

The Porphyrins: The Royal Purple?

GEOFFREY DEAN, MD, FRCP, Director, Medico-Social
Research Board, Dublin, Ireland

... I found
A thing to do, and all her hair
in one long yellow string I wound
Three times her little throat around
And strangled her.

Robert Browning, *Porphyria's Lover*

Porphyrins formed by the union of four pyrrole rings are involved in the main energy reactions upon which life is dependent. Chlorophyll, a compound of porphyrin and magnesium, converts the radiant energy of the sun into chemical energy, and the haem of haemoglobin, a compound of porphyrin and iron, catalyses stored energy for the formation of adenosine triphosphate (Figs 1 and 2). These reactions of energy storage and use are the basis of life on this

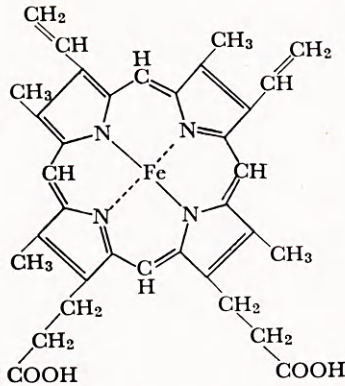


Fig. 1. The structure of haem.

planet. Porphyrins have the remarkable property of showing a brilliant pink fluorescence when viewed in ultraviolet light (Wood's lamp).

The porphyrias are disorders involving the metabolism of porphyrins and porphyrin precursors. They may be symptomless, may cause cutaneous

lesions, or may be responsible for an acute illness (acute porphyria), with profound psychological, neurological, and abdominal symptoms. Although they were originally described as 'inborn errors of metabolism' (Garrod, 1923), it is now appreciated that certain disorders of porphyrin metabolism may be acquired. A classification of the porphyrias is given in Table 1.

TABLE 1. Classification of the Porphyrias

I The Hepatic Porphyrias

1. Acute Intermittent Porphyria (Pyrroloporphyria or Swedish type genetic porphyria)
2. Porphyria Variiegata (Proto/coproporphyria or South African type genetic porphyria)
3. Coproporphyria
4. The purely cutaneous porphyrias:
 - (a) Symptomatic Porphyria (porphyria cutanea tarda) usually associated with the abuse of alcohol. There may possibly be a genetic predisposition.
 - (b) Acquired types, e.g. hexachlorobenzene induced porphyria.

II Erythropoietic Porphyrias

1. Congenital Erythropoietic Porphyria (Gunther's porphyria). The symptoms start in infancy.
2. Erythropoietic Protoporphyria. Causes a rash similar to urticaria.

PORPHYRIA VARIEGATA

On emigrating to South Africa in 1947 and starting practice in Port Elizabeth, in the Eastern Cape Province, I was called in consultation to see a number of patients, usually young women, who had become emotionally disturbed after a thiopentone anaesthetic or after taking barbiturates. They complained of abdominal and muscle pain, had attacks of vomiting and a rapid pulse, and showed marked muscle weakness. The first three patients I saw with this condition developed a peripheral neuritis and died. Their urine was dark and gave a brilliant pink fluorescence when examined in ultraviolet light with a Wood's filter. I realised that these patients had died from acute porphyria.

The first of these patients was a young nurse named van Rooyen. Her father had on the backs of his hands a sensitive skin that abraded easily when it was knocked, and a number of scars from previous sores could be seen (Fig. 3). He told me it was the 'van Rooyen skin' and that three of his brothers, and also his father and grandfather, had a similar skin. The patient's great-grandfather was Gerrit Renier van Rooyen, born in 1814, and I decided to trace all his

living descendants. There were 574 of them, and eventually I managed to trace them all, testing their urine, and later their stool, for increased porphyrin excretion. In this family group 74 were found to have porphyria and at least 16 had died from acute porphyria (Dean and Barnes, 1955). On average, half the children of a patient with South African porphyria inherited the



Fig. 3. Skin lesions in porphyria variegata. The skin lesions are not usually as severe as this.

disorder. There was a high concentration of porphyrin in the liver but not in the bone-marrow of those who had inherited porphyria and there was nearly always a high excretion of porphyrin in the stool, which would fluoresce in ultraviolet light. The stool porphyrin was a mixture of copro- and proto-porphyrin.

This South African porphyria was evidently inherited as a Mendelian dominant porphyria, and the disturbance of porphyrin metabolism was in the liver. This disorder could cause the exposed skin to abrade and blister easily and could also cause acute illness—acute porphyria—if certain drugs, particularly barbiturates and sulphonamides, were administered. Because the South African type of porphyria could present in a variety of ways, with skin lesions, with an acute attack, with either, neither or both, Barnes and I called it 'porphyria variegata' (Dean and Barnes, 1959).

Porphyria variegata is very common in South Africa for the same reason that the name Botha or van der Merwe is common. Half a million of the 3·5

million white people in South Africa hold 20 family names and derive these names from 20 original free burghers. A small number of early settlers living in ideal conditions have increased many thousand-fold in number. I succeeded in tracing the first 32 family groups of porphyrics that I studied back to

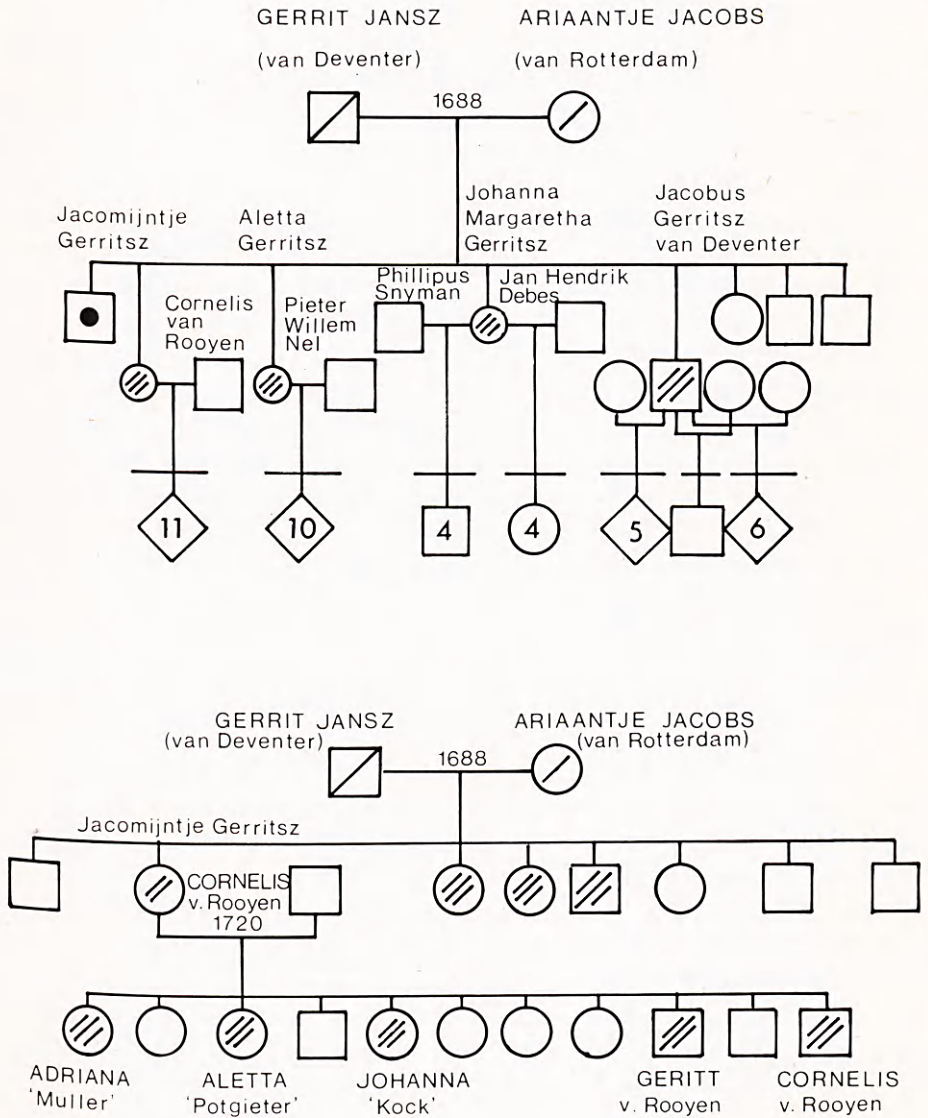


Fig. 4. Porphyria variegata traces back to four of the eight children of Gerrit Jansz and Ariaantje Jacobs. □ = male. ○ = female. ⊠ ⊡ = porphyric line of descent.

Gerrit Jansz (Gerrit the son of Jan, they had no surnames in those days) who came from Deventer in Holland and married Ariaantje Jacobs, one of the eight orphans sent out by the Lords Seventeen, the controlling Board of the Dutch East India Company, from the orphanage at Rotterdam on the ship *China* to be wives for the first free burghers. They were married on arrival at the Cape in 1688 (Dean, 1963) (Fig. 4).

Today there are about 9,000 white South Africans who have inherited porphyria variegata, in the 12th to the 16th generation, all descendants of this family. The incidence of porphyria variegata is highest in the Eastern Cape Province, as the early porphyrics were among the trek Boers who trekked eastwards from Cape Town. In Port Elizabeth the incidence of porphyria variegata among the white population is 1 in 250. For all white South Africans the estimated incidence is 1 in 400 (Dean, 1960). It is also fairly common among the Coloured people of South Africa and among them it has been traced back to Gerrit the son of Jan, and his wife Ariaantje.

INTERMITTENT ACUTE PORPHYRIA (PYRROLOPORPHYRIA)

Waldenström (1937) described a form of Mendelian dominant porphyria in Sweden, which he called intermittent acute porphyria. I went to Sweden to study this type of porphyria and found that acute attacks occurred after certain drugs, as in the South African type, but that the skin did not abrade unduly easily and sores and blisters did not occur. In the Swedish type, in adults, Ehrlich's aldehyde reagent usually caused a purple coloration of the urine, as shown by the Watson-Schwartz test (Watson and Schwartz, 1941), both in acute attacks and also in the quiescent phase, whereas in the South African type the Watson-Schwartz test was positive only during an acute

TABLE 2. Characteristic Findings in Three Different Forms of Porphyria

	<i>Porphyria variegata</i> (<i>'protocoporphyrin'</i>) (<i>South African type</i>)	<i>Acute intermittent porphyria</i> (<i>'pyrroloporphyria'</i>) (<i>Swedish type</i>)	<i>Coproporphyrin</i>
Skin Stool porphyrin	Often sensitive Usually increased (protoporphyrin more so than copropor- phyrin)	Not sensitive Normal or nearly normal	Not sensitive Usually increased (coproporphyrin more so than protopor- phyrin)
Urinary porphyrin	Slightly increased (uroporphyrin more so than coproporphyrin)	Normal or slightly increased	Slightly increased (coproporphyrin more so than uroporphyrin)
Watson-Schwartz test	Positive only during acute attack	Positive in adults	Positive only during acute attack

attack. There was also increased porphyrin in the urine if it was left to stand for some hours. In intermittent acute porphyria there is little or no increase in stool porphyrin (Table 2).

COPROPORPHYRIA

A third Mendelian dominant hepatic porphyria can cause acute attacks after barbiturates. This type has been well described by Goldberg and his colleagues, who called the disorder 'hereditary coproporphyria' (Berger and Goldberg, 1955; Goldberg *et al.*, 1967). In coproporphyria, as in porphyria variegata, the Watson-Schwartz test is positive only during acute attacks. In the quiescent phase there is usually an increase in the coproporphyrin and uroporphyrin in the urine but the increase may be slight. Skin lesions do not usually occur (*see* Table 2). A Portuguese family from Mozambique with this disorder has been described in South Africa (Dean, 1969).

ERYTHROPOIETIC PORPHYRIA

Besides the hepatic porphyrias, there are two rare forms of erythropoietic porphyria in which the disorder of metabolism occurs in the bone-marrow. The first to be described was congenital or erythropoietic porphyria inherited as a Mendelian recessive characteristic; that is, it shows only in the homozygote. The other form, erythropoietic protoporphyria, is inherited as a Mendelian dominant. In erythropoietic or congenital porphyria, the skin lesions occur in infancy and there is also anaemia, splenomegaly, and pink staining of teeth and bone (Fischer *et al.*, 1925). Fourie (1936) and Rimington (1936) described this type of porphyria in cattle, in which it is known as 'pink tooth disease'. Congenital porphyria is characterised by fluorescence of the normoblasts in the marrow in ultraviolet light. Erythropoietic protoporphyria causes an urticaria-like rash (Haeger-Aronsen, 1962).

SYMPTOMATIC PORPHYRIA

There is also a hepatic form of porphyria that is not, as far as we know, inherited, and which is associated with a gross disturbance of liver function. This type of symptomatic porphyria is sometimes called 'porphyria cutanea tarda symptomata' and is usually associated with the excessive use of alcohol (Brunsting, 1954). In South Africa it is common in the Bantu, especially in those addicted to a home-brewed alcoholic drink, skokiaan (Barnes, 1955) but surprisingly it is uncommon among the Africans of Nigeria who drink palm wine. Symptomatic cutaneous porphyria, usually associated with alcoholism, also occurs occasionally among white South Africans.

In symptomatic porphyria there is a high excretion of urinary porphyrin

and the urine is dark in colour. There is little or no increase in porphyrin in the stools. The exposed skin blisters and abrades easily, but acute attacks do not follow the taking of barbiturates.

From 1957 onwards a most unusual outbreak of symptomatic porphyria occurred in the eastern part of Turkey (Cam, 1959). It particularly affected

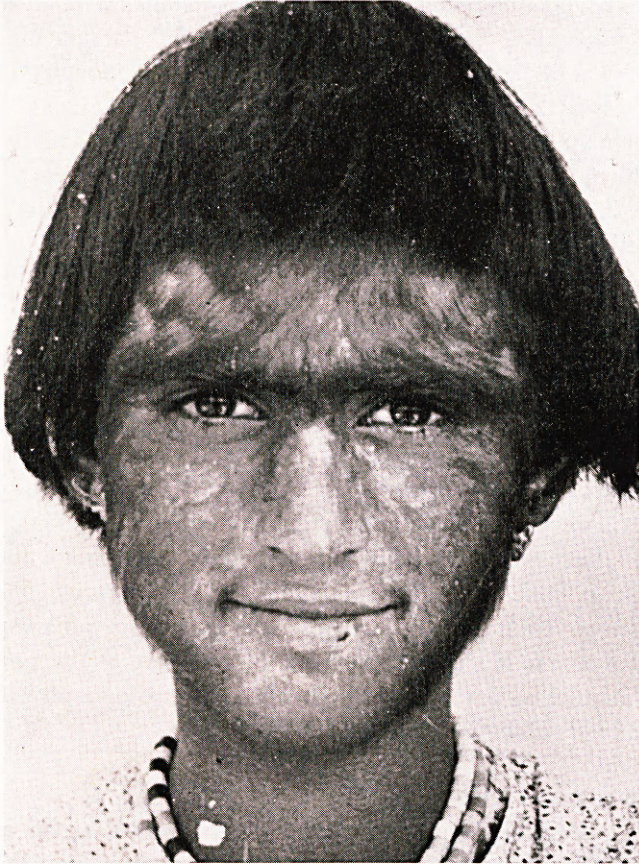


Fig. 5. Hirsutism of Turkish child with toxic porphyria due to eating bread made from seed wheat treated with hexachlorobenzene.

children, and over 5,000 children had the cutaneous lesions of porphyria, not only sores and blisters but also darkening of the skin and marked hairiness, so that they often looked like monkeys and were therefore called the monkey children (Fig. 5).

This outbreak was caused by eating bread made from seed wheat provided

by the United States of America, which had been treated with hexachlorobenzene to prevent destruction in the ground by the fungus *Tilletia Tritici*. Many of these children still have disturbed liver function and, in summer, the cutaneous lesions of porphyria.

THE SYNDROME OF ACUTE PORPHYRIA

The acute illness with emotional disturbance, abdominal and muscular pain and, finally, generalised peripheral neuritis and paralysis, may be inadvertently precipitated in intermittent acute porphyria, porphyria variegata, and coproporphyria by certain drugs, particularly barbiturates and sulphonamides. Other less commonly used drugs can also occasionally precipitate attacks, for instance, chloroquine diphosphate (Aralen diphosphate), griseofulvin, and the sulphones. Women who have inherited these types of porphyria may suffer from minor abdominal pains, especially in the premenstrual period and during pregnancy, when they are especially liable to be given a barbiturate sedative or to have an exploratory laparotomy under an anaesthetic such as thiopentone. The oral oestrogen-progesterone contraceptives may precipitate an attack of acute porphyria in acute intermittent porphyria, and a hepatotoxic reaction, with a great increase in skin blistering due to a high level of circulating porphyrin, in porphyria variegata (Dean, 1965).

The attack starts with severe pain in the abdomen, back or limbs. The patient is usually very emotional. She does not lie still and cries easily. Hallucinations may occur. Vomiting is frequent and there is constipation, increasing the risk that a misdiagnosis of intestinal obstruction will be made. There are often muscle twitches and sometimes convulsions. The pulse is usually rapid and the blood pressure may be raised. There is often a marked loss of salt in the urine. In the early stages there is no muscular weakness, but over the course of a few days the tendon reflexes disappear and muscle weakness becomes apparent. The voice may be weakened and the patient then talks in a whisper because the muscles of respiration are affected and she is in grave danger of death, although nowadays with good attention most patients recover. The time for recovery depends to a great extent on whether or not there is paralysis; if there is severe peripheral neuritis, recovery usually takes six to nine months. In porphyria variegata the recovery is complete, but in intermittent acute porphyria some degree of paralysis may persist for years. A depressive psychosis sometimes follows an acute attack.

In porphyria variegata, the tendency for the skin to abrade and blister easily may become more pronounced during an acute attack and persist for a long time after the acute attack is over.

LABORATORY FINDINGS

During an acute attack the urine is coloured, often like port wine, by the greatly increased porphyrin. If the urine is left to stand in sunlight, it becomes darker and may become the colour of one of the cola drinks. The presence of porphyrin can be confirmed by the characteristic spectroscopic absorption bands and by the pink fluorescence in ultraviolet light (using a Wood's filter).

Increased porphobilinogen in the urine is detected by the Watson-Schwartz test, using Ehrlich's aldehyde reagent. (To 2 ml of urine are added 2 ml of Ehrlich's aldehyde reagent and 4 ml of a saturated solution of sodium acetate. The mixture is shaken. A purple colour results if either porphobilinogen or urobilinogen is present, but urobilinogen is soluble in chloroform and may be distinguished by chloroform extraction.) In porphyria variegata and in coproporphyria, the Watson-Schwartz test is positive during an acute attack and, in adults, it is generally positive even when there are no symptoms. Examination of the blood and cerebrospinal fluid may show a marked fall in serum sodium, chloride, calcium, potassium, and magnesium during an acute attack, especially in porphyria variegata.

Intermittent acute porphyria, porphyria variegata and coproporphyria can be diagnosed before an acute attack has been inadvertently precipitated. In intermittent acute porphyria (pyrroloporphyria), the Watson-Schwartz test for porphobilinogen is usually positive in adults and is the simplest screening test, but it is of no value in detecting quiescent porphyria variegata or coproporphyria. In order to make sure that all the relatives, including the children, who have inherited the gene for pyrroloporphyria are identified, quantitative analysis of porphobilinogen and δ -aminolaevulinic acid can be undertaken and slight increases above the normal range can be detected (Mauzerall and Granick, 1958).

A slight increase in urinary porphyrin excretion can be detected by adding 1 ml of a solvent consisting of equal parts of amyl alcohol, glacial acetic acid, and ether to 10 ml of urine. The mixture is shaken, and the solvent will float to the top in 15 minutes. On examination in ultraviolet light, the solvent at the top of the urine will show a purple fluorescence if porphyrin is increased. It must be remembered that increased urinary porphyrin can also occur in other disorders, such as lead poisoning.

Examination of the faeces for increased porphyrin is the quickest and simplest way of screening for porphyria variegata and coproporphyria. The faecal porphyrin in this disorder is usually very high both in the quiescent phase and during an acute attack. The clinician can screen the stool for increased porphyrin by dissolving a small fragment of faeces, generally easily obtained on a finger-stall, in the ether solvent described above. If a marked excess of

porphyrin or chlorophyll is present, the solution will show a brilliant pink fluorescence in ultraviolet light, even when diluted several times. Chlorophyll can be separated from coproporphyrin or protoporphyrin by adding 2 ml of 1.5 normal hydrochloric acid to the solution. After the mixture is shaken and allowed to stand, the porphyrin will pass into the acid solution at the bottom of the test-tube (Dean, 1956). For confirmation, the quantitative methods of Holti and Rimington should be used (see Holti *et al.*, 1958). The diagnosis of porphyria variegata depends on a high faecal porphyrin, often combined with a slightly raised urinary porphyrin, and either a personal or family history of a tendency for the exposed skin to abrade and blister easily. The high excretion of coproporphyrin relative to protoporphyrin in the stool, or to uroporphyrin in the urine, distinguishes coproporphyrin from porphyria variegata. A high faecal porphyrin can also occur on occasion in other conditions, such as carcinoma of the stomach.

If a patient has intermittent acute porphyria (pyrroloporphyria), porphyria variegata or hereditary coproporphyrin, other members of the family are likely to have inherited the disorder. Diagnosis includes a detailed study of the family, so that those who have inherited the gene can be warned of the danger of certain commonly prescribed drugs.

TREATMENT

Prevention of attacks of acute porphyria is the most important part of treatment. Those who inherited porphyria variegata in South Africa and intermittent acute porphyria in Sweden increased and multiplied in the past as rapidly as the rest of the population before the introduction of certain modern drugs; this is strong evidence that acute attacks of porphyria causing the death of the patient must have been very uncommon before the beginning of this century. In my experience, attacks of acute porphyria in porphyria variegata have always followed the use of barbiturates or sulphonamides. Oral contraceptives sometimes aggravate the skin lesions and there are a few uncommonly used drugs that occasionally upset porphyrics. Nevertheless, in daily medical practice the drugs to be avoided in intermittent acute porphyria, porphyria variegata and coproporphyrin are the barbiturates, especially the pentobarbitones such as thiopentone, and the sulphonamides.

Acute porphyria, whether it has been precipitated in porphyria variegata, intermittent acute porphyria, or coproporphyrin, is characterised by abdominal and muscle pain, emotional disturbance, often vomiting and constipation, and a fast pulse. The Watson-Schwartz test on the urine will be positive during the acute attack.

In an acute attack the patient's life is in great danger and the patient

should be nursed in a single-bedded room in hospital. In porphyria variegata there is often a fall in the blood electrolytes and calcium. Perhaps the urinary loss of salt is due to excess antidiuretic hormone. Additional salt should be given, intravenously if necessary, because it may be necessary to keep the stomach empty for a while by Wangensteen's method. Calcium gluconate (1 g 12-hourly intramuscularly) lessens the risk of convulsions. Chlorpromazine (50 mg 8-hourly) is a good tranquilliser. Digitalis is not very effective in slowing the pulse.

There should be no delay in doing a tracheostomy and using a mechanical respirator, such as a Birds or Engström machine, if respiration is embarrassed, because these patients develop peripheral paralysis with respiratory involvement. We have had one such patient on a respirator for three months, and she eventually made a very good recovery. The members of a respiratory unit can be the greatest help in this situation. Every effort is worth while because, if the patient can be kept alive until the acute attack subsides, eventual recovery is excellent, although it may take some months (Dean, 1967).

The skin sensitivity that occurs in porphyria cutanea tarda (symptomatic porphyria) and porphyria variegata is treated by avoiding the use of alcohol and toxic drugs and by protecting the exposed skin from sunlight as much as possible, for instance by using gloves and a hat out of doors. The skin should also be protected from light in the erythropoietic porphyrias.

Those who have inherited porphyria variegata, intermittent acute porphyria, or coproporphyria should carry a letter stating the evidence for the diagnosis and mentioning the extreme danger of barbiturates and sulphonamides. They should be strongly advised to show this letter to any doctor they consult.

PORPHYRIA IN IRELAND

Porphyria may be more common in Ireland than in England (Gibson *et al.*, 1950; Kernohan and Perry, 1954; Gibson *et al.*, 1957; Jessop, 1960; Counihan and O'Malley, 1956; Hart, 1960). In 1959 Stevenson collected 27 cases in Northern Ireland, and in 1960 Fenelly *et al.* reported further cases in the Republic. The four patients with intermittent acute porphyria that I have seen in England were, perhaps by chance, of Irish stock. Most patients with acute porphyria in Europe and North America suffer from intermittent acute porphyria, although some families have porphyria variegata and coproporphyria. The 50 patients reported in Ireland in 1960 probably represent only the tip of an iceberg and there are, no doubt, several hundred people in Ireland who have inherited intermittent acute porphyria, perhaps from one Viking ancestor; it would be interesting to find out. In Sweden, Wetterberg

(1967) has described how most of those who have inherited intermittent acute porphyria belong to one large family from northern Sweden.

'THE ROYAL PURPLE'

In 1966, Drs I. Macalpine and R. Hunter published a paper entitled 'The "Insanity" of King George III. A Classic Case of Porphyria'. They ascribed His Majesty's attacks of mental disturbance, which were associated on occasion with abdominal pain and a dark urine, to acute porphyria caused by intermittent acute porphyria. In a second paper they claimed that the various illnesses of a number of his ancestors and collaterals back to the time of Mary Queen of Scots, and including James I, were caused by attacks of acute porphyria but this time it was porphyria variegata, not intermittent acute porphyria (Macalpine *et al.*, 1968). These claims were refuted at the time by a number of physicians well versed in the porphyrias (Dent, 1968a, b; Dean, 1968a, b; Eales and Dowdle, 1968; Maclean 1968, and Gajdos, 1968). Nevertheless, Dr Macalpine and Dr Hunter restated their claims in various articles and in a very well-produced and historically documented book, *George III and the Mad-Business* (Macalpine and Hunter, 1969). They have not so far produced any living descendant of the family, or specimens from them, to show to the physicians who did not believe they had proven their case.

Only half the children of a porphyric parent inherit the gene. Therefore, the odds against the gene persisting over so many generations in the Royal Line are very remote indeed. Furthermore, why are we not shown living descendants of Mary Queen of Scots alive today with demonstrable porphyria variegata? We know that members of the Royal Family over the last 300 years had large families, legitimate and illegitimate, and also that the families were very well recorded. For comparison, in South Africa one immigrant who came to the country 300 years ago with porphyria variegata has been responsible for over 9,000 white South Africans alive today with this disorder, and I have, in the last twenty-two years, seen over 1,000 of them. Dr Macalpine in her paper in the *British Medical Journal* mentions two possible living cases. In case A, a distinguished physician thought it was porphyria. The distinguished physician was not named and I have known many distinguished physicians make a mistake in this diagnosis. In patient B, the increase in porphyrin was so slight that it was quite impossible to make a diagnosis of porphyria from this alone.

We know from our South African studies that acute attacks only follow the use of barbiturates or sulphonamides or some other rarely used modern drugs. The mental disturbance that occurs with acute porphyria clears up as the acute attack subsides. Mary Queen of Scots had fits, and she suffered from an acute illness with pain in her side made worse by breathing; quite likely she

had pleurisy, this is not evidence that it was porphyria. She also had attacks of abdominal colic and diarrhoea; gastro-enteritis was very common in those days. James I's eldest son, who is claimed by Dr Macalpine *et al.* (1968) to have died from acute porphyria, had an acute illness with diarrhoea; in acute porphyria constipation is usual, not diarrhoea.

Some of these patients did apparently pass a dark urine but this, in my opinion, is no evidence that it was due to porphyrin because any dehydrating illness would darken the urine or, for that matter, the passing of blood or bile. James I is reported to have developed a pain in the left lumbar region and passed a red urine after horse-riding; his doctor attributed the symptoms at the time to gravel. His Majesty's doctor made a very sensible diagnosis, particularly as at autopsy James I had two concretions in his kidney.

There is, in my opinion, no good evidence that George III's attacks of mental illness were caused by attacks of acute porphyria, nor that a number of illnesses in the Royal Families of Europe from the time of Mary Queen of Scots were due to porphyria variegata. The drugs that precipitated acute porphyria variegata did not exist at the time of George III and, furthermore, there is no higher proportion of patients with porphyria variegata among the patients in mental hospitals in South Africa than among the general population (Dean and Barnes, 1959), and no special history of mental breakdown among the ancestors of present-day porphyrics in South Africa. Furthermore, porphyria variegata is very uncommon in Europe; other causes of mental breakdown, sometimes physical, are very much more common.

Before the hypothesis that many members of the Royal Family back to Mary Queen of Scots inherited porphyria variegata and suffered attacks of acute porphyria is accepted, the authors of this hypothesis should be able to produce conclusive and impartial evidence that at least a few of the living descendants, many of whom today must be very humble people, have the well-documented symptoms and biochemical findings of porphyria variegata. In the meantime their hypothesis is still not proven.

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Emergency Call

Dr Fordyce, a fashionable physician and frequenter of the Chapter Coffee-house in Paternoster Row was, according to Timbs: 'much addicted to the bottle, and was one evening called away from a drinking bout to see a lady of title, who was supposed to have been taken suddenly ill. Having heard her story which contained some odd symptoms, he sat down to take her pulse. He tried to reckon the number of its beats; the more he endeavoured to do this the more his brain whirled and the less was his self control. Conscious of the cause of his difficulty he inadvertently blurted out, "Drunk, by Jove!" The lady heard the remark but remained silent.' The next day he received another imperious summons to her house, and set off fearing at least a reprimand. 'The patient however began by thanking him for his immediate attention, and then proceeded to say how much she had been struck by his discernment on the previous evening, confessed that she was occasionally addicted to the error which he had detected and concluded by saying that her object in sending for him so early was to obtain a promise that he would hold inviolably secret the condition in which he found her.'