ACUTE INTERMITTENT PORPHYRIA
The Anaesthetic Problem and its Background

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SUMMARY
A brief review of the biochemistry of the porphyrins is followed by a short survey of the disorders of porphyrin metabolism. The aetiology, pathogenesis, and clinical features of acute intermittent porphyria are described and discussed with particular reference to the barbiturates. A case history of a patient with acute intermittent porphyria is presented. Symptoms and signs included, at some stage in the course of his illness, abdominal pain, hypertension, red-coloured urine, hysterical behaviour, and peripheral neuritis. The anaesthetic management of patients with acute intermittent porphyria who require surgery is considered. Death by paralytic respiratory failure often occurs and the anaesthetist, by providing mechanical ventilation of the lungs, may enable the patient to survive the acute phase of the disease.

THE BIOCHEMISTRY OF THE PORPHYRINS
The porphyrins are widely distributed in nature. The plant pigment chlorophyll is a porphyrin which contains magnesium within the porphyrin ring. Haemoglobin and the respiratory enzymes, the cytochrome oxidases, are iron-containing porphyrins bound to protein. Vitamin B\textsubscript{12} (cyanocobalamin) has also a porphyrin-like structure. Cobalt is incorporated in the molecule in the site occupied by iron in the haemoglobin molecule.

The word porphyria is derived from the Greek porphyros, purple. In 1871 Hoppe-Seyler obtained a purple pigment from haemoglobin by the action of concentrated sulphuric acid. Because of its origin and its colour he called the pigment haemtoporphyrin. This is an iron-free or pure porphyrin, the protoporphyrin of haemoglobin (Boyd, 1961).

Uroporphyrin is so named because it was first isolated from urine. Coproporphyrin is normally the predominant porphyrin in urine and faeces. When porphobilinogen is excreted in the urine, the urine darkens on standing. This is partly because the porphobilinogen forms uroporphyrin.

Further reference (fig. 3) shows that the condensation of four molecules of porphobilinogen condense to form the tetrapyrrolic structure uroporphyrinogen (reduced uroporphyrin). The formation of further porphyrins now proceeds along two isomeric lines.

It will be noted (fig. 3) that in the biosynthesis of haemoglobin, uroporphyrinogen III is converted to coproporphyrinogen III and then to protoporphyrin III, which is the porphyrin of haemoglobin mentioned above. Uroporphyrin III and coproporphyrin III, which are found in the urine and stools are formed as by-products of this process, resulting from the oxidation of their respective porphyrinogens (Dean, 1963).

Coproporphyrinogen is also formed as an intermediate in the metabolism of uroporphyrinogen to coproporphyrinogen. This compound is transformed in the liver into protoporphyrinogen and then into protoporphyrin by the action of a liver enzyme.

Further reference (fig. 3) shows that the condensation of four molecules of coproporphyrinogen III gives rise to two series of porphyrins I and III. This "simultaneous" formation along two isomeric lines is spoken of as the "dualism" of the porphyrins (Wintrobe, 1961).

Porphyrins of type I isomer series have no known physiological function, and are by-products of haem synthesis. It would appear that the biosynthetic pathway is so conditioned in vivo that
the formation of porphyrin of the type I isomer is insignificant, relative to the amount of haem produced (Dean, 1963).

There are four possible uroporphyrin isomers. Only two are found in nature, uroporphyrin I and III. All the naturally occurring porphyrins are theoretically derivable from uroporphyrin I to give rise to type I porphyrins and uroporphyrin III to give rise to type III porphyrins. In fact, as can be seen from figure 3, the naturally occurring porphyrins are derived from their respective reduced form of porphyrin termed porphyrinogen. In type I porphyrins the side chains are symmetrical and alternate regularly. In type III porphyrins one pair is asymmetrical—two propionyl groups being adjacent. As will be seen from figure 1, the porphyrin of haem is of type III.

**DISORDERS OF PorphyrIN METABOLISM**

These disorders may be divided into two groups, the porphyrinurias and the porphyrias. The porphyrinurias include such conditions as pernicious anaemia, lead poisoning, the haemolytic anaemias and hepatic cirrhosis in which there is an increased excretion of porphyrins in the urine and faeces, which is secondary to the disease concerned. In the porphyrias, on the other hand, there is a primary error in porphyrin metabolism, resulting in the excretion of large quantities of porphyrins.

In 1937 Waldenström classified the porphyrias into acute and congenital forms, and a third form known as porphyria cutanea tarda. The acute form, because it is really a chronic disease characterized by acute exacerbations and remissions, has subsequently been termed acute intermittent porphyria. We have, therefore, on an earlier classification: congenital porphyria; acute intermittent porphyria; porphyria cutanea tarda.

*Congenital porphyria.*

This is sometimes referred to as porphyria erythropoietica because it is thought that the bone marrow is the site of the abnormal production of
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FIG. 2
Summary of steps in the biosynthesis from glycine + succinate (from the tricarboxylic acid cycle) of porphobilinogen, the simplest pyrrolic substance known to be a precursor of haem and porphyrins.

Reproduced from Rimington (1959), in the British Medical Bulletin, by kind permission of the author and the editor.

type I porphyrins. Patients with this condition suffer from great sensitivity to light due to the histamine-releasing properties of the porphyrins resulting in erythematous and bullous lesions. The sensitivity appears at or soon after birth and persists throughout life. Severe scarring results from the healed lesions.

The uroporphyrin I in the red cells may cause a photosensitized haemolysis of the red cells. Splenectomy may be effective in reducing the rate of haemolysis.

Acute intermittent porphyria.

Here the disturbance of porphyrin metabolism is not in the haemopoietic system but in the liver. The condition is characterized by gastro-intestinal and neurological symptoms, and by an absence of photosensitivity. Porphobilinogen, which has been formed in the liver, is excreted in the urine in large amounts, in the acute and often in the latent phases of the disease. This is never excreted in congenital porphyria, and only occasionally in porphyria cutanea tarda. Attacks may be precipitated by the barbiturates.

Porphyria cutanea tarda.

This is sometimes called mixed porphyria as it has features in common with both the acute
and congenital types. Photosensitivity is much less severe, and some cases present with mild abdominal colic in addition to photosensitivity.

Recently Waldenström and Haeger-Aronsen (1963) have added two further types to this original classification—protocoprophyria and protoporphyria erythropoietica. They have concluded that there are at least five genetically determined types of inborn error of porphyrin metabolism. According to the newer classification, therefore, the following types can be distinguished: congenital porphyria; acute intermittent porphyria; porphyria cutanea tarda; protocoprophyria; protoporphyria erythropoietica.

Protocoprophyria.

This variety is found in South Africa. Because it can occur in various forms, it is sometimes known as "porphyria variegata". It has certain obvious parallels with acute intermittent porphyria, as high levels of porphobilinogen appear in the urine in the acute phase, neurological lesions occur, and barbiturates play a part in the development of the clinical symptoms. It differs from the acute intermittent form in the absence of porphobilinogen in the urine in the latent phase, in the presence of skin lesions, and in the high levels of protoporphyrin and coproporphyrin found in the faeces. It is the high level of protoporphyrin and coproporphyrin in the faeces which gives the condition its name. In northern climates, the cutaneous symptoms will fail to develop in the absence of strong insolation. If quantitative determinations of faecal porphyrins are neglected, then it may be supposed that many of these cases will be wrongly diagnosed. Rimington (1964) states that these patients appear to be the most sensitive of all porphyries to the exacerbating effect of barbiturates.

Protoporphyria erythropoietica.

Here, as in congenital porphyria (porphyria erythropoietica), the bone marrow is the site of the disturbance of porphyrin metabolism. In congenital porphyria large quantities of series I porphyrins are formed with uroporphyrin I predominating. In protoporphyrin erythropoietica the porphyrin in the bone marrow is mainly protoporphyrin which is of the normal isomeric type (series III) (Magnus et al., 1961). These patients are light-sensitive.

Porphyria is a rare disease in this country, being more prevalent in Scandinavia (acute intermittent porphyria) and South Africa (protocoprophyria). It is of interest to note that the inheritance of porphyria in the white population of South Africa has been traced to two early settlers from Holland.

Aetiology of Acute Intermittent Porphyria

Goldberg (1959), in a review of 50 cases of acute intermittent porphyria, discussed the genetic factor, the age and sex incidence, and precipitating factors in the aetiology of the disease.

The genetic factor.

Goldberg believed that the familial distribution is consistent with the hypothesis that the condition is inherited as an irregular Mendelian dominant character, that is, the persons affected are heterozygous for an abnormal gene. He states that it must be assumed that there is considerable variation in the degree of expression of the character, and that in one family all grades can be found, from the acute case through latent porphyria, to the apparently normal subject who excretes no porphobilinogen. In this study of 50 patients it was possible to examine the families of 11 in detail. From a study of these families it was concluded that apparently 25 per cent of the sibs of a patient may have porphobilinogen in the urine, and a high proportion of these are liable to an acute attack.

Age and sex incidence.

There is a preponderance of female subjects. It occurs most frequently in women in the third decade and in men in the fourth decade of life. It is questionable whether the sex incidence is genetically determined, or whether secondary precipitating causes such as pregnancy or barbiturate intoxication predispose to the sex difference.

Precipitating factors.

The barbiturates. There have been some conflicting reports on the possible relation between barbiturates and acute porphyria. For instance, Discombe and D'Silva (1945) reported a case of acute intermittent porphyria who was under observation for two years, during which time four exacerbations of the disease occurred. Phenobarbitone 60 mg, twice daily, was given for periods
of several weeks, during two of these attacks. Discombe and D'Silva concluded that there was no evidence that the drug affected the course of the attacks adversely.

Goldberg (1959), in a review of 50 cases suggested two types of relationship between barbiturates and acute porphyria. It seems probable that prolonged injection of barbiturates may precipitate an attack where the latent trait exists, and in such cases the clinical manifestations resemble those of chronic barbiturate intoxication.

A possible association was noted between the administration of barbiturates during an attack, and the onset of paralysis. In his series 77 per cent of patients with paralysis (24 out of 31) had been given barbiturates, while 35 per cent of those without paralysis (6 out of 17) had taken barbiturates (fig. 4). This difference is highly significant (P<0.01). In all 4 patients to whom quinalbarbitone was given a quadriplegia ensued and 2 of these patients died.

Quinalbarbitone has an allyl (CH$_3$=CH—CH$_2$—) group in the R$_1$ position. Goldberg (1954) had previously shown that barbiturates with one or more allyl groups were effective in disturbing the porphyrin metabolism of rabbits. In these experiments administration of diallyl barbituric acid (Dial), which has two allyl groups, resulted in a considerable rise in urinary coproporphyrin III, when given to the rabbits. Allylisopropylbarbituric acid (Alurate) and sodium allyl (1 methylbutyl barbiturate (quinalbarbitone), each with one allyl group, caused a moderate rise of urinary coproporphyrin III. Some barbiturates which do not possess an allyl group were used in the experiments. These either caused only a slight increase in urinary coproporphyrin, or did not alter the urinary coproporphyrin significantly. The dosage of barbiturate given to the animals was, weight for weight, greatly in excess of that normally taken by humans. In fact it is doubtful if humans could have survived a proportionate amount of barbiturates.

In 1955 Dundee and Riding reviewed the cases of porphyria reported in the British Medical Journal and the Lancet during the years 1948–53. They reviewed reports of 37 attacks of acute porphyria occurring in 32 patients. "There were details of 15 operations, the nature of the anaesthetic being unstated in the remaining 2. Paralysis occurred in all of the 13 thiopentone cases, and 5 patients died." Ten Eyck, Martin and Kernohan (1961), in their paper on the postmortem studies of 9 cases of porphyria, note that barbiturates had been administered to 8 of them.

Infection. In Goldberg's survey there are many examples of the role of infection in precipitating or aggravating an attack, as it may also in other metabolic diseases such as diabetes mellitus and Addison's disease.

Other precipitating factors. Evidence can be produced for and against menstruation and pregnancy as precipitating causes. Over-indulgence in alcohol, drugs of the sulpha group, and apronal (Sedormid) will also precipitate the acute manifestations of the disease (Brain, 1962).

APARALYSIS

The relationship between barbiturate administration and the onset of paralysis in 48 patients with acute intermittent porphyria. In two cases, not included in the analysis, it was not certain whether barbiturates had been given.

Reproduced from Goldberg (1959), in the Quarterly Journal of Medicine, by kind permission of the author and the editor.
**TABLE I**

*Chemical structure and effect of certain drugs on the porphyrin metabolism of rabbits.*
Reproduced from Goldberg and Rimington (1955), by kind permission of the authors and editor.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Effect on urinary porphyrin excretion</th>
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<tbody>
<tr>
<td>allyl-isopropyl-acetamide (A.I.A.)</td>
<td><img src="image1" alt="Structure" /></td>
<td>++ +</td>
</tr>
<tr>
<td>allyl-isopropyl-acetyl-urea (sedormid)</td>
<td><img src="image2" alt="Structure" /></td>
<td>++ +</td>
</tr>
<tr>
<td>t-propyl-isopropyl-acetamide</td>
<td><img src="image3" alt="Structure" /></td>
<td>-- --</td>
</tr>
<tr>
<td>allyl-isopropyl-acetic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>±</td>
</tr>
<tr>
<td>diallyl-barbituric acid (dial)</td>
<td><img src="image5" alt="Structure" /></td>
<td>+</td>
</tr>
<tr>
<td>sodium allyl-(1-methyl butyl) barbiturate (secinal)</td>
<td><img src="image6" alt="Structure" /></td>
<td>+</td>
</tr>
<tr>
<td>allyl-isopropyl-barbituric acid</td>
<td><img src="image7" alt="Structure" /></td>
<td>+</td>
</tr>
</tbody>
</table>

+ + + Very marked effect (much coproporphyrin, porphobilinogen and uroporphyrin).
+ + Marked effect (much coproporphyrin, some porphobilinogen and uroporphyrin in three out of eight rabbits).
+ Moderate effect (coproporphyrin only).
± Slight coproporphyrin rise only.
-- -- No effect.
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condensed with a carboxyl group. The barbiturates are diureides, that is compounds formed from the condensation of dicarboxylic acids with urea (fig. 5). The sedative carbromal is also a monoureide, but no reference has been found suggesting that it may precipitate porphyria. Glutethimide (Doriden) although not a ureide compound has a chemical structure of dimensions and shape similar to the barbiturates (fig. 5), and may possibly be suspect on this account.

Mention has already been made that the presence of an allyl group (CH$_2=$CH–CH$_3$–) on the barbiturate molecule (e.g. quinalbarbitone) increases the effectiveness of the barbiturates in disturbing the porphyrin metabolism of rabbits. It is of interest to note that the allyl group also occurs in apronal (Sedormid). A possible explanation is that unsaturation reinforces the toxicity and effectiveness of a drug (usually the toxicity more than the effectiveness).

Table I is taken from a paper by Goldberg and Rimington (1955) on "Experimentally produced porphyria in animals". They found that the constant chemical structure affecting the porphyrin metabolism of rabbits is CH$_3$=CH–CH$_3$–CHR–CO–NH. It may be concluded from the table that the chemical configuration necessary to produce this action is either a substituted allyl-acetamide (A.I.A.) or a ureide (Sedormid), or a cyclic ureide as in the barbiturate series. A.I.A. (allyl-isopropyl-acetamide) is not a hypnotic.

**CLINICAL FEATURES**

Goldberg (1959) groups the symptoms and physical signs under three main headings: gastro-intestinal, neurological, and cardiovascular.

**Gastro-intestinal features.**

Patients suffer from abdominal pain either alone or associated with constipation. Vomiting and more rarely diarrhoea also occur. The pain is predominantly colicky, situated mainly in the epigastrium and right iliac fossa, and is characteristically severe. All patients in Goldberg's series who complained of abdominal pain, and who were examined by him, had some degree of abdominal tenderness, but this was usually much less in degree than expected, considering the severity of the pain.

**Neurological features.**

In 22 per cent of the patients in Goldberg's series, neurological or psychological symptoms were predominant.
Motor disturbance. The majority of the patients with a motor disturbance present with a lower motor neurone type lesion. In five of the above series, however, extensor plantar responses were obtained, and in one of these there was muscular rigidity of the lower limbs, ankle clonus and increased tendon reflexes. The cranial nerves are sometimes involved. Respiratory paralysis may also occur due to involvement of the phrenic nerves, the intercostal nerves, or both.

Sensory disturbance. The sensory impairment may take the form of analgesia, hyperaesthesia, loss of joint and vibration sense or complete sensory loss.

Epilepsy. Patients may present as epilepsy of unknown causation. In the three cases reviewed by Goldberg, barbiturates were given to control the fits, and were associated with a deterioration of the general condition. In one of these patients the fits continued until the barbiturates were stopped.

Mental symptoms. These have been arbitrarily classified into three grades: (1) depressed, nervous, hysterical, lachrymose; (2) confused, hallucinated, disorientated or with personality changes; (3) legally certifiable.

Coma. Porphyria is an occasional cause of coma (Brain, 1962).

Cardiovascular findings.

Thirty-two patients of Goldberg's series had tachycardia during the acute phase of the disease. Pulse rates of 110–120 beats/min were observed. In a few the rate varied between 150 and 170 beats/min. As Waldenström (1937) had observed, the pulse rate was found to be a good index of the activity of the disease.

Twenty-seven patients had transient hypertension (with a systolic pressure of 150 mm Hg or more, and a diastolic pressure of 95 mm Hg or more). Some patients had marked hypertension. One patient developed hypotension.

PATHOGENESIS

It is possible to explain the main clinical features of acute intermittent porphyria on a neurogenic basis (Goldberg, 1959; Rimington, 1961). The symptoms and signs will vary according to the site of the demyelination. If demyelination occurs in the peripheral nerves, the presenting symptoms and signs will resemble peripheral neuritis. If the site of demyelination is in the cerebral white matter epilepsy or psychosis may occur.

Intestinal spasm alternating with dilatation has been observed at laparotomy and on radiography. This functional abnormality is the probable cause of the gastro-intestinal symptoms, and is probably accounted for by demyelination of the preganglionic fibres that innervate the abdominal viscera, leading to retrograde degeneration of their nuclei.

The hypertension and tachycardia can also be explained on a neurogenic basis. The vasomotor centre is controlled (inhibited) from the baroreceptors in the aortic arch and carotid artery, via the sino-aortic nerves. If the sino-aortic nerves are cut in the experimental animal, the vasomotor centre discharges maximally and hypertension
results. Here the same result is thought to ensue as a result of demyelination of these nerves or their subsequent pathways within the brain stem. Impulses from the baroreceptors stimulate the vagal nucleus, which in turn slows the heart. If the afferent fibres are demyelinated, the stimuli to the vagal nucleus are absent, and tachycardia results.

It is necessary to reconcile the demyelinating lesions of the nervous system, with the derangement of porphyrin metabolism in the liver of which the abnormal presence of porphobilinogen in the urine is the expression. Goldberg (1959) has put forward a hypothesis, which is illustrated in figure 6. He assumes a substance "X", of which porphobilinogen is the precursor and which is necessary for the nutrition of the myelin of the nervous system. Failure to synthesize substance "X" results in demyelination and the excess porphobilinogen (and δ-aminolaevulic acid) is now excreted in the urine. He suggests that a genetically determined deficiency of a specific enzyme might cause the block. The intermittent nature of the disease might be due to other factors, such as infection, or barbiturates acting on this abnormal pathway.

De Matteis and Rimington (1962) propose a fundamental impairment of the acetylating system (genetically determined), which through the action of precipitating agents such as the barbiturates and sulphanilamide may develop into a critical reduction of acetylcholine synthesis in the nervous system. This would account for the nervous symptoms.

A possible explanation for the hepatic overproduction of porphobilinogen is as follows. There are two cycles or pathways available by which the amino acid, glycine, can be metabolized to carbon dioxide—the acetate aminoacetone cycle and the δ-aminolaevulic acid cycle (fig. 7). If there were a decreased availability of active acetate (acetyl-coenzyme-A) as suggested above, this would produce a preferential metabolism of glycine through the δ-aminolaevulic acid cycle, and thus in the direction of porphobilinogen and the porphyrins (fig. 7).

**CASE REPORT**

The following case report illustrates several aspects of porphyria as an anaesthetic problem:

A man aged 23 was admitted in the early hours of May 17, 1962, complaining of abdominal pain of 24 hours duration. The pain had become gradually worse, and tended towards the right side of the abdomen. He had vomited once.

On examination, he was moving about the bed in pain. The temperature was 98.5°F, and the pulse rate was 58 beats/min. There was tenderness in the right iliac fossa, with guarding. Rebound tenderness was not present. The blood pressure was recorded as 190/110 mm Hg. A diagnosis of acute appendicitis was made, and an appendicectomy performed. At operation, a long inflamed paracæcal appendix was removed.

Anaesthesia had been induced with thiopentone and suxamethonium had been used to facilitate intubation. Anaesthesia was subsequently maintained using halothane, followed by further injections of suxamethonium as required for opening and closure of the peritoneum.

On the day following the operation, he complained of abdominal pain. During the ensuing night he slept little, getting out of bed, and sitting in a chair all night. The next day he again complained of abdominal pain.

On May 20 he was unwell. The temperature had risen to 99.6°F. The pulse rate was 110 beats/min. His abdomen was soft and not tender. Bowel sounds were scanty. A wound haematoma (probably getting infected) was diagnosed, and penicillin and streptomycin were prescribed.

On the following day, the patient was still complaining of very severe pain similar to that on admission. At times he was writhing in pain, and his behaviour was apparently quite hysterical. On examination his temperature was still raised. His abdomen was tender, but there was no rigidity. Bowel sounds were present. The blood pressure was recorded as 140/90 mm Hg.

This reading was taken subsequent to an injection of morphine. It was at this time that the urine was noted to be a mahogany colour, and a diagnosis of porphyria was now considered. On May 22 a laboratory test showed two specimens of urine to be free of porphy-
linogen = 25 mg/1.; coproporphyrin = 430 mg/1.; uroporphyrin = 60 µg/1. These values are all raised and indicative of acute porphyria.

On June 21 he complained of pain and tingling in all limbs. Because of a raised blood pressure he had been several times recorded, his urinary catecholamines were examined and not found to be increased. His evening temperature on June 2 was 98.6°F, but the pulse rate was now 130 beats/min. (It had been previously recorded twice as 120 beats/min.) During the previous night he had got out of bed and sat on the floor. On June 4, his complaints were of muscular weakness, an inability to sleep at night and "the way everybody looks at me". On examination he was thought to have no genuine loss of power. When the ward nurses tried to get him up and about he complained of generalized muscle pains, and could not stand for any length of time. He appeared to fall over deliberately when being observed.

On June 5 his temperature was normal. His pulse rate was 120 beats/min. He was very depressed. His behaviour was hysterical, and he was recorded as being "certainly not well mentally". He agreed to enter a mental hospital as an in-patient, and was transferred.

Two days later he was readmitted from the mental hospital, where it had been found that his arm reflexes were absent. There was also weakness of the upper limbs with tenderness present. To a lesser degree there was loss of power in the lower limbs. He had also apparently passed red-coloured urine.

Examination on readmission revealed a pulse rate of 138 beats/min. It remained between 120 and 140 beats/min for the next 2½ weeks, and remained above 100 beats/min up to the time of discharge nearly 5 weeks later. His blood pressure was now 130/100 mm Hg. Emotionally he was very labile, crying when spoken to. Power was diminished in all limbs. He could move his arms freely, but the grip was grossly diminished. He was unable to lift his lower limbs off the bed. The tendon reflexes were all present. The plantar response was flexor in both legs. There was no loss of touch or proprioception.

A laboratory test of urine now showed: porphobilinogen = 25 mg/1.; coproporphyrin = 430 µg/1.; uroporphyrin = 60 µg/1. These values are all raised and indicative of acute porphyria.

On June 26 edrophonium 1 ml was given with no effect. There was great emotional display during the injections. He made slow progress during the next fortnight. On July 7 he was discharged home, to attend for physiotherapy as he still had some residual weakness of the proximal muscles of his arms and of his pelvic girdle.

Comment.

At some stage in the course of his illness practically all the symptoms and signs of acute intermittent porphyria were seen—abdominal pain, hypertension, tachycardia, hysterical behaviour, and ultimately a fully developed peripheral neuritis. It is possible that infection may have converted the disease from the latent to the acute phase prior to hospital admission, and the condition was then made worse by barbiturates. As in all cases of porphyria, it is difficult to evaluate the effect of barbiturates on the course of the disease. Because of the very nature of the condition these patients are liable to be treated with barbiturates (during the latent phase they exhibit neurotic traits which may be treated with barbiturates); during acute attacks hysterical behaviour may receive similar treatment; or convulsions may be treated with thiopentone (Ten Eyck, Martin and Kernohan, 1961), or again thiopentone may be administered for a laparotomy for abdominal pain. It is difficult, therefore, to assess to what extent the barbiturates bear a causal relationship to the acute phase, and to what extent their prescribing is the result of the symptoms of the acute phase already present. However, the advice of Dundee (1956) is appropriate: "In the light of our present knowledge porphyria must be considered an absolute contraindication to the use of any barbiturate."

The question naturally arises as to how one can suspect that a patient presenting with an acute abdomen may have porphyria, which is either the cause of the "acute abdomen", or is present together with an "acute abdomen" from some other more common cause. The clue in this case may have been the patient's blood pressure on admission. This was 190/110 mm Hg in a man of 22 years. Assuming that the active phase of the disease had already commenced prior to admission, this could explain his raised blood pressure. Such a raised blood pressure should perhaps constitute
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a warning. It is possible, of course, to dismiss such a blood pressure as being due to nervousness in a patient who has just been admitted to hospital; the diastolic pressure was also raised.

Whenever an active case of acute porphyria is discovered, the urine of the relatives must be examined for the presence of porphobilinogen (and likewise the faeces for any increase in porphyrins), so that they and their medical advisers may be warned against the use of barbiturates. This will also prevent delays and errors of diagnosis should an acute attack occur. Because protocoproporphyria (porphyria variegata) is very common in Southern Africa, Dean (1963) advises routine testing for all patients of Caucasian origin in Southern Africa before they are given barbiturates, and especially thiopentone anaesthetics.

The anaesthetic management.

The choice of anaesthetic agents in the patient known to suffer from porphyria is discussed by Norris and MacNab (1960). The use of drugs commonly used in premedication, such as opiates, pethidine, and belladonna derivatives, appears to be quite safe. As regards anaesthetic drugs, thiopentone is of course absolutely contraindicated, nitrous oxide is safe, ether has been safely used, and cyclopropane is reported as having been safely used during a Caesarean section. With regard to muscle relaxants, Norris and MacNab recommend suxamethonium, in order to avoid the use of anticholinesterases. It is known that the phosphorus-containing insecticides with anticholinesterase activity may produce demyelination, and on these grounds relaxants, which may require neostigmine for reversal, are better avoided altogether. Lepinskie (1963) considers this preference for suxamethonium theoretical rather than pragmatical.

Howells (personal communication, 1964) suggested that for induction purposes the non-barbiturate intravenous engelol derivative propanidid (FBA.1420) might be used (fig. 5). Propanidid is related to G.29.505. (It differs from G.29.505 in having a propoxy-acetyl in place of the allyl group. It is thought to be decomposed predominantly in the liver by splitting of its ester bond.)

An inhalational method of induction seems preferable, using either pre-oxygenation followed by nitrous oxide and oxygen, or cyclopropane and oxygen as used in the two cases described by Norris and MacNab.

As in other neurological diseases, local anaesthetic techniques are probably better avoided altogether, otherwise these are liable to be blamed for any subsequent disability.

The anaesthetist may play an active role in the treatment of porphyria. Many of these patients die of paralytic respiratory failure. The natural history of the disease is one of acute exacerbations followed by remissions. If the patient in paralytic respiratory failure can be tided over the acute stage, with the aid of mechanical pulmonary ventilation, there is every possibility that the condition may remit again to the latent phase. Doll, Bower and Affeldt (1958) describe three such cases. The three patients reported all developed paralysis of the respiratory muscles, and also accumulated secretions in the airway due to bulbar paralysis or inadequate cough. Treatment included tracheotomy and mechanical respiratory assistance. All three patients subsequently became free of respiratory care.

Zilkha (personal communication, 1964) describes two cases who have recovered from the acute episode with respiratory assistance. In connection with artificial ventilation Dean (1963) points out that difficulty in speaking is often a premonitory symptom of respiratory paralysis.

ACKNOWLEDGMENTS

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**PORPHYRIE INTERMITTENTE AIGÜE. LE PROBLEME ANESTHESIQUE ET SON ARRIÈREFOND**

**SOMMAIRE**

Une revue succincte de la biochimie des porphyrines est suivie par un bref rappel des troubles du métabolisme des porphyrines. L'étiologie, la pathogénèse et les aspects cliniques de la porphyrie intermittente aiguë sont décrits et discutés particulièrement en comparaison avec les barbituriques. Presentation d'un cas de porphyrie intermittente aiguë. Parmi les signes et symptômes présentés par ce malade à un stade quelconque de sa maladie on cite la douleur abdominale, l'hypertension, l'urine colorée en rouge, le comportement hystérique et une névrite périphérique. On envisage la marche de l'anesthésie chez les malades atteints de porphyrie intermittente aiguë et devant être opérés. Souvent la mort survient par défaillance respiratoire paralytique et en assurant une ventilation mécanique des poumons l'anesthésiste peut permettre au malade de survivre à la phase aiguë de sa maladie.

**AKUTE INTERMITTIERENDE PORPHYRIE DAS ANÄSTHESIEPROBLEM UND DIE GRÜNDE DAFÜR**

**ZUSAMMENFASSUNG**