Though an excessive consumption of carrots is the most common cause of pigmentation in healthy people, other vegetables and fruit have also been implicated—for example, a Japanese woman who ate 1200 oranges within six weeks developed an intense yellow coloration, a condition described as aurantiasis.

Hypercarotenaemia in itself may not be harmful but persons eating such a bizarre diet may easily develop other nutritional deficiencies. They may, for instance, simply be taking in too little energy. Cases of hypercarotenaemia have been reported due to an inherited failure to convert carotene to retinol; such patients may develop a deficiency of vitamin A.[2] A few other causes of hypercarotenaemia have been reviewed by Cohen.[3]

The death of a 48 year old man was widely reported in the press some years ago. The coroner attributed death to addiction to carrot juice. In this instance, however, the dietary regimen that eventually proved fatal included not only large quantities of carrot juice but also up to six tablets of retinol acetate (up to 90 mg retinol) daily.[4] A combined overdosage of both retinol and carrots is most unusual. Possibly addiction to carrots may have reduced the patient's intake of more nourishing food.

Capsules of Orobronze, which contain a carotenoid derivative canthaxanthin, are being used as a suntanning agent. This compound discolours plasma orange—an effect which has caused surprise and alarm in blood transfusion centres, since the colour is noticeable in the plasma of blood donations received from people who have consumed the capsules for only four days and it continues for a further four weeks after finishing the course. The plasma discoloration may mask haemolysis within a plasma sample but otherwise seems to be harmless.[5]

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Mesangial IgA nephropathy

Diffuse deposits of immunoglobulins in the glomerular mesangium associated with focal and segmental glomerulonephritis were described first in London in recurrent haematuria in childhood.[1] Probably many of these children had mesangial IgA associated nephropathy, a condition described two years later by Berger and colleagues, in which diffuse mesangial IgA deposits are associated with focal and segmental proliferative glomerulonephritis.[2,3]

In many countries mesangial IgA associated nephropathy is now recognised as the commonest form of glomerulonephritis.[4-10] Early reports from Britain suggested that it was infrequent[11]; nevertheless, in Scotland a recent study has found that, as in other countries, mesangial IgA nephropathy accounted for roughly one fifth of all cases of primary glomerular disease.[12] The immunopathogenesis and causal mechanisms in mesangial IgA nephropathy have recently been reviewed by Clarkson *et al*.[13]

Early reports suggested that the course was benign, particularly in children. Over the past decade, however, it has become apparent that sometimes the condition progresses to renal failure.[14] Mesangial IgA glomerulonephritis accounts for just over a fifth of all biopsy proved glomerulonephritis causing end stage renal failure in Australia,[15] and death or deterioration to end stage renal failure has been reported in half of patients aged over 20.[16]

We have recently reported the clinical course in 244 adults with mesangial IgA associated with nephropathy, confirming the poor prognostic implications of hypertension, heavy proteinuria, and impaired renal function—all of which are usually late manifestations.[17] We identified sclerosis of one in 10 glomeruli in the first biopsy specimen as a more powerful predictor of subsequent deterioration than any of the above (relative risk = 3·7). Because half of our patients had no symptoms and were discovered only because of abnormalities of the urine detected on routine testing, the time of onset could not be identified. A history of proteinuria or haematuria was obtained in three fifths of patients, and in one patient this had been present for as long as 28 years. The implication that the disease may persist over many years was confirmed in that clinical resolution occurred in only 15 of 217 patients followed up for a mean of five years. Although these 15 patients lost their proteinuria and microscopic haematuria, subsequent biopsy specimens in all five showed persisting mesangial proliferative glomerulonephritis and mesangial deposition of IgA. Hence probably once the condition has been diagnosed the histological lesions persist indefinitely—unlike those of poststreptococcal glomerulonephritis, which resolve rapidly.

Clearly we need to identify prognostic features in the individual patient before he develops renal impairment, since only in patients with disease that is likely to progress is therapeutic intervention justified. As no treatment has been shown to be effective, however, therapeutic intervention should be limited to controlled trials. In our series urinary erythrocyte counts consistently above 10^5/ml were associated with the highest risk of subsequent functional deterioration. The presence of glomerular crescents in the first biopsy specimen was another index of "activity," rather than advanced disease, which carried a high relative risk of deterioration. Normally persisting high urinary erythrocyte counts indicate continuing activity in the form of focal and segmental crescents. We have found glomerular crescents in almost four fifths of biopsy specimens in patients with over 10^6 urinary erythrocytes/ml and in all when biopsies were performed during an episode of macroscopic haematuria.[18]

Whether macroscopic haematuria is a poor prognostic feature is controversial. It is the presenting symptom in 80–95% of children with mesangial IgA nephropathy, but in only 40% of adults (predominantly young men); hence this feature is clearly related to age.[19,20] In our age matched group of adults those with macroscopic haematuria had a significantly higher serum creatinine concentration than those with no such history[18]; nevertheless, a recent large series from Italy has shown a better prognosis in the group with recurrent macroscopic haematuria.[21] Others have also reported a benign course in patients with recurrent macroscopic haematuria, but in most studies the patients with this feature were significantly younger.[7,22-25] In the study by Clarkson *et al*, for example, the mean age of patients with macroscopic haematuria was 27, whereas patients with asymptomatic proteinuria discovered on routine tests had a mean age of 38 and, not surprisingly, a higher serum creatinine concentration.[7]

The clinical picture of mesangial IgA nephropathy which emerges is persistent glomerulonephritis which begins in

childhood or early adult life and does not resolve. Though four fifths of patients survive for at least 10 years, progression to end stage renal failure continues, so that only half of patients are alive with functioning kidneys at 20 years.[16] Fifteen of our 19 patients who developed end stage renal failure had impaired renal function at presentation and progressed to renal failure over a median period of only 2·5 years. In 58 of our patients who deteriorated, however, the calculated time for progression to renal failure ranged from five to 25 (median 17·2) years.

Just over a quarter of patients followed up for at least a year had deterioration in renal function but other studies have shown that when followed up for 10 years or more half deteriorate.[16] The long term prognosis may, however, be excellent, some patients showing no functional or histological deterioration over 20 years. (At the other end of the spectrum, a small group of patients show rapid deterioration.[26,27])

The results of treatment have been disappointing. In patients with disease running a rapidly progressive course steroids, cyclophosphamide, and plasma exchange have been tried with some anecdotal accounts of improvement. We have found that, although renal function improves during plasma exchange, it deteriorates abruptly when plasma exchange is stopped.[26] Tonsillectomy and phenytoin may produce some benefit, and of particular interest is phenytoin because it significantly lowers the serum IgA concentration.[28,29] Although Clarkson *et al* did not show any benefit from phenytoin,[30] a recent controlled trial from Spain showed a clear cut reduction in episodes of macroscopic haematuria and urinary erythrocyte counts.[31] Our data suggest that such a reduction reflects a reduction in the number of glomerular crescents.[18] Circulating IgA immune complexes are also reduced by phenytoin and these almost certainly have a role in the progression of IgA nephropathy.[13] In a controlled study we observed reduction in the urinary erythrocyte count in the group treated with doxycycline 100 mg daily for 12 months.[32] Recently a report from Japan has documented a study in two groups of patients with impaired renal function in a trial of eicosapentaenoic acid.[33] Significant benefit was reported in the treated group, and the simplicity of using fish oil rather than immunosuppressive drugs to treat glomerulonephritis has great appeal.

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Lung biopsy

Samples of lung tissue may be obtained through the bronchoscope—transbronchial lung biopsy, brush biopsy, and bronchoalveolar lavage; through the skin—needle aspiration, screw needle biopsy, cutting needle biopsy, and high speed trephine biopsy; through the thoracoscope; and by open lung biopsy.

Transbronchial biopsy is commonly used to investigate diffuse lung shadowing. Initial enthusiasm for the technique has been tempered by disappointing results in some conditions, such as fibrosing alveolitis, where recognising the pattern of lung inflammation is so important.[1,2] The overall diagnostic rate is 38-64%,[1-4] but it is higher in conditions with specific histological features such as sarcoidosis (67-88% positive[1,2,5]), diffuse malignancy (67-80% positive[1,2]), opportunistic infection,[1,6,7] and alveolar proteinosis. Other useful techniques that may be employed at bronchoscopy include bronchial biopsy (often giving positive results in sarcoidosis and diffuse malignancy), brush biopsy,[6,8] needle aspiration,[9] and bronchoalveolar lavage.[1,10,11] The last may be particularly helpful in diagnosing opportunistic infection. In one study 15 of 16 episodes of infection in immunosuppressed patients were correctly diagnosed with lavage.[10] Complications of transbronchial biopsy are uncommon but include the hazards of bronchoscopy.[12] Pneumothorax occurs in 3-5% of patients; it is more common in those with pulmonary fibrosis.[1,4,5,8] Clinically important haemoptysis is uncommon except in uraemic patients.[6,8] Postbronchoscopy pneumonia and fever are occasionally reported,[5] and patients at risk of endocarditis should receive antibiotic prophylaxis. The mortality has been estimated as 0·2%.[2]

A percutaneous method is preferable to transbronchial biopsy for investigating pulmonary nodules not seen bronchoscopically. With percutaneous needle aspiration adequate samples for cytological and microbiological exami-