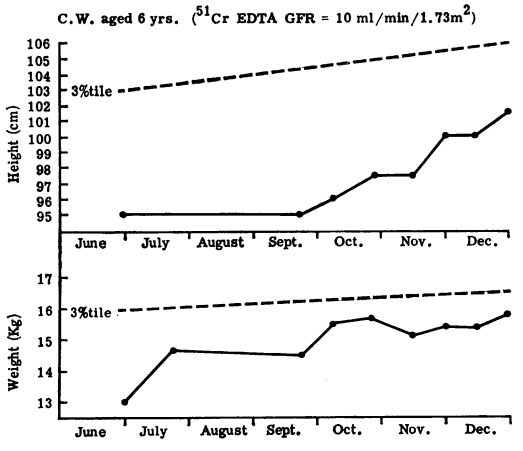

Fig 1 *Height and weight of a 6-year-old girl with renal failure due to obstructive uropathy. After peritoneal dialysis for 1 month she was given a diet containing 2·5 g/kg body weight of protein (74% of which was first class), and at least 100 cal/kg body weight. She began to grow one month after starting this diet and grew 5 cm in four months*

repeatedly to avoid hypercalcæmia and nephrocalcinosis. Manifestations of secondary hyperparathyroidism are usually controlled with vitamin D but if the plasma calcium and phosphate product rises above 70, soft-tissue calcification may occur; in this circumstance attempts to reduce the plasma phosphate with oral aluminium hydroxide and dietary phosphate restriction should be made before starting vitamin D. Vitamin D is discontinued when bone healing has occurred and is not continued prophylactically because of the serious dangers of hypercalcæmia.

Transfusion is not usually required in treating the anæmia of chronic renal failure unless demanded by symptoms; it may lead to immunization against transplantation antigens and possibly to serum hepatitis. The control of uræmia often leads to worthwhile increase in hæmoglobin levels (Shaw 1968).

Infection may lead to vomiting and dehydration and to increased protein breakdown with worsening of the uræmia. Infection of the urinary tract will lead to further renal destruction. Antibiotics and other drugs must be chosen carefully in patients with renal failure because so many are excreted by the kidneys. Tetracycline, in particular, is totally contraindicated for there is evidence that it will lead to further renal damage. Other drugs excreted by the kidneys such as kanamycin, gentamicin, phenobarbitone, digoxin, &c., can be used but the dosage must be determined in relation to the glomerular filtration rate, and where possible frequent monitoring of plasma levels is desirable. The penicillin group, cephalothin, chloramphenicol, erythromycin, phenytoin, medium-acting barbiturates and chloral hydrate can be given in the usual dosage as they have non-renal routes of excretion (Hollenberg & Epstein 1969).

Children with acidosis, infection, bone disease and anæmia do not grow normally (West & Smith 1956) but even if these abnormalities are corrected some children with renal failure still do not grow. Calorie intake is often inadequate in children with renal failure and Holliday (1970) has obtained resumption of growth by supplementing the diet with synthetic high calorie products (*see* Fig 1).

Finally, the pædiatrician also has a responsibility for the social and psychological problems which may affect the health and education of this group of chronically handicapped children.

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Meeting April 16 1971

Cases

Hereditary Angio-œdema

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P J W, boy born 22.6.66
Since the age of 1 year he has had attacks of œdema (eyelids, hands, arms and feet) spreading later to the abdomen and accompanied by severe abdominal pain. Attacks last for 24 hours and are followed by 24 hours of vomiting.

The parents are not blood relatives and show no evidence of œdema. There is one sibling, a boy aged 6, also asymptomatic. The paternal grandmother, now aged 58, has had attacks of angio-œdema since the age of 12 (Dr J W Paulley, personal communication).

Estimation of plasma C'1-esterase inhibitor (Dr P J Lachmann): P J W: enzymatically and antigenically 25% of normal. Grandmother: enzymatically 0, antigenically 45% of normal. These results confirm the diagnosis of hereditary angio-œdema (HAE) in both cases.

Comment

Hereditary angio-œdema is a rare disease, quite distinct from allergic angioneurotic œdema, and is inherited as an autosomal dominant trait. Clinically it presents with acute non-inflammatory œdema in skin, in subcutaneous tissues or in the mucosæ. In skin the swelling is hard and pale, may be painful and does not itch. In the gastrointestinal tract HAE causes severe abdominal pain, often with nausea, vomiting and/or diarrhœa, and may even lead to surgical intervention. In the upper respiratory tract it produces œdema of the glottis, trachea or larger bronchi which may lead to fatal asphyxia, in up to 25% of cases in some reported series (Hadjiyannaki & Lachmann 1971).

The acute attack tends to last 2–4 days and may recur at intervals varying from days to years. Precipitating factors seem to include local trauma or pressure, stress and psychological excitement, staphylococcal infections and other systemic infectious diseases in children.

Pathogenesis: The essential abnormality in HAE is a marked deficiency of the serum inhibitor of the activated first component of complement (C'1-esterase inhibitor), which is highly specific for the disease. This inhibitor also acts on several other plasma enzymes, e.g. kininogenase, PF/dil, plasmin and C1r, and can now be measured both antigenically and enzymatically. Diagnosis of HAE should not prove difficult if it presents with skin lesions, but there may be considerable difficulty if the symptoms are primarily mucosal.

C1, the first component of complement, can be separated into three sub-components, C1q, C1r and C1s. C1q carries the binding site for the immune complex Ag–Ab. C1r is the activator of C1 to C'1. C1s is the pro-esterase, and after activation exhibits enzymatic activity, and is therefore called C'1-esterase. Its only known substrates are C'2 and C'4, and it has no effect on other complement components or on cell membranes. It also increases vascular permeability, which may depend on production of anaphylatoxins as an eventual result of the formation of a little C'42a in solution (Lachmann 1968).

C'1-esterase inhibitor occurs in normal serum. It is an α_2-neuraminoglycoprotein which combines with the enzyme, probably at its active site, and inhibits both its enzymatic and its hæmolytic functions. It does not react with unactivated C1. It is known to play an important part in inactivating any C'1-esterase where it would destroy C'4 and C'2, thus giving rise to increased capillary permeability. It is also active against two other mediators of increased capillary permeability, kallikrein and PF/dil. Lastly, it inhibits plasmin activity and C1r (which is responsible for activating C1 to C'1). This inhibition is irreversible, and the inhibitor is irreversibly consumed in the process.

It appears probable that ε-aminocaproic acid (EACA) acts not only by inhibiting the activation of C1 to C'1, but also by having a C'1-inhibitor-sparing effect. This it does by preventing or diminishing the activation of any of the enzymes with which inhibitor reacts (C1r, C1, kininogenase, plasmin, PF/dil). By thus reducing the drain on the already short supply of inhibitor, it reduces the likelihood of its local exhaustion and therefore the incidence of attacks. Conversely, any condition which increases the activity of these enzymes will increase the drain of inhibitor and so predispose to attacks of HAE.

Treatment: Antihistamines are of limited value, reducing the severity but not the incidence of attacks. Small doses of methyltestosterone have been used with reported success.

In recent years two methods have been introduced on the basis of an improved knowledge of the pathogenesis of HAE:

(1) Transfusion of fresh-frozen, normal plasma during attacks. This is effective by providing additional supply of inhibitor. Dangers include possible transmission of serum hepatitis, and the theoretical possibility of introducing more substrate for C'1 and kininogenase, with the result that exacerbation of the attack may occur before improvement. It would obviously be better to transfuse purified inhibitor, but this might prove too expensive.

(2) Prophylaxis by treatment with EACA. This substance inhibits the activation and often the activity of plasmin and other serum esterases (Hadjiyannaki & Lachmann 1971) and also the activation of C1 to C'1 (mediated by C1r). It has been widely used as an antifibrinolytic agent (Nilsson *et al.* 1966) and is known to be free from major toxicity. By regular treatment with doses of 0·1 g/kg/day, both the incidence and the severity of the attacks have been reduced (Champion & Lachmann 1969). As any attack could produce glottic œdema, we propose to begin treatment of our patient now.

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(Meeting to be continued)