimate of risk from all these studies. Moreover, the problems of recall bias and misclassification of exposure inherent in retrospective studies demand cautious interpretation of the results.

Six large, population based, case-control studies conducted in Australia,^{7,8} Europe,^{9,10} and North America^{11,12} provide the most complete and comparable data on sunburn and melanoma. Each study had a well defined base and appropriate controls and ascertained only incident cases of melanoma. In addition, the similarity of definition of sunburn provides a reasonable basis for comparison.

The unadjusted relative risk of melanoma for people reporting frequent sunburns throughout life was increased two to threefold in five of the six studies (no crude data were available for the Western Australian study⁸). Adjusted relative risks were less consistent across the studies, but these depended on the choice of confounding variables used in the final analysis. Skin type (that is, the susceptibility of the skin to burning) was included as a confounder in three studies, which substantially reduced the strength of the association. Green *et al.*⁷ and Weinstock *et al.*¹² however, asserted that sunburn is a biological marker of high dose ultraviolet radiation penetrating to the melanocytes at the base of the epidermis, regardless of the degree of pigmentation in the epidermis. If this argument is pursued it follows that skin type is a determinant of sunburn and therefore should not confound the observed relation between melanoma and sunburn. The studies by Green *et al.*,⁷ Weinstock *et al.*,¹² and Osterlind *et al.*⁹ each retained a clear association between sunburn and melanoma after adjustment for factors other than skin type.

These studies therefore suggest an association between sunburn and melanoma, but the increase in risk is modest. What cannot be determined from these studies is whether the recall of sunburn is merely a marker of other substantial, but unremembered, exposures to sunlight. Thus the association may reflect heavy exposures in general that did not necessarily result in sunburn. Also the possibility of greater reporting of sunburn by people with melanoma compared with controls cannot be ruled out.

Another important question is whether the risk related to sunburn is constant throughout life or whether a critical period exists during which exposure is more harmful. In Italy Zanetti *et al.* reported a fivefold increase in risk associated with sunburn in childhood after controlling for episodes of sunburn later in life.¹⁰ Significantly increased risks associated with sunburn in childhood have also been reported in the United States, England, and Denmark.^{9,12,13} On the other hand, a Scottish study suggested that sunburn in adulthood may also be a contributing factor.¹⁴ (This study did not consider childhood exposure in its analysis.)

Once again, it cannot be determined from these data

whether the explanation is a specific and critical age related sensitivity to sunlight in childhood or a difference in dose. Recent memory of sunburn in adults is likely to be more accurate than past memory of sunburn in childhood. Past memories may merely reflect a global recall of considerable exposure in childhood; children have more leisure time than adults and are more likely than adults to have their clothes off during that time.

What do these data mean for the programmes that are being developed and delivered at present? They offer some support for the view that we should recommend reduced exposure to sunlight sufficient to cause sunburn, particularly in childhood. Migration studies showing a substantially reduced risk of melanoma in people who were protected from strong sunlight in childhood also support special precautions in childhood.¹⁵ Whether preventing only sunburn severe enough to be remembered many years later will reduce appreciably the incidence of melanoma is debatable. Nevertheless, in most European countries and the northern United States there seems to be a case for targeting programmes at behaviours that lead to episodic exposure to strong sunlight, particularly on such occasions as holidays in the Mediterranean, Caribbean, or Asian-Pacific regions.

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