good control but leave open the risk of acute, severe exacerbations.

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Oxalate, livers, and kidneys

Combined renal and hepatic transplants transform the outlook in primary hyperoxaluria type 1

The incidence of calcium oxalate nephrolithiasis is reaching epidemic proportions in Western societies, in which it is usually associated with idiopathic hypercalciuria. Many of the patients who have recurrent calcium oxalate stones have hyperoxaluria, which, although mild, assumes greater importance because of its disproportionate effect on the solubility product for calcium oxalate.[1,2] A few patients, however, present with particularly aggressive recurrent oxalate urolithiasis caused by excessive oxalate biosynthesis due to deficiency of hepatic peroxisomal alanine:glyoxylate aminotransferase (primary hyperoxaluria type 1). These patients usually present in childhood and are dead by the age of 30. Until recently their prognosis was hopeless, but it has been transformed by aggressive dialysis with early renal transplantation, and, in particular, orthoptic liver transplantation.

Primary hyperoxaluria type 1 needs to be distinguished from type 2, a deficiency of D-glycerate dehydrogenase (glyoxylate reductase) which is not confined to the liver,[3,4] and from type 3, due to oxalate hyperabsorption.[5] The enzyme defect may be diagnosed biochemically in a specimen taken by percutaneous needle liver biopsy.[6] Occasionally patients present with end stage renal disease at any age from the neonatal period onward, and diagnostic liver biopsy is of particular help in these cases.

Pyridoxal phosphate is the cofactor for alanine:glyoxylate aminotransferase, and in some patients with primary hyperoxaluria type 1 pharmacological doses of pyridoxine reduce urinary oxalate concentrations. But for those not responding to pyridoxine the outlook has been bleak. Until recently the results of renal transplantation have been poor because the graft has been destroyed through rapid oxalate deposition in the perioperative period and the later development of obstruction due to calculi in the collecting system. Treatment by conventional dialysis regimens only prolongs life, and instead of dying quickly from uraemia patients die miserably after possibly years of increasing morbidity because of the serious effects of extrarenal systemic deposition of oxalate (oxalosis). These complications include painful osteodystrophy, cardiomyopathy and cardiac conduction defects, peripheral neuropathies and mononeuritis multiplex, synovitis, arteriopathy with disseminated occlusive vascular lesions, and ulcerating subcutaneous calcium oxalate calcinosis.

Once the creatinine clearance falls below about 25 ml/min/1·73 m^2 the combination of continued oxalate overproduction by the liver and reduced oxalate excretion in the urine produces a rapid increase in body oxalate concentrations and the development of systemic oxalosis.[7] Any acute reduction in renal function, produced, for example, by ureteric obstruction, may lead to extensive renal oxalosis and irreversible acute on chronic renal failure; patients who reach this stage when no plans have been made for their future management have a very poor prognosis.

It is now clear that the chances of successful renal transplantation are improved if it is performed while there is some useful residual renal function and before serious systemic oxalosis has developed.[8] Vigorous perioperative haemodialysis to keep plasma oxalate concentrations as low as possible and maintaining high urine volumes throughout reduces the risk of stone formation. Two of our patients treated in this way have normal graft function four years and three and a half years after transplantation, and one has completed a successful pregnancy.[9] The risk of stone formation in the transplant can be reduced by diuresis and crystallisation inhibitors such as magnesium or phosphate ions, and any stones that do form can be dealt with by percutaneous nephrolithotomy or extracorporeal shock wave lithotripsy.

The definitive treatment of primary hyperoxaluria type 1 by simultaneous hepatic and renal transplantation was first successfully accomplished about four years ago; this patient remains in full time employment, with near normal renal function.[10] An earlier patient in whom biochemical correction was proved died from an opportunistic infection eight weeks after the operation.[11] About 30 further cases world wide have now been treated in this way, with gratifying results. The combined operation corrects the underlying defect in the liver and replaces the damaged end organ, the kidney, which is then no longer subject to attack by oxalate overproduction.

Heterotopic auxiliary liver transplantation has been proposed because it does not necessitate removing the whole of the patient's liver. Nevertheless, glyoxylate accumulating behind the metabolic block in the patient's liver peroxisomes is unlikely to reach the normal alanine:glyoxylate aminotransferase in the donor liver peroxisomes because lactate dehydrogenase, which catalyses the oxidation of glyoxylate to oxalate, is highly active in liver cytosol and blood plasma. Furthermore, competition from the patient's own liver, which functions normally except for the alanine:glyoxylate aminotransferase deficiency, would also militate against a successful liver graft in these patients.

These recent developments have raised several questions. Should these patients be offered an orthotopic liver transplant before renal damage has occurred?[12] Alternatively, should patients entering end stage renal failure be treated firstly by a kidney transplant alone, with aggressive perioperative dialysis and a well matched kidney from a living related donor, with hepatic transplantation being held in reserve? Finally, should the first step for a patient established on dialysis with the complications of oxalosis be a liver transplantation to cut off excessive oxalate synthesis followed by a kidney transplant later, when the miscible oxalate pool has been depleted by vigorous haemodialysis or haemofiltration? The reverse of this strategy, with renal transplantation 250 days before liver transplantation, has also been reported.[13] The relative merits of these strategies are still being evaluated. Clearly, however, the dramatic and curative advance was the application of orthotopic liver transplantation. These patients demand a high level of collaboration between several disci-

plines, and their care should be based in a few specialist centres that can offer the appropriate skills.

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Tanning with ultraviolet A sunbeds

Should be discouraged

Up to a fifth of British adults have used ultraviolet A sunbeds to induce artificial sun tans (CCE Meulemans, unpublished observations).[1] Yet a growing body of evidence indicates that such exposure may be harmful. To determine what the hazards are the British Photodermatology Group recently examined the data on the health effects of artificial ultraviolet A radiation and produced a set of guidelines for exposure.

Despite the sales talk ultraviolet A radiation is not uniformly effective in producing a tan. Ultraviolet A sunbeds generally produce a tan in people who tan well in sunlight (sun reactive skin types III and over),[2] but those who tan poorly or not at all or who are burnt easily by the sun (skin types I and II) are likely to be disappointed with the cosmetic results.[3,4] Moreover, up to half of all users develop minor annoying cutaneous effects such as redness, itching, and dryness.[3,4]

Some users have potentially more serious effects. People taking drugs or applying cosmetics with photosensitising potential and who then use ultraviolet A sunbeds may develop a photosensitivity reaction, generally an itchy or painful rash, sometimes followed by pronounced pigmentation.[5] Sunbeds can also cause the common photodermatosis polymorphous light eruption—a transient, irritating, papular reaction[4,6]—and they exacerbate light aggravated dermatoses, such as systemic lupus erythematosus.[7] Immunological changes, both cutaneous and systemic, have been seen after exposure to ultraviolet radiation from a sunbed.[4,8,9] Although these changes diminish immunological responses and, theoretically, immunological surveillance, their actual biological importance is unknown.

Excessive use of ultraviolet A sunbeds—defined as exposure for 30 minutes or more a week over several months—produces increased skin fragility and blistering.[10,11] It may also cause melanocytic lesions with malignant potential,[12,13] though these lesions have resulted primarily from using sunbeds at home, where the duration and frequency of use are likely to be greater than in a salon. In mice long term exposure to ultraviolet A radiation causes premature photoaging of the skin.[14,15] Although this effect has not been shown in human skin, it would be expected. Likewise, the non-melanoma skin cancer that has been induced in animals after long term exposure to ultraviolet A would also be expected in humans.[16,17] Extrapolation from animal studies and from epidemiological data on the incidence of non-melanoma cancer and exposure to sunlight suggests that the relative risk is probably small (<2) if sunbeds are used for no more than 20 half hour sessions a year through adult life,[18,19] but no data on humans support this estimate.

The data suggest that the use of ultraviolet A sunbeds is a weak risk factor in inducing melanoma.[20,21] Further studies are needed to confirm this and to establish the causal relation between pattern of exposure, the nature of the ultraviolet lamp, and melanoma.

Although many gaps in the knowledge of the effects of ultraviolet A radiation remain, the accumulating evidence suggests ever more strongly that the radiation has deleterious effects. The British Photodermatology Group has therefore recommended that the use of ultraviolet A sunbeds for cosmetic tanning should be discouraged. In particular several groups should not use them at all: children aged under 16; people who burn easily, do not tan, or tan poorly; those taking drugs or using cosmetics thought to be photoactive; those suffering from a skin disorder induced or aggravated by exposure to sunlight; those with a history of skin cancer; and those with risk factors for cutaneous melanoma. The risk factors include more than 20 benign pigmented naevi above 2 mm in diameter; a tendency to freckle; clinically atypical naevi; a history of severe sunburn, particularly in childhood or adolescence; and a family history of cutaneous melanoma. People who, despite this advice, want to use ultraviolet A sunbeds should not exceed two courses a year, each of no more than 10 sessions. Each session should last no longer than the time that it takes to produce just perceptible reddening of the skin eight to 24 hours later, up to a maximum of 30 minutes.

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