Erythropoietic protoporphyria

In the metabolic disorders grouped together as the porphyrias, one or more porphyrins are produced in excessive amounts; this is presumably due to a deficiency of one of the enzymes in the biosynthetic pathway that leads to haem, the iron-containing portion of the haemoglobin molecule. Simple precursors, such as delta-aminolaevulinic acid and porphobilinogen, are converted into cyclic compounds (which may sensitise the skin to light) and the metabolic pathway continues through the tetrapyrroles formed from porphobilinogen and ends with protoporphyrin IX; this combines with iron to form haem. Porphyrins are probably made in all cells of the body, but the main sites are the liver and bone marrow.

There are two broad groups of porphyrias. In the hepatic porphyrias excess porphyrins are found mainly in the liver, while in the erythropoietic group the excess is mainly in the red cells. One of the most common of these rather unusual conditions is erythropoietic protoporphyria, which is characterised by the presence of excess protoporphyrin in the red cells, where it can be detected by fluorescence microscopy. In affected people attacks of acute photosensitivity occur shortly after exposure to sunlight, often starting with a burning sensation that may be almost intolerable and soon followed by erythema and swelling. Between attacks there is usually little evidence of the disease apart from mild superficial scars and thickening of exposed skin.

Some patients have liver abnormalities as well as skin manifestations, and in a few the liver damage may be severe and even fatal. They may also develop gall stones pigmented by porphyrin. The relatives of these patients may have mild abnormalities of liver function. Needle-shaped crystals and minor histological changes may also be found in liver biopsy samples from patients whose liver function has appeared normal, but the clinical significance of this finding is not yet clear.

The diagnosis of erythropoietic protoporphyria may be suspected clinically from the history and from the skin lesions.

Finding a raised concentration of red-cell protoporphyrin and fluorescent red cells confirms the clinical diagnosis. Erythropoietic protoporphyria must be differentiated from other eruptions caused by light, including xeroderma pigmentosum. Treatment is difficult. Beta-carotene by mouth is widely recommended, but its value has been questioned.

Erythropoietic protoporphyria seems to be inherited as an autosomal dominant with partial penetrance; again the details are obscure. Latent forms exist, and these may be more common. The condition is widely distributed throughout the world; in the south of England it is the porphyria most often seen by dermatologists.

A national register of cases of erythropoietic protoporphyria is being set up (p 1508), and this should brighten the prospects for understanding the disease better. The register is intended to facilitate detailed follow-up of sufficient patients and some of their relatives, and so to clarify the natural history, prognostic factors, and genetic aspects. Effective trials of treatment should also now become possible.

Antihypertensive treatment in the elderly

Many physiological and pathological changes associated with advancing years modify both pharmacokinetics and the response to drugs in the elderly. Aged affects distribution, metabolism, and renal elimination of drugs and may cause changes in responsiveness. Doctors tend to prescribe more often for their elderly patients, who in turn are more likely to misunderstand or forget the prescriber's instructions, so the frequency of adverse drug reactions is hardly surprising—they are two to three times more common in patients over 60 than in younger adults. Since the incidence of hypertension increases with advancing years—and antihypertensive drug medication, once begun, is usually needed for the rest of the patient's life—treatment for hypertension is one of the main causes of drug-induced illness in the elderly. Clearly, therefore, treatment should be started only in the presence of well-defined and justifiable indications.

Hypertension is known to be an important risk factor for stroke and coronary heart disease in the elderly, but reducing the blood pressure has yet to be shown to diminish either morbidity or mortality. In 1973 the European Working Party on High Blood Pressure in the Elderly (EWPH) was set up to study this problem. Since then more than 600 patients over 60 with mild-to-moderate hypertension have been allocated to two groups in a double-blind multiple-treatment trial. Half the patients have been treated with a combination of hydrochlorothiazide and triamterene, methyldopa being added where control of blood pressure was not achieved; the other half have been given placebo.

A review of the results so far has shown a significant
Alcoholic heart muscle disease

The damaging effect of alcohol on the heart muscle has been shown very clearly in studies both on animals and in man.1-3 More recently, it has been found to have an adverse effect on skeletal muscle too.4 Biopsy specimens were taken from non-alcoholic volunteers maintained on a high-protein diet enriched with vitamins and repeated after one month of alcohol intake.5 No changes were found in the microscopic appearances of the muscle before and after alcohol consumption—but ultrastructural examination showed intracellular oedema, lipid droplets, excessive glycogen, deranged elements of sarcoplasmic reticulum, and abnormal mitochondria in the specimens after alcohol consumption. These are similar to those found in patients with heart disease due to alcoholism.6 8 (Since the term cardiomyopathy is now reserved for diseases of heart muscle in which no cause can be established,6 cardiac damage from alcohol is best termed "alcoholic heart muscle disease" rather than "alcoholic cardiomyopathy.")

The results of attempts to detect early myocardial damage from alcohol by biochemical tests have so far been disappointing.9 Estimations of the serum concentrations of creatine kinase and lactic dehydrogenase isoenzymes in 73 patients known to have alcoholism showed no examples of raised concentrations of the cardiac-specific isoenzymes.

Once the asymptomatic stage has passed, both acute and chronic forms of alcoholic heart disease may be recognized on clinical grounds and if alcoholic abuse is continued these may culminate in recurrent acute episodes of myoglobinuria and irreversible congestive heart failure.4 Even at the early stage the condition may be diagnosed with reasonable certainty if the patient admits to regular, heavy consumption of alcohol. In practice, however, alcoholism is seldom admitted, and the clinician is faced with the difficulty of distinguishing heart failure due to alcohol from that due to congestive cardiomyopathy. No specific morphological criteria distinguishing the two conditions have been defined in the heart,9 10 but advances have been made since the introduction of the "biotome",11 12 which has permitted small samples of endomyocardial tissue to be taken for analysis.

Patients with heart failure associated with alcoholism have been found to have negative indirect fluorescence and raised serum concentrations of IgA when compared with those whose heart failure was due to congestive cardiomyopathy. Biopsy specimens from patients with congestive cardiomyopathy showed preferential binding of IgG and IgA.13 In another study14 the content of lactate dehydrogenase isoenzymes (LDH) was analysed in biopsy specimens from patients with congestive cardiomyopathy and alcoholic heart disease. The patients were then grouped on haemodynamic criteria, when a higher proportion of LDH (H subunits) was found in those with alcoholic heart disease. This may prove a useful test for distinguishing the two clinical groups. Analysis of endomyocardial tissue samples has shown raised activity of enzymes such as creatinine phosphokinase, lactic dehydrogenase, and α-hydroxybutyric dehydrogenase in patients with alcoholic heart disease when compared with those with established congestive cardiomyopathy.15 16

These investigations are important, since accurate diagnosis has great relevance to prognosis. In alcoholic patients the outcome depends on the degree and stage of the damage to the heart (or skeletal muscle). Both preclinical and acute varieties of muscle damage are usually reversible if the patient stops drinking alcohol. Death may, however, occur in cases of permanent congestive failure or acute rhabdomyolysis and fatal myoglobinuria.4

Probably between 1% and 2% of chronic alcoholics reach the phase of heart failure.8 If they can be persuaded to abstain from further drinking the progression of muscle damage can be arrested or improved. Continuing the high alcohol intake, however, will eventually lead to irreversible myocardial damage, when the prognosis may then become poor. In contrast, patients with congestive cardiomyopathy almost invariably have a poor prognosis, with a 10-year mortality of 70-90%,16 although a few patients may recover normal or near-normal cardiac function.17

British Medical Journal, 1972, 2, 877.
Rubin, E, New England Journal of Medicine, 1979, 301, 28.