THE PORPHYRIAS

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A lecture on The Porphyrias was delivered by Dr. Geoffrey Dean, M.D. at the S.A.S.P. National Council Meeting in Port Elizabeth in May, 1968.

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In spite of the old maxim "he is a good doctor who does his patient no harm," most doctors know in their hearts that on a few occasions in their lives they have been inadvertently responsible for the death of a patient. In certain forms of inherited porphyria commonly prescribed drugs may precipitate an acute and often fatal illness.

Porphyrin, from the Greek "porphyros," meaning purple, is a pyrrol pigment that forms the essential part of the molecule of respiratory enzymes that are necessary for all the forms of life that use oxygen; from one-celled organisms to the most complex ones. Chlorophyll is a compound of porphyrin and magnesium, the *haem* of haemoglobin is a compound of porphyrin and iron. Porphyrin has the remarkable property of showing a brilliant pink fluorescence when examined in ultra violet light (Wood's light). The porphyrias are disorders of porphyrin metabolism.

Until a few years ago porphyria was regarded as a very rare medical curiosity, but we now know that in South Africa it is very common among the White and Coloured population. The patient with porphyria becomes ill after taking barbiturate sedatives, or after a thiopentone anaesthetic (Pentothal). The patient then appears to be hysterical and complains of severe pain in the abdomen, back and limbs. These patients frequently vomit and are constipated. Their urine darkens on standing and resembles the colour of port wine or Coca Cola. When the urine is examined in ultra violet light it shows a brilliant pink fluorescence and spectroscopically the absorption bands of porphyrin are present. During attacks of acute porphyria a precursor of porphyrin, porphobilinogen, can easily be detected in the urine by means of Ehrlich's aldehyde reagent (the Watson-Schwartz test).

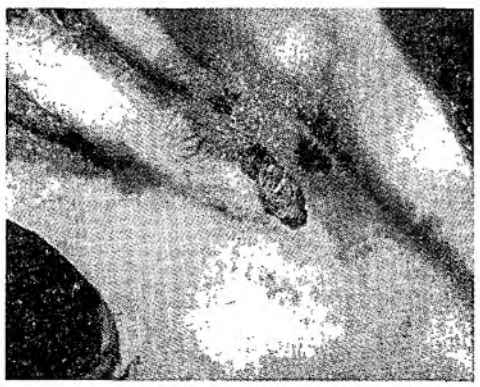
On studying the family histories of the patients who had had attacks of acute porphyria I found that a number of their relatives, usually young women, had died with very similar symptoms. Many of the family, particularly the men, would have an unduly sensitive skin on the back of the hands, a skin that abraded easily when it was knocked: when the skin was particularly troublesome it would often blister. Examination of the back of the hands would generally show a few sores or depigmented scars from previous sores.

On studying these porphyric families it soon became clear that porphyria of South African type was inherited as a Mendelian dominant character: this means that on average half of the children of a porphyric parent will inherit the disorder. It occurs in both sexes, and it can present with acute attacks, usually after barbiturates or sulphonamides it can cause a sensitive skin or it can be symptomless.

We later found that the simplest way of detecting South African porphyria, which because it presented in various forms we named *porphyria variegata*, was by the very high excretion of porphyrin in the faeces. A solution made from a small fragment of faeces dissolved in a solvent consisting of equal parts of amyl alcohol, glacial acetic acid and ether shows a brilliant pink fluorescence in ultra violet light if the patient has porphyria variegata. Excessive chlorophyll can also cause pink fluorescence, however, if hydrochloric acid is added to the mixture, human porphyrin will dissolve in the acid mixture which settles at the bottom but chlorophyll remains in the ether solution at the top. An excess of porphyrin in the faeces does not prove that the patient has porphyria variegata, because a few other conditions can cause a slight excess of stool porphyrin, but the suspicion is raised.

Onset of Attack

The acute attack of porphyria usually starts with pain in the abdomen, back or limbs and the patient is very emotional. Often there is vomiting and constipation so that a major abdominal disorder may easily be suspected and then there is a grave risk that the doctor will be tempted to open the abdomen perhaps under a thiopentone anaesthetic. The pulse is usually fast. There is often a marked fall in the blood sodium, chloride, potassium and calcium. Convulsions may occur. Over the course of a few days a general paralysis, due to peripheral neuritis, may develop and at this stage the patient may easily die.



A porphyric hand, showing sores and blisters.

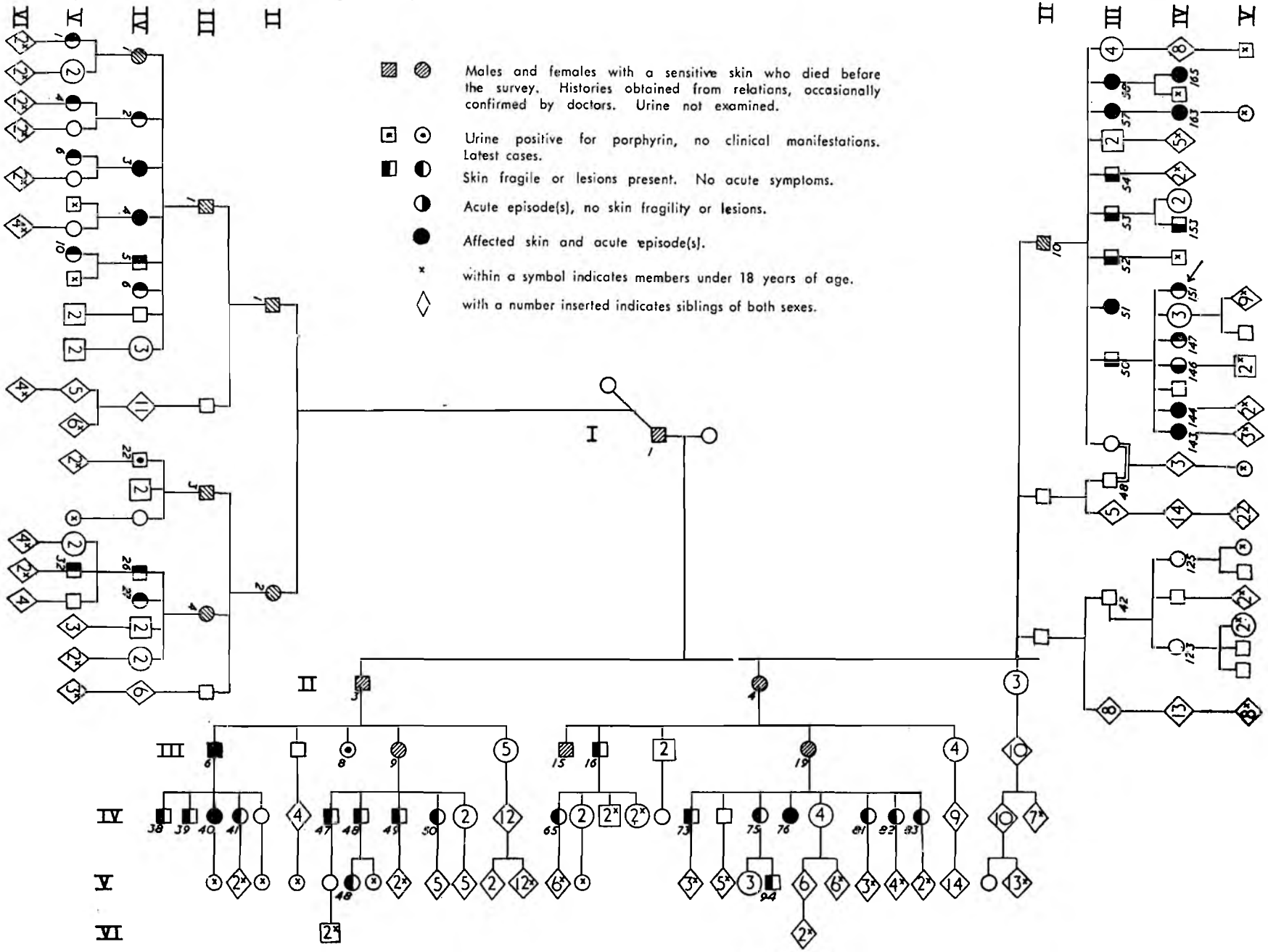
The problem was how to diagnose porphyria in the latent phase before an acute attack was accidentally precipitated by drugs and we found the easiest way of doing this was by routine screening of the faeces in ultra violet light. If a great excess of porphyrin is found in the faeces examination of the urine for increased porphyrin excretion and examination of the patient, and of the patient's family, for a sensitive skin on the back of the hands nearly always makes it quickly possible to determine whether or not the patient has inherited porphyria variegata.

Importance of Observation by Nurse

Often it has been the nurse who has been the first to notice the sensitive skin on the back of the hands that abrades easily and sometimes blisters and leaves sores. The nurse can then draw the doctor's attention to the possibility that the patient may have porphyria variegata. All nurses should familiarise themselves with the appearance of the sensitive skin on the back of the hands that is often seen, particularly in men who are much out in the sun. Often only the small pigmented scars of previous healed sores can be seen and on talking to the patient he or she will admit that they have a "sagte vel" or the "van Rooyen skin".

Histories of Porphyric Families

All the porphyric families that I had studied were of Afrikaner stock and descendants of old boer families. Eventually it was possible to trace the first 32 family groups that were studied back to four of the eight children of Gerrit, the son of Jan Gerrit Jansz, who was married at the Cape in 1688 to Ariaantje, the daughter of Jacob, one of



the eight orphans sent to South Africa from Rotterdam on the ship *China*, by the Lords Seventeen of the Dutch East India Company. They were sent to be wives for the first free burgers at the Cape of Good Hope.

Translation of Extract from a letter to Commander Simon van der Stel, Commander at the Cape of Good Hope, and his Council, from the Directors of the Chamber of Rotterdam, of the Dutch East India Company. Dated 23.12.1687.
Extract from the Records, Cape Archives: C. 416, *pp.* 1030 *to* 1032.

. . . . Whereas in a Resolution of the Council of Seventeen dated 3rd October, 1685 it is already laid down that the Cape Station should be provided with persons who understand agriculture and the soil, both men and women, with a view to establishing in due course an important Colony and place of refreshment for the use of the Company and to the benefit of the inhabitants; We now therefore have favoured the eight young women with a passage to the Cape of Good Hope on the ship *China* (which is a large vessel), proceeding from this Chamber, and they are to remain at the Cape for the above purpose under a five year contract, in accordance with the Resolution of the latest meeting of the Council, whereas prior to this date it was a contract for 15 years, and subject to the regulations drawn up and laid down for Free burghers. The names are:

Arijaentgen Jansz van Son of	Rotterdam
Willemtgen Arijens de Wit	do.
*Arijaentgen Jacobs van den Berg	do.

*Also known as Ariaantjie Jacobs.

Judith Jansz Verbeecq	do.
Petronelle Cornelis van Capelle	do.
Jongeten Cornelis van den Bout	do.
Catharina Jans van der Zee	do.

and Anna Eltrap van Kleef conversant with (farm work and) the cultivation of the soil. And it is the intention of the Lords Seventeen to employ these and other young women as agriculturists. We therefore request and earnestly recommend to you that you see that they are suitably placed, or if they marry, see that they do so with honest, capable and industrious men engaged in farming or of definite intention to undertake such work, and with whom these young women may be able to make a living, while (at the same time) as far as possible dissuading them from marriage with military men, as this is not within the intentions of the Lords Seventeen.

In the meantime, and until the marriage of these young women, it is incumbent upon you to provide them with the necessary sustenance and housing, maintain such discipline as you may deem suitable, and providing them appropriate handiwork or honest employment, so that their occupations and deportment may further their own advancement; and the management and conducting of this recommendation we entrust to your Honours' discretion. . . .

Because the early settlers married young and had very large families, there has been a malthusian explosion of population since then so that today one million of South Africa's three million White population hold 40 names and have received these names from 40 original settlers. By chance one of the early settlers, either Gerrit or his wife Ariaantje, brought to South Africa the gene for porphyria variegata and rapid multiplication of their descendants has caused the high frequency of the gene in the population today. The gene did little harm before the introduction of barbiturates and sulphonamides. Gene-frequency studies show that the prevalence of porphyria variegata among the White population of South Africa is 3 in 1,000. The prevalence of porphyria variegata varies however from district to district, for instance it is higher in the Eastern Cape and lower in Durban.

Gerrit Jansz (van Deventer) had eight children and four of these children inherited porphyria. The first daughter, Jacomintje, married Cornelis van Rooyen, the first van Rooyen in South Africa: five of their children inherited the gene for porphyria variegata. Another daughter married a Nel, and a third married twice—first Debes, and then Phillipus Snyman: she had porphyric descendants by both marriages. The fourth porphyric child was a son who carried on the name Van Deventer. Even today porphyria is more common among those who can trace a Van Rooyen, Nel, Snyman or Van Deventer among their ancestors. Other families that intermarried at an early date with the porphyric families are: Barnard, Greeff, Van Niekerk, Ferreira, Meyer, Rautenbach, Knoetze, Potgieter, Prinsloo, Van der Vyver, Cellier and Van der Merwe. But today a porphyric may hold any name, including English surnames, because porphyria variegata is not linked to the male sex, and women take their husband's name on marriage.

Every South African-born nurse should arrange to have her own specimen tested for excess porphyrin excretion and this routine test is already carried out at many South African hospitals. The test on the stool, described above, screening the solution in ultra violet light, is a very simple test and all nurses should take any opportunity they can to learn how to do the test themselves.

The Classification of the Porphyrias

In 1937 Professor Jan Waldenstrom, of Lund University, Sweden, described a form of acute porphyria, usually precipitated by barbiturates or sulphonamides, which is fairly common in Sweden, particularly in the North. He called the disorder Intermittent Acute Porphyria. This is the type of acute porphyria that is most commonly seen in Europe and North America; it is also inherited as a Mendelian dominant character but skin lesions do not occur. It is very rare in South Africa. It differs from porphyria variegata because porphobilinogen, a precursor of porphyrin, is usually present in adults even in the quiescent stage and there is little increase in the stool porphyrin. In porphyria variegata the porphobilinogen is only present during the acute attack but the stool porphyrin is high both during the acute attack and in the quiescent phase. There is yet another mendelian dormant porphyria in which effects of acute porphyria may occur after drugs. It is known as Coproporphyria because most of the porphyria in the stool is coproporphyrian.

It has long been known that a form of cutaneous porphyria in which the exposed skin blistered and abraded easily occurred without any familial history particularly in men who were addicted to taking excessive alcohol. It is often called descriptively *porphyria cutanea tarda*. The urine will be dark from excessive porphyrin excretion but attacks of acute porphyria do not occur after taking barbiturates. This type of acquired or idiopathic porphyria is the commonest cause of cutaneous porphyria in Europe and North America. It is very common among the Bantu of Southern Africa who are addicted to drinking a home-brewed alcohol, "skokiaan," but it is surprisingly uncommon in West Africa—perhaps because the national drink there is palm wine. It is uncommon among White South Africans among whom cutaneous porphyria is usually the inherited form, porphyria variegata.

A most interesting epidemic of acquired porphyria started in Eastern Turkey in 1955, when Doctor Cam, of Diyarbakir noticed he was seeing a large number of children who had sores and blisters on their hands and face. Their dark urine showed the typical fluorescence of porphyrin in ultra violet light (Wood's Light). He realised that these children were suffering from an acquired porphyria which he traced to poisoning from eating bread made from seed wheat sent to Turkey from the United States. The seed, clearly marked "not for consumption," had been treated with a fungicide hexachlorobenzene to protect it against the wheat fungus "Tilletia Trictici." Before the epidemic was finally stopped by using an alternate fungicide over 5,000 children were seriously affected. These children often grew a great excess of hair on their face and arms and their skin darkened; they were known as the monkey children by the country people.

Intermittent acute porphyria, porphyria variegata and acquired porphyria are all due to disturbed porphyrin function in the liver and they have been grouped together as the hepatic porphyrias. There may also be an inherited form of cutaneous porphyria in which acute attacks do not occur.

The Porphyrias:

1. Hepatic in origin.
    1. Intermittent acute porphyria (Sweden).
    2. Porphyria variegata (South Africa).
    3. Coproporphyria.
    4. Purely cutaneous porphyrias,
       Alcohol,
       Hexachlorobenzene,
       etc.
2. Erythropoietic in origin.
    1. Congenital porphyria.
    2. Erythropoietic protoporphyria.

There may be other inherited porphyrias.

There are also two very rare erythropoietic porphyrias in which the disturbance in porphyrin metabolism takes place in the bone marrow. In one type, erythropoietic porphyria or congenital porphyria, children are affected and it is inherited as a Mendelian recessive character. Besides the sensitive skin that abrades and blisters and the pink urine containing a great excess of porphyrin, there is usually anaemia and an enlarged spleen. Often there is pink staining of the teeth and bones which will fluoresce in ultra violet light. This type of porphyria has been described in cattle in South Africa by Fourie and Rimington at Onderstepoort; it is known as "Pink Tooth Disease". Another form of erythropoietic porphyria, inherited as a Mendelian dominant character, causes urticaria—it is known as *erythropoietic protoporphyria.*

During the last few years the hospitals in Port Elizabeth, followed by a number of other hospitals in South Africa, have instituted routine screening of the patient's stool for porphyrin before the patient is given a thiopentone anaesthetic, other barbiturates or sulphonamides. By this means porphyria variegata can be diagnosed before the acute attack has been precipitated by drugs.

In conclusion, nurses are often able to warn the doctor in attendance that their patient might have porphyria variegata, either by noticing the sensitive skin on the back of the patient's hands or, during an attack of acute porphyria after the administration of barbiturates or a thiopentone anaesthetic, by noticing that the urine is port wine coloured or like Coca Cola. The earlier it is recognised that the patient has inherited porphyria the less is the risk that the patient will die from an acute attack.

Once a patient has been found to have porphyria of inherited type a full family study should be undertaken because others will be found among the relatives who have inherited the gene. One patient suggested to me that she should have tattoed on her abdomen "I have porphyria do not open me." This is perhaps an extreme measure but porphyrics should be given a letter stating that they have porphyria and this letter should be shown to any doctor they may consult.