Br. J. clin. Pharmac. (1989), **27**, 491–497

Acute intermittent porphyria in two patients on anticonvulsant therapy and with normal erythrocyte porphobilinogen deaminase activity

A. L. HERRICK, K. E. L. McCOLL, M. R. MOORE, M. J. BRODIE, A. R. ADAMSON[1] & A. GOLDBERG

University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT and [1]Royal Lancaster Infirmary, Ashton Road, Lancaster, LA1 4RP

1 Acute intermittent porphyria (AIP) is sometimes termed a 'pharmacogenetic' disease. Patients with genetic deficiency of the enzyme porphobilinogen deaminase are liable to develop acute attacks of porphyria if exposed to a variety of drugs.

2 Two patients are reported who had no evidence of deficiency of erythrocyte porphobilinogen deaminase yet developed typical attacks of AIP while on anticonvulsant therapy.

3 Normal activity of erythrocyte porphobilinogen deaminase does not completely exclude porphyria.

4 Acute porphyria should be suspected if clinical deterioration occurs during therapy with anticonvulsants, or other porphyrinogenic drugs, even in the absence of an underlying genetic defect in haem synthesis in peripheral blood cells.

Keywords anticonvulsant porphyria pharmacogenetic

Introduction

Acute intermittent porphyria (AIP) is the commonest of the acute hepatic porphyrias in the United Kingdom. It is the result of partial deficiency of the enzyme porphobilinogen (PBG) deaminase and is inherited as a Mendelian autosomal dominant trait (Goldberg *et al.*, 1987). As a consequence of this partial enzyme block in the pathway of haem biosynthesis, there is increased activity of the initial and rate-controlling enzyme δ-aminolaevulinic acid (ALA) synthase which is under negative feedback control by haem. During clinical attacks of porphyria and sometimes also during remission, there is overproduction of the porphyrin precursors ALA and PBG which are formed prior to the enzyme defect and these are excreted in excess in the urine.

Patients who have inherited the underlying genetic defect in the enzyme normally enjoy good health but if exposed to a variety of commonly prescribed drugs are liable to develop severe and potentially fatal attacks of acute porphyria. For this reason, AIP can be termed a 'pharmacogenetic' disease. Some patients, however, with the underlying genetic defect may take such drugs without ill effect and conversely others develop attacks without exposure to exogenous precipitants (Goldberg *et al.*, 1987).

We report two unrelated patients who had no evidence of any underlying genetic defect in the pathway of haem biosynthesis and yet developed biochemical and clinical evidence of acute intermittent porphyria while receiving anticonvulsant therapy.

Methods

Urinary ALA, PBG and total porphyrins in 24 h urine collections and faecal porphyrins were measured by the methods of Moore (1983) using

Correspondence: Dr K. E. L. McColl, University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT

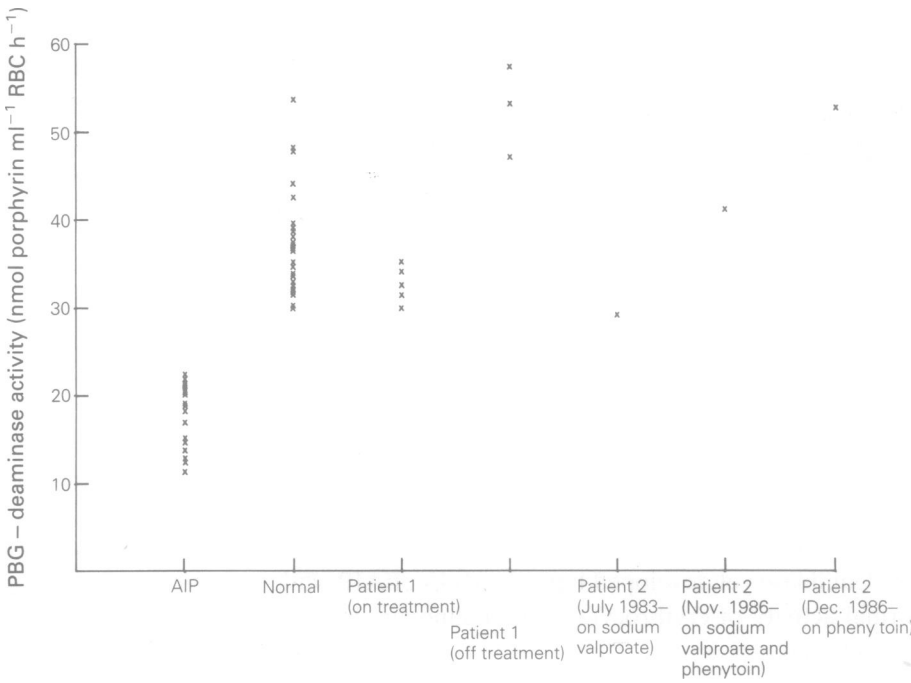

Figure 1 PBG deaminase activity in patients 1 and 2 on the different occasions studied. For comparison, the enzyme activities in 24 normal individuals and 17 patients with AIP are given.

standard kits (Bio-Rad Laboratories). Leucocyte ALA synthase was assayed by the method of Brodie *et al.* (1977a), erythrocyte PBG deaminase by the method of Piepkorn *et al.* (1978), and erythrocyte ALA dehydratase, the second enzyme of the haem biosynthetic pathway converting ALA to PBG, by the European standardised method (Berlin & Schaller, 1974). Anticonvulsant concentrations were measured by standard enzyme immunoassay (EMIT, Syva, Palo Alto).

To allow comparison with the cases studied PBG deaminase activity was measured in 24 normal subjects (10 males, 14 females, age range 17–81 years) and 17 patients with acute intermittent porphyria from 13 families (two males, 15 females, age range 15–59 years) (Figure 1).

Case reports

Case 1

The first patient who had been mentally retarded since birth was admitted aged 40 years with a 1-week history of mental confusion, not eating and passing dark urine. She had sufferent generalised tonic-clonic seizures since 2 years old and had been taking sodium valproate 1.2 g day^{-1} and clonazepam 3 mg day^{-1} until 6 weeks prior to her admission when the clonazepam was substituted with carbamazepine 200 mg twice daily. She had experienced approximately one tonic-clonic seizure per week for several years. There was no family history of porphyria.

On admission she had a sinus tachycardia of 100 beats min^{-1} and blood pressure was 150/90 mmHg. There was no evidence of peripheral neuropathy. Serum sodium valproate concentration was 36 mg l^{-1} and 3 days later 63 mg l^{-1} (target range = 50–100 mg l^{-1}) and the serum carbamazepine concentration was 7.7 mg l^{-1} (target range = 4–10 mg l^{-1}). Routine haematology, including haemoglobin, white cell and platelet count was normal. EEG showed disorganised cerebral rhythms consistent with an interictal state. A CT scan of brain showed no abnormality. There was an increased urinary excretion of ALA, PBG and total porphyrins being 178 μmol 24 h^{-1} (normal < 44), 237 μmol 24 h^{-1} (normal < 16) and 1,687 μg 24 h^{-1} (normal < 300) respectively. The activity of the enzyme PBG deaminase measured in erythrocytes was normal at 33.8 nmol porphyrin formed ml^{-1} erythrocytes h^{-1} (normal adult female range = 30–54 (Figure 1) and that of ALA synthase measured in leucocytes also normal at 158 nmol ALA g^{-1} protein h^{-1} (normal range = 50–300).

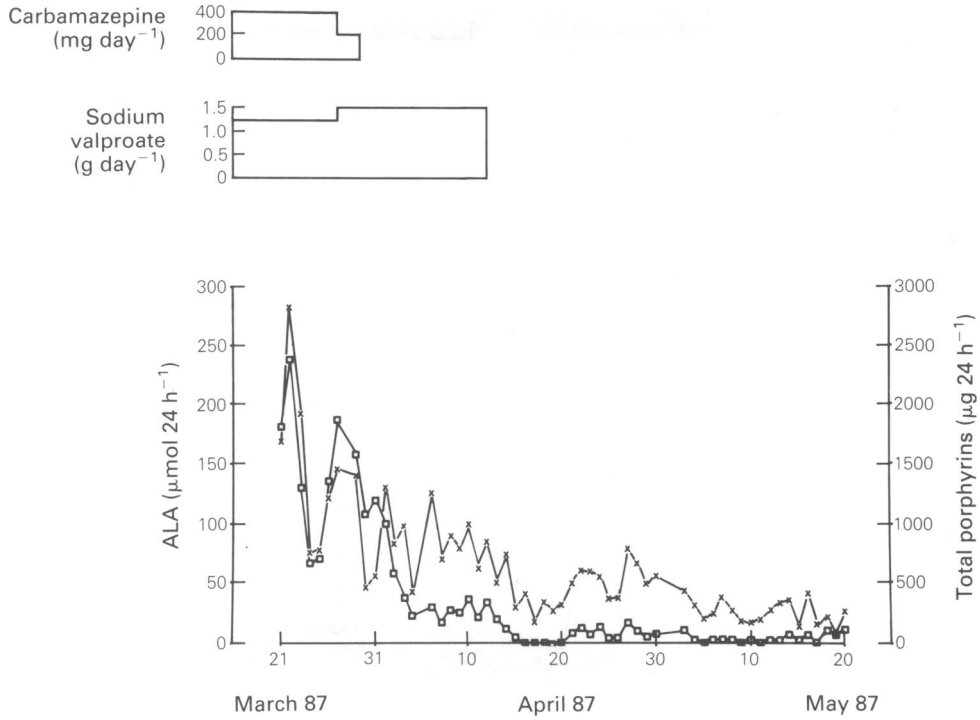

Figure 2 24 h urinary excretion of ALA (□) and total porphyrins (x) in patient 1, during and after treatment with carbamazepine and sodium valproate.

Faecal porphyrin excretion was not significantly elevated.

The markedly increased urinary excretion of porphyrin precursors confirmed acute porphyria and although ALA, PBG and total porphyrin excretion all fell 4 days after admission prior to any alteration to the anticonvulsant regime, levels were again elevated 3 days later (Figure 2). As the recent introduction of carbamazepine had probably precipitated the attack it was decided to try and maintain the patient on sodium valproate alone, closely monitoring her clinical and biochemical progress. ALA and PBG excretion subsequently returned virtually to normal at 37 μmol 24 h^{-1} and 26 μmol 24 h^{-1} respectively but total porphyrin excretion, although reduced from previously, remained elevated at 796 μg 24 h^{-1}. There had been no increase in her seizure frequency since discontinuing carbamazepine and it was felt justifiable, under hospital supervision, to discontinue sodium valproate. Total porphyrin excretion then fell to normal (Figure 2). The activity of ALA synthase and PBG deaminase remained within the normal range on withdrawing the anticonvulsants: in fact the PBG deaminase activity rose. The patient's general condition improved with stopping the drugs and there was no increase in the frequency of her convulsions which continued to occur approximately weekly. The only family members screened were her mother, brother and sister, all of whom had normal PBG deaminase activity (47.6, 47.0 and 38.1 nmol porphyrin formed ml^{-1} erythrocytes h^{-1} respectively).

Case 2

This 49 year old man was admitted to his local hospital in 1982 with abdominal pain, nausea, constipation and limb weakness. He was on primidone and sodium valproate for convulsions which he had suffered since childhood. Acute porphyria was suspected clinically and although quantitative assays of ALA and PBG were not available at the time, retrospective analysis of stored samples showed urinary excretion of both to have been elevated. Primidone was stopped but sodium valproate continued, with the addition of clobazam. While the acute symptoms resolved with lessening of his limb weakness the frequency of his convulsions increased—two generalised tonic-clonic seizures a month contrasted with one every 6 months on primidone. To assess further the possibility of acute por-

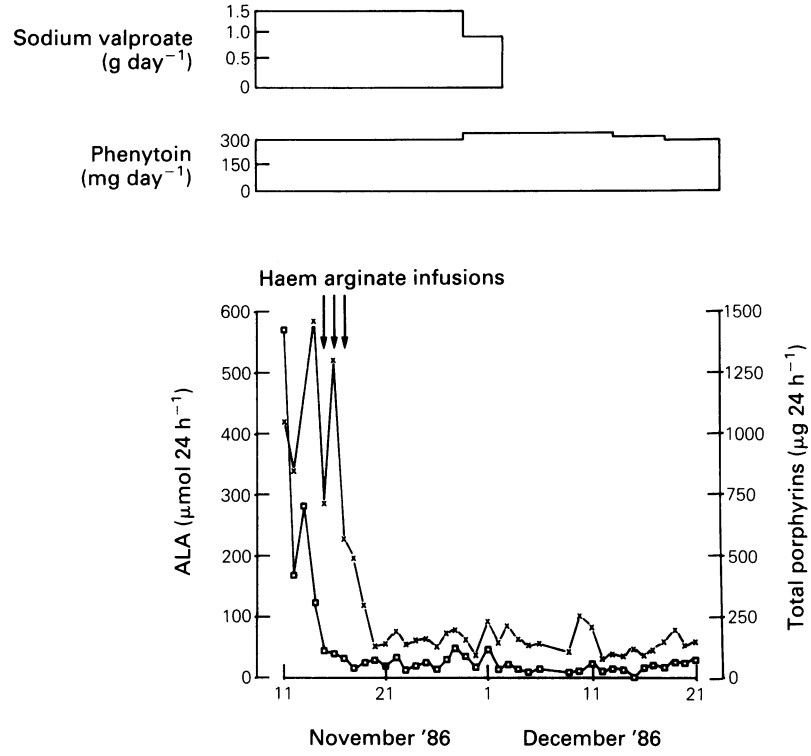

Figure 3 24 h urinary excretion of ALA (□) and total porphyrins (x) in patient 2, during treatment with phenytoin and during and after treatment with sodium valproate. Intravenous infusions of haem arginate (3 mg kg^{-1}) were administered as shown on 3 consecutive days.

phyria, he was transferred to the Porphyria Unit, in the Western Infirmary, Glasgow, in July 1983. Studies there showed normal urinary excretion of ALA and PBG being 11 μmol 24 h^{-1} (normal < 40) and undetectable (normal < 16), respectively. Faecal porphyrin excretion was also normal. The activity of PBG deaminase in erythrocytes was normal at 29.6 nmol porphyrin formed ml^{-1} erythrocytes h^{-1} (normal adult male range = 24–49) (Figure 1) and that of ALA synthase also normal at 185.7 nmol ALA g^{-1} protein h^{-1}. Under close supervision he was commenced on phenytoin, continuing on sodium valproate and clobazam, and over the subsequent week there was no increase in urinary porphyrin or precursor excretion and enzyme activities remained normal.

He remained well until October 1986 when he developed back pain, constipation and vomiting and dark urine. He was re-admitted to the Porphyria Unit 1 month later, when anticonvulsant treatment comprised phenytoin 300 mg daily, sodium valproate 1.5 g daily and clobazam 10 mg daily. His urinary excretion of ALA, PBG and total porphyrins was markedly increased being 561 μmol 24 h^{-1}, 342 μmol 24 h^{-1} and 1046 μg 24 h^{-1} respectively. The activity of PBG deaminase in erythrocytes was again normal but ALA synthase activity was raised at 1594 nmol ALA g^{-1} protein h^{-1}. The serum phenytoin concentration was 12.4 mg l^{-1} (target range 10–20 mg l^{-1}) and that of valproate was 36 mg l^{-1} (target range 50–100 mg l^{-1}). The EEG showed a discharging focus in the right hemisphere with discharges independently and secondarily from the left hemisphere. The patient had no close living relatives and so no information from any family screening was available. There had been no family history suggestive of porphyria.

The clinical findings and increased urinary excretion of porphyrin precursors indicated an acute attack of porphyria and he was treated with intravenous infusions of haem arginate. This resulted in marked reduction in urinary excretion of porphyrin precursors (Figure 3) and ALA synthase activity fell to normal (96 nmol ALA g^{-1} protein h^{-1}). Sodium valproate was reduced, then discontinued, and he was dis-

charged on phenytoin and clobazam. Over this period his porphyrin precursor excretion and PBG deaminase activity remained normal (Figure 3).

Discussion

Both of the patients described above presented with clinical features of acute intermittent porphyria and the diagnosis was confirmed by demonstration of increased urinary excretion of ALA and PBG. Our patients were remarkable in having no evidence of reduced activity of PBG deaminase in their erythrocytes. Nor was there any increased activity of the initial enzyme of the haem pathway, ALA synthase, which can be demonstrated in leucocytes (McColl *et al.*, 1982), except for an increase noted on one occasion in patient 2 and which may have been explained by his drug therapy.

It seems likely that in both patients anticonvulsant treatment precipitated the porphyric crisis. In patient 1, carbamazepine, an enzyme inducer, was the probable trigger although the marginally increased total porphyrin excretion on sodium valproate alone suggested that the combination of the two drugs may have been particularly porphyrinogenic. The two porphyric attacks in patient 2 were less clearly related to anticonvulsant treatment. However, there was no other precipitant for the acute attacks and interestingly urinary porphyrin and precursor excretion remained persistently low after their dramatic reduction by haem arginate, instead of gradually rising as is usually seen in patients with AIP (Mustajoki *et al.*, 1986). This suggested to us that the attack described in patient 2 was atypical and possibly causally related to the sodium valproate treatment which was discontinued.

The reason for the normal activity of PBG deaminase in our patients is unclear. Interestingly, Pierach *et al.* (1987) found that four of 107 patients with AIP had erythrocyte PBG deaminase activity well within the normal range. Mustajoki and Tenhunen presented a Finnish family in whom affected members had clinical attacks of AIP with accompanying increased urinary excretion of ALA and PBG but had normal PBG deaminase activity (Mustajoki & Tenhunen, 1985). On administration of an ALA load, their excretion patterns were typical of AIP and the authors concluded that this was a variant of AIP in which the enzyme defect was expressed in the liver which is the major site of porphyrin synthesis, but not in the peripheral blood cells. Our patients may represent other examples of this variant. Unfortunately, we were unable to examine sufficient relatives to ascertain whether there was a familial pattern similar to that seen in the Finnish case, and in both our patients administration of an ALA load was felt unethical because of the risk of precipitating status epilepticus which is very difficult to treat in porphyric patients.

An increased reticulocyte count has been shown to increase PBG deaminase activity in red blood cell haemolysates and could result in a normal value in patients with acute intermittent porphyria. Neither of our patients had an elevated reticulocyte count.

Another possibility for our patients' normal PBG deaminase activity was that anticonvulsant treatment was increasing PBG deaminase activity, so giving a falsely high result. Patient 1 was on carbamazepine and sodium valproate. It has been suggested that carbamazepine reduces PBG deaminase activity (Rapeport *et al.*, 1984) but it has subsequently been appreciated that it is the activity of ALA dehydratase that is reduced by this drug (McGuire *et al.*, 1988a). It should be noted, however, that even on admission, ALA dehydratase activity (21.7 nmol PBG h^{-1} ml^{-1} erythrocytes: normal range 15–30) and PBG deaminase activity were not abnormally low and would not account for the acute porphyric attack and that reduced ALA dehydratase activity would result only in raised urinary excretion of ALA and not of PBG. Previous human studies have shown that sodium valproate does not alter PBG deaminase activity (McGuire *et al.*, 1988b) and yet interestingly PBG deaminase activity in both patients rose on discontinuing valproate (Figure 1). Patient 2 was receiving sodium valproate with clobazam when first studied, with further studies done when on phenytoin together with sodium valproate and clobazam, and finally on phenytoin and clobazam. Studies of patients on various combinations of anticonvulsant drugs have shown that erythrocyte PBG deaminase activity can be either normal or reduced (Yeung *et al.*, 1983). The anticonvulsant therapy, therefore, cannot account for the normal PBG deaminase activity in our patients and may possibly have reduced it.

A final possible explanation is that our patients do not have any inherited genetic defect in haem biosynthesis and their disorder is totally explained by their anticonvulsant drug therapy. Some anticonvulsants, carbamazepine, phenytoin, phenobarbitone, primidone (metabolised in part to phenobarbitone), are potent inducers of haem biosynthesis and consequently can precipitate biochemical and clinical exacerbations in patients who have the underlying genetic defect. How-

ever, even in normal subjects, anticonvulsants have been shown to induce the rate controlling enzyme of haem biosynthesis (Rapeport *et al.*, 1984; McColl *et al.*, 1980). Sodium valproate, although not an enzyme inducer, stimulates porphyrin production in normal individuals by mechanisms as yet unclear (McGuire *et al.*, 1988b). As PBG deaminase is a secondary rate-controlling step in haem biosynthesis (Brodie *et al.*, 1977b), marked induction of the primary rate-controlling enzyme ALA synthase could result in accumulation of porphyrin precursors similar to that occurring in AIP. The relative reduction in PBG deaminase activity in our patients when on anticonvulsant treatment, albeit to levels within the reference range, may have contributed to the situation in their case. In 1911, Gunther described an acute porphyria precipitated by drugs without genetic predisposition—'haematoporphyria acuta toxica'. While this entity has been challenged on the basis that drugs such as sulphonal may simply have precipitated acute attacks in those genetically predisposed, it has been claimed that were this the case, the number of sulphonal related acute attacks would have been lower (With, 1971). It is well known that some patients with the genetic enzyme deficiency for acute porphyria may take porphyrinogenic drugs with impunity. Our patients may represent the other end of their spectrum in that they may develop attacks of porphyria on exposure to anticonvulsant therapy without any underlying enzyme deficiency.

Whatever the explanation for our findings, they have important implications with regard to screening for AIP. The measurement of the activity of the enzymes of haem biosynthesis in peripheral blood cells has been recognised to be the most sensitive method of diagnosing latent cases of AIP—only 50% of whom have increased excretion of porphyrin precursors. The major shortcoming when using erythrocyte PBG deaminase for screening has been the overlap between activity in normal and porphyric subjects and in which 20% of those screened may fall (McColl *et al.*, 1982). The findings of our own study and the previous studies in Finland and the U.S.A. demonstrate that AIP cannot be excluded even with normal enzyme activity well clear of the overlap zone.

We are grateful to Mrs Ann Cook and Mr George Thompson for assays of haem precursors and haem enzymes.

References

Berlin, A. & Schaller, K. H. (1974). European standardised method for the determination of 5-aminolaevulinic acid dehydratase activity in blood. *Zietschr. Klin. Chem. Klin. Biochem.*, **12**, 389–390.

Brodie, M. J., Thompson, G. G., Moore, M. R., Beattie, A. D. & Goldberg, A. (1977a). Hereditary coproporphyria: demonstration of the abnormalities in haem biosynthesis in peripheral blood. *Quart J. Med.*, **182**, 229–241.

Brodie, M. J., Moore, M. R. & Goldberg, A. (1977b). Enzyme abnormalities in the porphyrias. *Lancet*, **ii**, 690–701.

Goldberg, A., Moore, M. R., McColl, K. E. L. & Brodie, M. J. (1987). Porphyrin metabolism and the porphyrias. In *Oxford Textbook of Medicine*, eds Weatherall, D. J., Ledingham, J. G. C. & Warrell, D. A., pp. 9: 136–145. Oxford: Oxford University Press.

Gunther, H. (1911). Die Haematoporphyrie. *Deutsch. Arch. Klin. Med.*, **105**, 89–146.

McColl, K. E. L., Moore, M. R., Thompson, G. G. & Goldberg, A. (1980). Induction of 5-aminolaevulinic acid synthase in leucocytes of patients on phenytoin therapy—comparison with changes in rat hepatic tissue. *Br. J. clin. Pharmac.*, **9**, 327–321.

McColl, K. E. L., Moore, M. R., Thompson, G. G. & Goldberg, A. (1982). Screening for latent acute intermittent porphyria: the value of measuring both leucocyte delta-aminolaevulinic acid synthase and uroporphyrinogen-1-synthase activities. *J. med. Genet.*, **19**, 271–276.

McGuire, G. M., Macphee, G. J. A., Thomson, G. G., Park, B. P., Moore, M. R. & Brodie, M. J. (1988a). Effect of chronic carbamazepine treatment on haem biosynthesis in man and rat. *Eur. J. clin. Pharmac.*, **35**, 241–247.

McGuire, G. M., Macphee, G. J. A., Thompson, G. G., Moore, M. R. & Brodie, M. J. (1988b). Effects of sodium valproate on haem biosynthesis in man: Implications for seizure management in the porphyric patient. *Eur. J. clin. Invest.*, **18**, 29–32.

Moore, M. R. (1983). Laboratory investigation of disturbances of porphyrin metabolism. *Association of Clinical Pathologists Broadsheet*, **109**. London: British Medical Association.

Mustajoki, P. & Tenhunen, R. (1985). Variant of acute intermittent porphyria with normal erythrocyte uroporphyrinogen-I-synthase activity. *Eur. J. clin. Invest.*, **15**, 281–284.

Mustajoki, P., Tenhunen, R., Tokola, O. & Gothoni, G. (1986). Haem arginate in the treatment of acute hepatic porphyrias. *Br. med. J.*, **293**, 538–539.

Peipkorn, M. W., Hamernyik, R. & Labbe, R. F. (1978). Modified erythrocyte uroporphyrinogen-1-synthase assay and its clinical interpretation. *Clin. Chem.*, **24**, 1751–1754.

Pierach, C. A., Weimer, M. K., Cardinal, R. A., Bossenmaier, I. C. & Blommer, J. R. (1987).

Red blood cell porphobilinogen deaminase in the evaluation of acute intermittent porphyria. *J. Am. med. Ass.*, **257**, 60–61.

Rapeport, W. G., Connell, J. C., Thompson, G. G., Moore, M. R. & Brodie, M. J. (1984). Effect of carbamazepine on haem biosynthesis in man. *Eur. J. clin. Invest.*, **14**, 107–110.

With, T. K. (1971). Acute porphyria, toxic and genuine in the light of history. *Dan. Med. Bull.*, **18**, 112–121.

Yeung Laiwah, A. A., Rapeport, W. G., Thomson, G. G., Macphee, G. J. A., Philip, M. F., Moore, M. R., Brodie, M. J. & Goldberg, A. (1983). Carbamazepine-induced non-hereditary acute porphyria. *Lancet*, **i**, 790–792.

(*Received 6 June 1988, accepted 29 November 1988*)