The porphyrias are a group of disorders resulting from decreased activity of the enzymes in the haem biosynthetic pathway, the clinical and biochemical manifestations being determined by which particular enzyme is deficient. One problem that is common to three of the porphyrias, however, is the acute neurological crisis. This occurs in variegate porphyria (VP, South African genetic porphyria), acute intermittent porphyria (AIP, Swedish type) and hereditary coproporphyria (HC), and in each case it represents the most serious event that can occur in the medical history of a porphyric patient. The excessive frequency of VP in South Africa makes a working knowledge of this condition essential to every South African practitioner. Sadly, however, this knowledge is lacking in many cases and every year many patients in whom the diagnosis has not been considered or who have been incorrectly managed are admitted to hospital. In this paper current concepts of the pathogenesis, clinical features and treatment of this disease are outlined.

Pathogenesis

A syndrome can only be managed scientifically if the pathogenesis of the symptoms is understood; unfortunately, little definite is at present known about this aspect of porphyria. The fact that α-aminolaevulinic acid (ALA) and porphobilinogen (PBG) levels are increased during acute attacks in all patients has led to a considerable amount of research on the role of these compounds in the production of the clinical features and treatment of this disease are outlined.

Pathology

The acute neurological crisis is the most significant complication of variegate and acute intermittent porphyria and hereditary coproporphyria. If it is managed correctly, the mortality rate should be negligible. An outline is given of the major symptoms and signs encountered in the acute attack, and the therapy which should be used for their relief is discussed. Mention is made of forms of treatment which may decrease the activity of the haem biosynthetic pathway and thus specifically influence the clinical problems.

Summary

The acute neurological crisis is the most significant complication of variegate and acute intermittent porphyria and hereditary coproporphyria. If it is managed correctly, the mortality rate should be negligible. An outline is given of the major symptoms and signs encountered in the acute attack, and the therapy which should be used for their relief is discussed. Mention is made of forms of treatment which may decrease the activity of the haem biosynthetic pathway and thus specifically influence the clinical problems.

Clinical features

Since much of the available therapy is aimed at symptomatic relief, the major symptoms of the acute attack will be described in turn, each in conjunction with the applicable treatment. We will conclude the review by discussing the few methods at present available specifically to affect the metabolism of the haem biosynthetic pathway and thereby influence the course of the illness.

Gastro-intestinal tract

The most frequent feature, occurring in 90% of attacks, is colicky and deep-seated abdominal pain. It may occur in any part of the abdomen and from there radiate to the back, thighs and even the chest. Nausea and vomiting occur very frequently, and the latter may continue for protracted periods. Constipation is a usual complaint and may be extreme, thus simulating acute intestinal obstruction. Examination of the abdomen reveals little to account for the severity of the symptoms, and a striking feature is the lack of rigidity or rebound tenderness. Some distension may be evident, however, and radiographs of the abdomen frequently show segmental dilatation and spasm.
Relief of pain is mandatory and morphine or pethidine may be necessary. In less severe cases aspirin or paracetamol can be tried. The vomiting should be controlled with chlorpromazine or prochlorperazine. Rarely, the constipation may be so severe as to need treatment, and here neostigmine or prostigmine may be useful.

Nervous system
This is the site of the most serious involvement. Perhaps the most common problem encountered is anxiety, which may be associated with considerable emotional lability; this is often a problem even in the absence of other neurological signs. Progression to confusional or frankly psychotic states can occur. These disturbing symptoms are best controlled with phenothiazines such as promazine or chlorpromazine. Generalized seizures may occur and in the acute situation these should be managed with intravenous benzodiazepines, the few anecdotal reports of their porthyphrinogenicity being inadequate reason for their being withheld when indicated. Involvement of the limbs is the most common objective evidence of neurological dysfunction. The first symptom may be pain in the muscles; this is followed by a motor neuropathy, usually of the lower motor neuron type, which spreads to involve all four limbs. The proximal muscles may be involved more than the distal ones, but the effect is usually symmetrical. The onset of bulbar involvement with aphonia and dysphagia heralds the more serious problems, and respiratory paralysis is the most dreaded complication. Less commonly involved are the cranial nerves (10%) and the sensory system, which is more frequently affected subjectively than objectively.

Clearly the most important aspects of the care of paralysed patients lie in the hands of the nursing staff and paramedics such as physiotherapists and occupational therapists. Particular care should be taken to avoid contractures. Patients should be assessed carefully for evidence of respiratory difficulty; positive-pressure respiration may be life-saving if introduced at the correct time. It must be stressed that clinical assessment is often inadequate for this decision and should be supplemented by the use of arterial blood gas measurements as well as basic tests of lung function, particularly the vital capacity.

Cardiovascular system
An almost invariable finding is hypertension and sinus tachycardia, which together with sweating are suggestive of an autonomous neuropathy. Hypertension rarely reaches dangerous levels and is usually transient. Beta-blockade is indicated for these problems; propranolol has usually been the compound chosen, doses of up to 600 mg/d being required.9

Biochemical abnormalities
The most frequent finding is severe hyponatraemia, which is often associated with hypokalaemia, hyperchloremia and azotaemia. This has often been attributed to inappropriate antidiuretic hormone secretion (SIADH),10 but this probably occurs very rarely and the total exchangeable sodium content of the body has been found to be low when measured.11 The condition probably arises as a result of salt loss through vomiting and inappropriate intravenous fluid replacement. Hyponatraemia and hypokalaemia may also present a problem. A careful clinical assessment of the state of hydration should be made, and this must be supplemented by measurement of the serum and urine sodium, chloride, urea and creatinine levels and osmolality. The majority of patients will require rehydration, and intravenous hypotonic or isotonic sodium chloride will usually be appropriate. Hypertonic saline will rarely be necessary. Fluid restriction is recommended in the very rare cases in which a true SIADH develops, but it must be stressed that this will be unusual. Potassium depletion must be corrected, but because of the potential dangers of intravenous potassium the oral route is preferred if possible.

Therapies specific for the acute attack
Apart from the above, which should be standard practice to any good physician, various specific remedies have been suggested for these patients. These are all aimed at depressing the activity of the rate-limiting enzyme ALA-S.

Carbohydrate loading. A high carbohydrate intake has been shown to be beneficial in the acute attack12,13 and to be associated with a fall in the level of porphyrin precursors in the urine14 and in ALA-S activity. A further postulated indirect mechanism is that hyperglycaemia may block the inductive effects of glucocorticoids on ALA-S.15 The carbohydrate is best given orally and an ideal preparation is Hydrol (Beecham), which contains 420 kcal (1764 kJ) in 390 ml of water, or Caloreen, which has the advantage of being tasteless. Two hundred grams of carbohydrate should be given daily. If the patient is vomiting intravenous carbohydrate can be used, and in this situation 20% dextrose has been found to be convenient.16 It is, however, necessary to give this via a central venous route to prevent thrombophlebitis.

Beta-blockade. This has been mentioned above for symptomatic relief, but in addition it has been suggested that propranolol may act specifically on haem biosynthesis, decreasing the activity of ALA-S in chick embryo liver cells in vitro.17 It has been suggested that the effect may be indirect via suppression of the effect of catecholamines.

Folic acid. It has recently been proposed that pteridine derivatives stimulate the activity of the enzyme PBG deaminase and this may be useful in patients with AIP.18 It has not been widely tested and should theoretically have no role in the treatment of patients with VP or HC.

Haematin. Finally, mention must be made of this compound which is scientifically the logical therapy for porphyria because haem is known to inhibit ALA-S activity. Its use was pioneered by workers in Minneapolis19 and they more recently recorded their excellent results with its use.20 Its predicted effect on ALA-S activity has been shown in leucocytes,21 and it may have more effect on the biochemical features than on the clinical response.22 Renal insufficiency has been reported as a complication following its use23 and it is also irritating to the veins. Moreover, the outcome in the majority of patients will be favourable without haematin and its routine use is not recommended. There may, however, be a place for its introduction in the occasional non-responsive patient.

Conclusion
It is clear that the combination of abdominal pain, anxiety and tachycardia is by no means specific for porphyria. Even without the neurological problems which are so suggestive of the syndrome, however — in this country, where there are at least 10 000 patients with VP — the diagnosis should at least be considered by the attending doctor. Moreover, the test for PBG in the urine is so easy to perform that it should be part of the clinical examination of any patient with acute undiagnosed abdominal pain. Using the therapeutic regimen outlined above, mortality from the acute attack at Groote Schuur Hospital, Cape Town, is extremely low. Sophisticated monitoring equipment may be necessary, however, particularly in the case of the unconscious patient in respiratory failure, and it is recommended that patients with acute attacks should be managed in large medical centres with access to the necessary
Measles notifications — the first year

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Summary

Measles is a major cause of childhood mortality in the developing world. Observed trends in the USA confirm the efficacy of a measles control programme. South Africa launched such a programme in 1975 with the introduction of free vaccine for all children. In order to enhance and monitor this campaign, measles became a notifiable condition on 24 August 1979.

Notifications received in the first year are reviewed and the observed patterns are discussed.

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Date received: 16 April 1981.

In South Africa developed and developing communities live cheek by jowl; all are equally susceptible to measles infection and practically everyone will contract measles unless adequately immunized. However, it seems that measles affects these communities in very different ways.

In a developed country such as the USA, measles is a mild illness with peak incidence in the 10 - 14-year-old group (Fig. 1, Table 1). In 1976 there were only 12 deaths due to measles in the USA, giving an overall case fatality ratio of 0.03%.

In developing countries, measles is recognized as a serious illness, occurring at a younger age and with a far higher mortality rate. Up to 30% of cases may occur in infants under 1 year old, and by the age of 5 years almost all children will have had measles. Measles is a leading cause of both hospitalization and death in children in developing countries. During periods of famine up to 50% of all childhood deaths may be due to measles, and case fatality ratios range from 5% to over 20% in hospital, and from 1.5% to 7% in the general community.

In South Africa some 2 years ago, the medical and lay press carried articles which gave prominence to the high death toll of measles, especially in the developing segments of the population. In 1975 there were an estimated 3 148 deaths due to measles.