PORPHYRIA, A FAMILIAL DISEASE: ITS DIAGNOSIS AND TREATMENT

GEOFFREY DEAN, M.D., M.R.C.P.

Honorary Physician, Provincial Hospital, Port Elizabeth

Porphyria, a disorder involving profound disturbances in the metabolism of pyrrole pigments, is common in South Africa and occurs in both Europeans and non-Europeans.[1,5] In Europeans it is a familial disorder inherited as a non-sex-linked Mendelian dominant characteristic, and causes cutaneous, psychological and neurological symptoms. In South Africa nearly all European cases are of old Afrikaner stock and a future paper will show that these cases are descendants of one forbear who came to this country nearly 300 years ago. A very rare form of 'congenital' porphyria, with marked skin sensitivity, pink staining of teeth and bone, anaemia and enlarged spleen is also occasionally seen. This form is inherited as a Mendelian recessive characteristic.[6,8]

Familial porphyria usually causes no symptoms in childhood; although on average one in two children of a porphyric parent inherit the disorder, it is difficult to decide which have done so before adult life is reached. Even in adults the symptoms in the latent stage may be very mild or absent; usually, however, there is a slightly increased sensitivity of the exposed skin, which blisters and abrades easily, and a few scars may be present on the back of the hands (Fig. 1). The skin sensitivity is generally more pronounced in men, although many woman who inherit the disorder do know that their skin is slightly more sensitive than average and may remember a time when it blistered easily. A useful test is to scrape the skin on the back of the hand 4 or 5 times with a finger nail; in porphyria the superficial layer often abrades. The skin is sometimes more pigmented than usual and the women may show pre-auricular hypertrichosis. Enquiry may reveal that other close relatives also suffer from a sensitive skin, but repeated and careful questioning may be necessary. Although most male porphyrics remain well throughout life, many of the women complain of abdominal discomfort and they are likely to be given barbiturate sedatives, which then aggravate the condition. If abdominal pains are acute, appendicitis, intestinal obstruction or some other abdominal emergency is often diagnosed and the abdomen may be opened after administration of a thiopentone anaesthetic. This anaesthetic nearly always precipitates an attack of acute porphyria. During pregnancy symptoms are usually

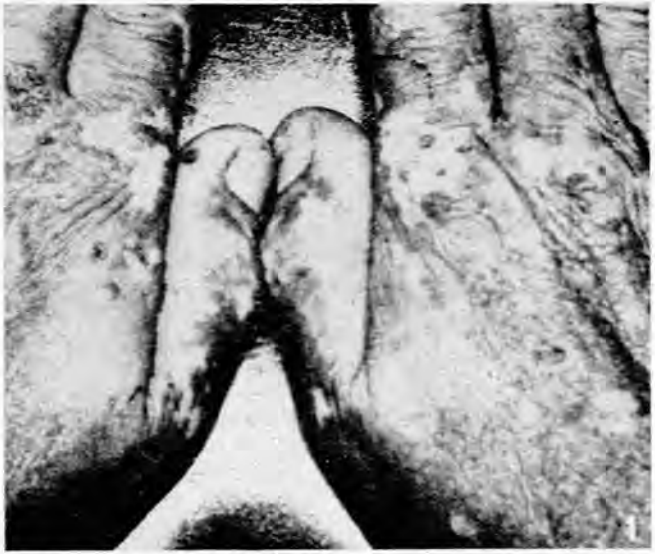

Fig. 1. Skin sensitivity in porphyria. These hands show blisters, sores and healed de-pigmented scars. The lesions are not usually so marked even in male porphyrics.

more pronounced and there may be a history that previous pregnancies were terminated because of pains, vomiting and hysteria. Sub-acute porphyria may be mistaken for Addison's disease, but examination of the urine and faeces will settle the diagnosis. In this country porphyria is common and Addison's disease is rare. Hysteria, mental disorder and hyperthyroidism may also be considered in the differential diagnosis.

In many cases a family group is first found to be porphyric when one of its members has an acute attack. In my experience acute attacks are always precipitated by drugs, chemicals or alcohol. Attacks of acute porphyria occur much more frequently in women, although both sexes inherit the disorder equally and skin sensitivity is usually more marked in men. The reason for the predominance of acute attacks in women is not fully understood; there may be endocrine factors, and perhaps women are more liable to take sedatives and to be operated upon for abdominal pain. Acute attacks are commoner in pregnancy—a time when sedatives are often prescribed. Porphyria is one of the few conditions where the doctor may be responsible for the patient's acute illness and perhaps death.

In an acute attack of porphyria the behaviour is very emotional. The patient complains of severe pain all over the body but particularly in the abdomen. Nutrition is often difficult to maintain, there may be vomiting and constipation, and there is usually a marked loss of weight. Unless the symptoms subside she will soon complain of weakness in the limbs, which at first may be regarded as hysteria; then in a few days it will be realized that a lower-motor-neurone type of paralysis has developed. The reflexes disappear, the pupils are dilated, the heart rate is rapid and the blood pressure may be raised. If the patient does not die the peripheral neuritis may persist for many months. During an acute attack there is evidence of impaired liver-function and usually a leucocytosis. The cerebrospinal fluid is normal. The electrocardiograph shows a tachycardia but no characteristic change. In some cases epileptic convulsions occur. The urine is reddish-brown in colour and darkens on standing; a great excess of porphyrin and porphobilinogen will be present.

THE INHERITANCE OF PORPHYRIA

In order to study the inheritance of porphyria the author has now traced the genealogies of 32 porphyric family groups, all of old burgher stock. A total of 324 members (168 male and 156 female) had clinical manifestations of porphyria. One of these family groups, which is typical of the others, was intensively investigated (Dean and Barnes[4]); see Fig. 1. The forbear of this group, born in 1814, had had 478 descendants, 434 of whom were still alive. Members of this family were traced to Germany, France, England, the United States and the Rhodesias. All living members of the family were contacted and after considerable perseverance specimens of urine were obtained from all of them and examined for porphyrin. In many cases a number of specimens of urine were examined and a quantitative analysis made of faecal porphyrin.

According to Mendelian law, if a dominant characteristic is present in one partner only, half the descendants should inherit the dominant characteristic. There are 60 porphyrics among the 125 descendants of a porphyric parent in this group, excluding those under the age of 18 years. In all cases only one parent is a porphyric. Five of the 10 children in the 2nd generation are porphyrics. In the 3rd generation there are 16 porphyrics among the 37 children with a porphyric parent. In the 4th generation there are 32 porphyrics among the 59 children with a porphyric parent. In the 5th generation there are 7 porphyrics among the 19 descendants with a porphyric parent, all young but over the age of 18 years. In this family 48% of the adults with one porphyric parent inherited porphyria; 24 out of the 41 male descendants with a porphyric parent and 36 out of 84 female descendants. These figures conform with the theoretical requirements of a non-sex-linked Mendelian dominant type of inheritance.

Only 4 of the 36 women who inherited porphyria had severe skin sensitivity; 14 of the 36 have died, and 8 of the 14 died with typical symptoms of acute porphyria. Of the 25 men, 8 have died, but only 1 from acute porphyria; of the 17 who are alive 16 have scars on their hands from previous sores and the skin of their hands is easily abraded. Most of them are free of symptoms except for the skin sensitivity, and do not take drugs. Acute porphyria is much less common in male porphyrics.

CASE HISTORIES

The following are typical cases of acute porphyria from this family:

III. 6. Male, died aged 46, Johannesburg (1932). Since he was a young man, his wife says, he had had a sensitive skin that blistered easily. He often complained of attacks of abdominal pain and when he was 30 a laparotomy was carried out. His final illness occurred while he was taking barbiturates; he complained bitterly of abdominal pain, frequently vomited and was very constipated. He lost 80 lb. in weight. A barium meal showed some delay in the small bowel and a bromethol anaesthetic was given by rectum so that a laparotomy could be performed; he died before the abdomen was opened. His hospital notes state that his urine was port wine in colour. Of his 5 children 4 are porphyrics.

III. 51. A woman died aged 57, Bloemfontein (1949). She had suffered periodically throughout her adult life from attacks of abdominal pain. Her skin did not blister but was unduly sensitive. During her last illness barbiturates were prescribed for her; her pains increased, she lost 40 lb. in weight and complained of marked weakness in her arms and legs. She was admitted to hospital where her urine was 'port wine in colour'; porphyrin and porphobilinogen was present. She became paralysed and died.

III. 58. Morgenzon, Transvaal (1953). This woman was traced during this investigation. Her urine was negative when tested for porphyrins but her daughter's urine was positive. She was warned that she was a porphyric and that certain drugs were dangerous, particularly sedatives and especially a 'pentothal' anaesthetic. She was asked to show her doctor the warning letter. In spite of these precautions she allowed her doctor to give her a thiopentone anaesthetic and developed an acute attack of porphyria with paralysis. She then produced the warning letter, the diagnosis was confirmed, all drugs were stopped and she slowly recovered over a period of months.

IV. 3. A woman died aged 40, Cape Town (1953). This member of the family was only traced with great difficulty after about 2 years' research. A letter was sent to her warning her that she might be a porphyric and asking for a specimen of urine. Her daughter replied and described how her mother had suffered from a sensitive skin and attacks of abdominal pain for many years; how a few days before the arrival of the letter she had started taking Nembutal

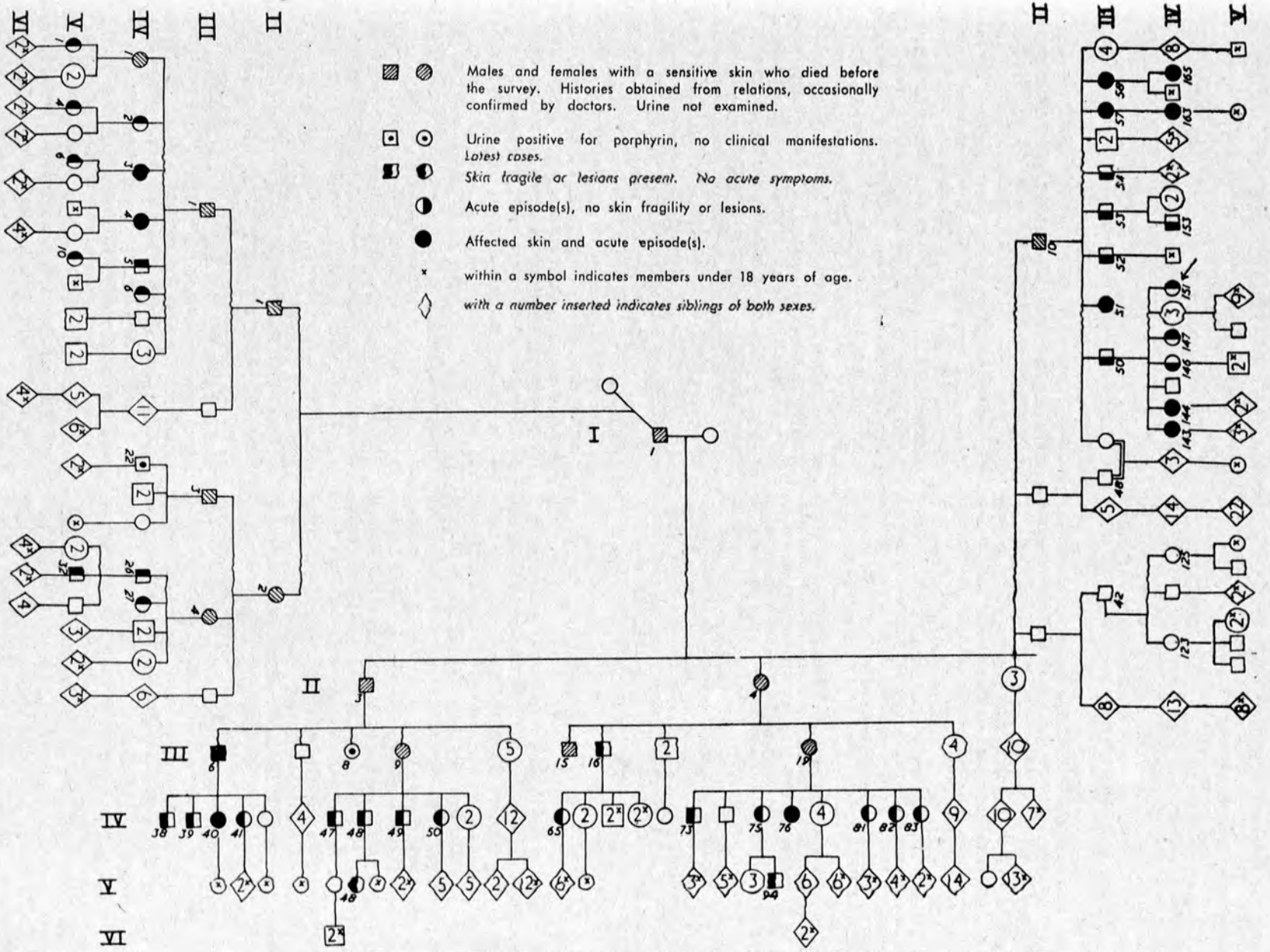

Fig. 2. Genealogical tree. (*British Medical Journal*)

at night. Her pains increased and she became delirious and passed a red urine. The urine contained a great excess of porphyrin and porphobilinogen. She became paralysed and died a few days later. The letter warning her was just too late.

IV. 4. A woman died aged 33, in France (1928). The husband of this woman was last heard of in 1928 at the time of his wife's death. He was eventually traced to his home in France through the assistance of the Cardiff police. He described how his wife had suffered from a sensitive skin and recurrent attacks of abdominal pain. After taking certain drugs at the beginning of her 3rd pregnancy she developed severe abdominal pain, became delirious and passed red urine. Over the course of a few days she became paralysed and died. Death was certified as due to 'blackwater fever'.

IV. 151. A nurse, aged 19, Uitenhage (1951). This case was seen by the author and led to detailed study into this family group. Her skin was slightly sensitive but did not blister. She had always been of a nervous disposition and often complained of pains in her abdomen and limbs. She started taking barbiturate drugs in large doses and her abdominal pains increased, she vomited frequently and was extremely constipated, and she was thought to have an intestinal obstruction. A laparotomy was performed and thiopentone was used to induce anaesthesia. After the operation her symptoms increased and over the course of a few days she became completely paralysed. Her urine was dark amber in colour and the Ehrlich's test for porphobilinogen was strongly positive; although all sedatives were stopped as soon as the diagnosis was made, she died 2 days later.

IV. 163. A woman died aged 24, Durban (1950). For 3 years before her death she complained of attacks of abdominal pain. She was given barbiturates but her symptoms increased, she vomited frequently and was very constipated. She lost a great deal of weight. She was admitted to hospital where it was noted that her urine was 'port wine in colour'. She developed a generalized paralysis and died.

IV. 165. A woman, aged 24. Acute porphyria (1954). She was traced during the investigation of the family and her urine was found to contain porphyrin. The danger of drugs was emphasized. Seven months later, believing herself pregnant, she took certain drugs and developed an attack of acute porphyria. She showed the doctor attending her the warning letter, all sedatives were stopped, and she recovered.

TESTS FOR PORPHYRINS

In the latent stage the urine is normal in appearance. The increase in porphyrin excretion may be so slight that it can only be detected by careful spectroscopic examination of a layer several inches deep; the urine may even be normal. However, the characteristic bands of porphyrin can frequently be detected by those who have experience in spectroscopic examination. Porphobilinogen is seldom present in the quiescent phase. An extract from the faeces will usually show brilliant red fluorescence in ultra-violet light. Normal faeces shows green fluorescence or a slight pink, with a Wood's filter. A fragment of faeces is placed in a small test-tube and dissolved, with the aid of a glass rod, in ½ inch of a mixture consisting of amyl alcohol, glacial acetic acid and ether. More precise information can be obtained by a quantitative analysis of faecal porphyrin[9] and this analysis is essential in doubtful cases. If latent porphyria is suspected, 4 ounces of urine, with a few drops of chloroform added as a preservative, and a sputum jar half full of faeces should be sent to a biochemist specially trained in porphyrin analysis.

In the acute stage the urine may immediately suggest porphyria because of its reddish-brown colour, and it will darken considerably on standing, particularly after the addition of hydrochloric acid. The fresh urine should also be tested for porphobilinogen by the Watson-Schwartz test. Ehrlich's aldehyde saturated with sodium acetate should be added to 5 ml. of urine, and the mixture shaken with chloroform; when porphobilinogen is present a purple colour will remain in the aqueous layer. Urine in acute porphyria will show marked red fluorescence in ultra-violet light, and the presence of porphyrin is confirmed by spectroscopic examination. It should be remembered that blood, beetroot and certain drugs may also cause a red urine.

TREATMENT

When porphyria is diagnosed treatment consists primarily in stopping all drugs that may be aggravating the condition. This includes a wide range of substances, particularly sedatives such as barbiturates. The doctor must advise the patient that there may be some discomfort, but that all will be well as long as drugs and chemicals that aggravate the disorder, including patent medicines and alcohol, are scrupulously avoided. Penicillin may safely be given, but sulphonamides are harmful. The extreme danger of thiopentone anaesthesia must be pointed out to the patient and to the relatives, and to convince them they should be given a few anonymous case-histories to read. If an operation is unavoidable because of serious organic disease, gas, oxygen and ether can safely be given but no barbiturates. If the skin is photosensitive the patient should keep out of the sun as much as possible and wear a hat and keep his sleeves down out of doors. Protective creams, such as 5% tannic acid in vanishing cream, are of some value for the hands. In the very rare 'congenital' disorder splenectomy may lessen the anaemia and porphyrin production.

In the acute stage good nursing, preferably in a private room in a hospital, is the most important single factor in aiding recovery. As there is as yet no specific antidote for porphyria, treatment depends on maintaining the patient's general condition and avoiding harmful drugs. These patients do best if given no sedatives whatever. In my experience it is possible to keep them fairly comfortable during the acute attack with the aid of cortisone and placebos such as vitamin tablets. Kind but firm nursing is essential, and visitors should be discouraged. If there is vomiting the nutrition and electrolyte balance must be carefully watched and maintained by intravenous feeding. Repeated examination of the blood and urine chlorides and the blood potassium may be required. As there is often evidence of liver damage I give these patients a high-protein, high-carbohydrate diet and high fluid-intake. ACTH or cortisone makes them feel better and appears to be of definite value; 25 mg. of cortisone may be given 6-hourly for 2 or 3 days and then half this dose for a similar period. As an aid to general nutrition I give daily 2 ml. of whole-liver extract by injection and a multi-vitamin preparation. Convulsions are best controlled in my experience by 30% ether in oil given over a period of hours by rectal drip. At the same time Epanutin may be given (1½ gr. 6-hourly) by stomach tube. The patient can also be fed through the tube. After ether has been given the rectum should be irrigated with normal saline. In the recovery stage physiotherapy is of great value if paralysis has occurred.

Once a case of porphyria has been diagnosed it is the doctor's responsibility to investigate the family history fully and the best method is to work out a family tree, which may take several months to complete if a number of generations are studied. Enquiry must be made in order to discover which side of the family is affected and which members on the affected side have inherited porphyria. The urine and faeces of the relatives on the affected side should be examined for porphyrins. It must not be forgotten that the syndrome will present in different ways in different members of the family. Some may have complained of symptoms the cause of which will not have been known, and the doctor will be able to make the correct diagnosis in patients who have long been regarded as neurotic. All affected members of the group should be interviewed, and they should be given a letter stating the evidence on which the diagnosis has been made and mentioning the danger of barbiturates and other drugs in this condition; this letter they should show to any doctor they may consult in future.

SUMMARY

Porphyria, a potentially serious familial disorder, is common in South Africa. In Europeans it is inherited as a non-sex-linked Mendelian dominant characteristic. A clinical genealogical study is recorded of 32 porphyric families in which 324 members had clinical manifestations of porphyria.

In the latent stage diagnosis depends on a full personal and family history, with special reference to skin sensitivity in the family, 'nervous breakdowns', abdominal pains, operations, pregnancy, and drugs that have been taken. The diagnosis can usually be confirmed in the quiescent stage by careful examination of the urine and faeces for increased porphyrin excretion. This should be carried out by a biochemist with experience in quantitative porphyrin analysis.

Acute porphyria must be considered in the differential diagnosis of all cases of severe abdominal pain, and the abdomen should not be opened until the urine has been examined. In an acute attack the urine is reddish-brown in colour and excess porphyrin and porphobilinogen will be present.

Prevention of acute attacks is the most important part of treatment. Barbiturate drugs are especially dangerous. If one case of porphyria is diagnosed enquiry will usually reveal several other cases among the relatives, who can then be warned of the inherent danger.

Porphyrics should be given a letter stating the evidence that confirms the diagnosis and mentioning the danger of certain drugs. They should be instructed to show the letter to any doctor they consult in the future.

This research has been aided by a grant from the Council for Scientific and Industrial Research.

REFERENCES

1. Barnes, H. D. (1951): S. Afr. J. Clin. Sci., **2**, 117.
2. Barnes, H. D. and Marshall J. (1952): Ann. Derm. Syph. Paris, **79**, 521.
3. Dean, G. (1953): Brit. Med. J., **2**, 1291.
4. Dean, G. and Barnes, H. D. (1955): *Ibid.*, **2**, 89.
5. Barnes, H. D. (1955): S. Afr. Med. J., **29**, 781.
6. Waldenstrom, J. (1937): Acta med. scand. Suppl. 82.
7. Watson, C. J. in Duncan G. G., ed. (1952): *Diseases of Metabolism*, 3rd. ed., Philadelphia: Saunders.
8. Cockayne, E. A. (1933): *Inherited Abnormalities of the Skin and its appendages*, London: Oxford Univ. Press.
9. Rimington, C. (1952): 2nd Int. Congr. Biochem. Paris.