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ROUTINE TESTING FOR PORPHYRIA VARIEGATA

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It is now well established that a Mendelian dominant form of porphyria, which is not sex-linked and which may present with acute attacks or with a sensitive skin, is common among the White and Coloured populations of South Africa.[1-7] This form of porphyria, porphyria variegata, is a different disorder from intermittent acute porphyria[8] — the Mendelian dominant porphyria described by Waldenström in Sweden.[9,10] In other parts of the world both intermittent acute porphyria and porphyria variegata occur although they are comparatively uncommon. Among the Bantu population of South Africa symptomatic cutaneous porphyria, generally secondary to disturbed liver function, is frequently seen,[11] and it occasionally occurs among the White citizens of this country.

The high incidence of porphyria variegata among the White population of Southern Africa is shown by the fact that during the last 10 years I have personally attended 73 patients during attacks of acute porphyria and have detected 897 porphyrics in 118 porphyria-variegata families. In a screening experiment in 1957 two groups of White South Africans were screened for porphyria variegata using the methods described below.[12] Among 608 patients at a mental hospital 4 were found to have porphyria; and among 645 nurses, a special group with a high incidence of Afrikaners, 8, after full investigation, were found to have inherited the gene. Most attacks of acute porphyria follow the taking of barbiturates and particularly thiopentone anaesthetics. In 1958, 8 patients at the Provincial Hospital, Port Elizabeth, were known to have developed acute porphyria following thiopentone anaesthetics, and of these 3 died. A number of undiagnosed milder attacks of acute porphyria probably occurred. No patients with intermittent acute porphyria have been seen in Port Elizabeth.

Until we started routine testing for porphyria in Port Elizabeth there were usually one or two patients receiving treatment at the hospital for acute porphyria. As these patients generally required treatment in a private room with a special day and night nurse, the cost to the Administration must have been high, because they were often in hospital for some months and required a great deal of medical and nursing attention. The cost in suffering for the patients concerned and for their relatives was of much greater importance. Highly experienced physicians and surgeons frequently overlook the disorder and prescribe barbiturates or give a thiopentone anaesthetic to porphyrics.

It is by no means inevitable that patients who have inherited porphyria will develop acute porphyria after thiopentone. Some patients were given barbiturates or thiopentone on two or three occasions without a severe acute attack. In my own mind I liken the reaction to the firing of a gun: the pressure required to fire off an attack of acute porphyria varies from person to person and from time to time in the same person. For instance, acute porphyria is rare in children, and I have not seen a single case in a child under the age of 16; it is also uncommon after the age of 60. In males the incidence of acute porphyria is at its highest between the ages 17 and 60; and in women between the age of 17 and the menopause.

DIAGNOSING SOUTH AFRICAN GENETIC PORPHYRIA: PORPHYRIA VARIEGATA

In order to screen patients as a routine for porphyria variegata a very simple test is required. Patients are generally admitted to hospital the night before operation, and the test must be carried out before they are given thiopentone the following morning to exclude latent or quiescent porphyrics. In porphyria variegata there is nearly always, but not invariably, a high excretion of porphyrin in the stool during adult life, particularly during the period when the patient is most at risk. There is generally a slight increase in the stool porphyrin in children, but in many cases not enough to detect that they are porphyrics, unless a careful quantitative analysis is carried out. In old people the stool-porphyrin levels also drop. There is no simple single test for porphyria variegata that can be guaranteed to detect every case, because porphyria is a varying metabolic disorder. In many patients with quiescent porphyria there is a slight increase in the urinary porphyrin, but this also occurs in many conditions other than porphyria. On the other hand, an increased urinary porphyrin may not be found in porphyria if the urine is dilute. In my experience routine testing for increased porphyrin excretion in the stool is much more reliable than routine testing for increased urinary porphyrin. Furthermore, there are so many false-positive reactions in routine urinary testing that it is not possible to obtain the cooperation of a large group of doctors in using this test before operation.

In order to carry out the simple screening test that we use in Port Elizabeth, a small fragment of stool, such as can, if necessary, be obtained on a finger stall, is collected on a glass rod or wooden stick which is then inserted into a test tube containing 2 ml. of a solvent consisting of a mixture of equal parts of amyl alcohol, glacial acetic acid, and ether. The solvent is stirred until it has reached a light-brown colour and the liquid is then decanted into a clean test tube. The solution is then examined in ultraviolet light using a Wood's filter in a darkened room or a darkened box. In normal light the solution will look light brown in colour, whether or not it has come from a porphyric patient. In ultraviolet light the porphyric stool will show a brilliant pink fluorescence. This fluorescence is usually so strong that it persists even when the solvent is diluted several times. If the patient is not a porphyric the solution will be green or grey or perhaps just slightly orange when examined by a Wood's light. A quantity of chlorophyll in the stool also causes a pink fluorescence, because chlorophyll is a

porphyrin. The porphyrin of chlorophyll can be separated from copro- and protoporphyrin by adding 2 ml. of 1·5 normal hydrochloric acid to the solvent, shaking the mixture and allowing the acid solution to separate out to the bottom of the test tube. Copro- and protoporphyrin will pass into the acid solution at the bottom; chlorophyll porphyrin will remain in the ether solution at the top.

A high excretion of porphyrin in the stool does not necessarily mean that the patient is a porphyric, because a few other disorders can also cause a high stool porphyrin.[13] It has been found that some patients, who excrete increased porphyrin in the faeces but who are not porphyrics, have disorders in their alimentary tracts; 6 of these in the past year had cancer of the stomach or colon.

If a high excretion of porphyrin is found in the stool the patient should not be given barbiturates or sulphonamides until it is known whether or not the increased porphyrin is caused by porphyria. Further investigations must then be undertaken. The urine should be examined for excess porphyrin because usually, but not always, in porphyria variegata there is an excess of porphyrin in the concentrated urine as well as in the stool. The patient should be examined for a sensitive skin (on the back of the hands) and for a skin that abrades easily, and a careful history should be taken to ascertain whether any other members of the family, particularly on the male side, suffer from a sensitive skin. By correlating the personal and family history, the patient's symptoms and signs, and the presence or absence of porphyrin in the urine as well as in the stool, it is usually fairly easy to decide quite rapidly whether or not the patient is a porphyric. A patient born in Europe is unlikely to have porphyria variegata. It may be necessary in doubtful cases to repeat the examination of the stool on a few occasions, because in porphyria the porphyrin excretion continues, whereas in temporary disorders it is intermittent. I also make a practice of carrying out a barium meal and barium enema X-ray examination on patients who have a definite excess of porphyrin excretion in their stool, and whom I do not consider, from their personal and family history, to be porphyrics. This is done because some have been found to have cancer of the gastro-intestinal tract.

If an excessive amount of porphyrin is found in the stool and there is any doubt about the diagnosis, a quantitative analysis of porphyrin should be carried out. Fortunately in porphyria variegata the excretion of porphyrin is often 10 or 20 times the normal amount or even more. The upper limit of normal is arbitrary, but, if the coproporphyrin is above 30 μg. and the protoporphyrin is above 60μg., or the combined porphyrin above 75 μg./g. dry weight, the possibility of porphyria should be considered. In most adult patients with porphyria variegata the stool prophyrins are more than 200 μg./g. dry weight, and often more than 500 μg./g. dry weight. In this survey 20 specimens of stool from patients who had been found to have porphyria on routine testing were analysed quantitatively for stool porphyrin; the range was from 3,330 μg./g. dry weight to 164 μg./g. dry weight. The average was 1,339 μg./g. (686 μg./g. copro-, and 653 μg./g. protoporphyrin).

Increased porphyrin excretion in the urine can occur in many other conditions besides porphyria, in particular in lead poisoning and in disordered liver function; examination of the urine does not, therefore, provide such a useful screening test for South African genetic porphyria in the quiescent phase as screening the stool. It is, however, a very useful confirmatory test. A simple way of examining the urine for excess porphyrin is to use the solvent mentioned above. One ml. of the solvent is added to 10 ml. of urine; the mixture is well shaken and then left to stand for a few minutes so that the solvent floats to the top.[14] The liquid is then examined in Wood's light and, if an excess of porphyrin is present, the ether solution at the top of the test tube will show a red fluorescence. The urine should also be examined spectroscopically, but considerable practice in the use of the spectroscope is necessary before the small increase in porphyrin excretion often found in the urine in quiescent porphyria can be detected.

In Swedish porphyria, or intermittent acute porphyria, porphobilinogen and delta-aminolaevulic acid are usually found in the urine during the quiescent phase.[10] However, in porphyria variegata there is no increase in the porphobilinogen in the quiescent phase, but it is present during an acute attack. This fact can be used to differentiate acute from quiescent porphyria variegata. In acute porphyria variegata the Watson-Schwartz test for porphobilinogen is strongly positive.[15] This test is carried out by adding 2 ml. of Ehrlich's aldehyde reagent to 2 ml. of urine and shaking the mixture. Two ml. of a saturated solution of sodium acetate is then added and, if either porphobilinogen or urobilinogen is present, a purple colour results. The urobilinogen is soluble in chloroform and, therefore, if chloroform is added to the mixture and it is shaken again and allowed to separate, urobilinogen will come down in the chloroform layer, but porphobilinogen will stay in the aqueous solution. If acute porphyria is suspected in porphyria variegata, the Watson-Schwartz test with Ehrlich's aldehyde will quickly show whether or not the patient has an acute attack. This test, it must always be remembered, cannot be used for detecting quiescent porphyria variegata, because in the quiescent phase this test is negative.

ROUTINE TESTING IN PORT ELIZABETH

At a hospital committee meeting at the Provincial Hospital in Port Elizabeth in 1959 my proposal was accepted by the Medical Superintendent, Dr. J. H. McLean, and the committee, that all patients who were admitted to hospital should have their stools tested as a routine for porphyrins before a thiopentone anaesthetic is given or barbiturates administered. The Provincial Hospital in Port Elizabeth is an open hospital attended by about 160 doctors, and only a very high degree of cooperation among these doctors, and especially among the anaesthetists, made this routine testing possible. Normally a specimen of stool was sent to the South African Institute for Medical Research* the day before the operation. If necessary, the stool was obtained by an enema or by a gloved finger. In emergencies the patient was sent direct to the theatre and the anaesthetist carried out the routine test in the anteroom of the theatre. A screening lamp was kept in the main theatres and at the maternity block in the hospital. Routine testing was also instituted at St. Joseph's Hospital, a

* The Port Elizabeth branch.

private nursing home, where the sisters tested the specimens. Records were kept and I was informed about every positive stool or about every 'query positive' result. In these cases I investigated the faeces and urine and the patient personally. During the first 2 months there was an excessive number of false positives due to extreme zeal on the part of the laboratory technicians who carried out the tests and who reported every specimen which showed a slight orange colour. With increasing experience the number of false positives became small. There were, however, probably as many patients who excreted slightly increased porphyrin without being porphyrics, as there were those who were found to have porphyria on thorough investigation.

Between 1 April 1959 and 31 March 1960, 23 patients were found to have porphyria at the Provincial Hospital and 5,647 tests were carried out on adults (1,929 male and 3,718 female). A number of these patients belonged to known porphyric families, and a few of the patients were known porphyrics who had been diagnosed previously. If a patient had not been investigated previously and was discovered on routine testing, a specimen of stool was sent to Dr. H. D. Barnes, of the South African Institute for Medical Research, Johannesburg, for a quantitative analysis of the stool porphyrin. He carried out a quantitative analysis of stool on 20 of the porphyrics. Most porphyrics whose porphyrin was analysed had a very high stool porphyrin, but, as can be seen from Table I, 2 of the older patients (Nos. 17 and 19) did not have a greatly increased stool porphyrin and, in fact, No. 19 was missed by the technician who did the routine tests. Nevertheless, few patients with porphyria could have been missed among those who were tested, because, unlike in previous years, we did not have unexpected attacks of acute porphyria.

At St. Joseph's Hospital 6 patients with porphyria were admitted during the 12-month period and 811 routine tests were carried out. During the early days of routine testing a young man, No. 24, was admitted to the hospital complaining of severe abdominal pain, vomiting, and constipation. Two enemas gave no result and the stool was not tested for porphyria as a routine. Unfortunately the urine was not tested either and the surgeon, who knew porphyria well and who had diagnosed a number of patients with porphyria in the past, nevertheless suspected that this patient had intestinal obstruction. The patient was given 0·35g. of thiopentone so that a laparotomy could be performed. At operation no definite pathology was found, but it was thought a condition of partial obstruction was present, and a caecostomy was carried out. Two days later the sisters noticed that the urine was dark-red in colour and, as soon as it was examined, it was found to contain a great excess of porphyrin and the Watson-Schwartz test was strongly positive. The patient became delirious and had to be fed intravenously. He was given intravenous saline, calcium by injection, potassium, etc. He developed a number of epileptic attacks and also tetany. When the anaesthetist, who had given him the thiopentone, visited the ward to see another patient, the patient with acute porphyria attacked him with a water bottle and injured his head. (The patient was delirious and had not recognized the anaesthetist, but thought he was a burglar.) Unfortunately this patient become paralysed and died from acute cardiac collapse. At autopsy a very high level of porphyrin was found in his bile and in his liver. On investigation two members of his immediate family were found to have porphyria. This unfortunate catastrophe encouraged the anaesthetists to make certain that their patients were given a routine test before the administration of thiopentone.

The details about the 29 patients who were found to have porphyria during the 12 months are described in Table I. Certain patients require special mention:

Case 1, No. 3

This patient had 2 previous laparotomies with thiopentone anaesthetic and the surgeon remembered that he had a very stormy convalescence — he became very agitated and ruptured the wound. On this occasion he was admitted for a repair of his post-operation abdominal hernia. Porphyria was detected by routine testing, and he was given a gas, oxygen and ether anaesthetic. He had no ill effects after the operation. The surgeon commented that his excellent convalescence was quite unlike the previous occasions.

Case 2, No. 5

This patient was also admitted for repair of his hernia after a previous operation when he had thiopentone. On the previous occasion the abdominal repair ruptured and had to be re-sutured. Unfortunately, although the anaesthetist knew that the patient had porphyria, he was not convinced of the danger and he gave him 0·3 g. of thiopentone. One week later the patient developed severe abdominal pain, vomited repeatedly and was clearly very ill. The Watson-Schwartz test by then was positive. He ruptured his wound.

Case 3, No. 7

This patient was admitted from the country with the diagnosis of acute porphyria after taking nembutal. She made a good recovery.

Case 4, No. 12

This patient belonged to a large porphyric group that had been previously investigated. She had not been tested for porphyria before admission, but she had been warned about the danger; nevertheless, she did not inform her doctor that she belonged to a porphyric family. On routine testing she was found to have porphyria and was given no barbiturates.

Case 5, No. 16

This patient developed a mild attack of acute porphyria after taking seconal tablets for a few nights. A previous stool test had been reported negative, but when I saw her the stool test was positive. She had a mild attack of acute porphyria, but she made a good recovery.

Case 6, No. 19

This 60-year-old patient was admitted to hospital for a hysterectomy. I had attended her daughter for cutaneous porphyria in the past and had also investigated the family. Nine members of her family had porphyria. This patient refused investigation because she would not admit that she had inherited any genes from an Afrikaner ancestor. She was convinced that she was of pure 1820 British settler stock. Her stool test was negative, and she was given thiopentone and made a good recovery. A quantitative analysis of her stool some weeks after the operation showed, however, that there was some increase in the stool porphyrin. Ten years ago she became acutely ill a few days after a cholecystectomy; she was emotionally disturbed and passed dark urine. It took her 3 months in hospital to recover.

Case 7, No. 28

This patient was admitted for laparotomy because he was deeply jaundiced. His stool was clay-coloured and his urine contained a great excess of bile. He belonged to a known porphyric family and previously he had had a great excess of porphyrin in his stool. His son is also a porphyric. He had an obstruction to his bile duct from a neoplasm of the pancreas, and neither bile nor porphyrin was escaping into his intestinal tract. His urine contained increased porphyrin. It must be remembered that if there is obstruction

TABLE I. PATIENTS FOUND TO HAVE PORPHYRIA VARIEGATA ON ROUTINE SCREENING, APRIL 1959 - MARCH 1960

PROVINCIAL HOSPITAL, PORT ELIZABETH, ROUTINE TESTS: 5,647 (1,929 MALES, 3,718 FEMALES)

No.	*Sex*	*Age*	*Initial*	*Diagnosis on admission*	*Screening faeces*	*Screening urine*	*Watson-Schwartz test*	*Skin sensitive*	*Treatment instituted*	*If routine stool test*	*Analysis/porphyrin stool dry weight*		*Porphyrics found in family*	*Outcome*
											Copro μg.%	*Proto* μg.%		
1	F	27	B	Abdominal pain, insomnia, on seconal for sleep	++++	+++	++	+−	Acute porphyria diagnosed, conservative treatment	Yes	750	720	3	Recovered
2	F	31	S	Menorrhagia—for D & C, porphyria diagnosed 1958	++++	+	−	−	Gas, oxygen, no pentothal	Yes but known porphyric	−	−	−	Recovered
3	M	45	D	Had 2 previous laparotomies with pentothal, now admitted for repair abdominal hernia	++++	+++	−	++	Gas, oxygen, ether. No ill effects after operation	Yes	294	494	3	Recovered
4	F	35	W	For colporrhaphy	++++	−	−	−	Gas, oxygen, ether. No ill effects after operation	Yes	595	870	2	Recovered
5	M	32	C	For hernia repair after previous operation, when he had pentothal. On previous occasion abdominal repair ruptured and had to be resutured	++++	+	−	++	Although anaesthetist knew he had porphyria, 0·3 g. of pentothal was given. One week later abdominal pain and vomiting. Watson-Schwartz test positive. Ruptured wound	Yes	395	610	3	Recovered
6	F	25	deK	In labour. Had acute porphyria June 1958 after seconal	++++	+	−	−	No barbiturates given	Known porphyric	−	−	4	Recovered
7	F	33	E	Admitted as acute porphyria after nembutal	++++	+++	+++	−	Intravenous glucose, saline, calcium, and potassium	Acute porphyria	−	−	3	Recovered
8	F	39	deR	Admitted for hysterectomy	++++	−	−	−	Gas, oxygen, ether. No pentothal	Yes	750	850	3	Recovered
9	F	36	M	Admitted for hysterectomy	++++	+	−	+	Gas, oxygen, ether. No pentothal	Yes	486	794	6	Recovered
10	F	31	P	In labour	++++	+	−	+	No barbiturates given	Yes	1,210	1,260	1	Recovered
11	M	42	P	After a few days of seconal had acute abdominal pain and vomiting; admitted for laparotomy	++++	++	+++	+	Treated conservatively; salt, calcium, etc.	Yes	1,195	860	−	Recovered
12	F	27	W	Hypertension during pregnancy	++++	+	−	−	Conservative. Although not previously tested, a member of a porphyric group already investigated. Her father and cousin died a few years ago of acute porphyria at this hospital. She had been warned about porphyria but did no tell her doctor	Yes	510	600	33	Recovered
13	F	45	N	Admitted as severe cutaneous porphyria	++++	+++	−	+++	Conservative	Known porphyric	−	−	3	Recovered
14	F	27	E	Cutaneous porphyria suspected by dermatologist	++++	+++	−	+++	Conservative	Suspected porphyria	−	−	4	Recovered
15	F	79	E	Known porphyric. Admitted for operation—lipoma on leg	+++	+	−	−	Gas, oxygen, ether	Yes. Known porphyric	−	−	11	Recovered
16	F	49	M	Acute porphyria after seconal. A previous stool test had been reported negative	+++	+++	+++	−	Glucose, saline drip, calcium gluconate, potassium chloride, etc.	Yes	200	206	2	Recovered

PROVINCIAL HOSPITAL, PORT ELIZABETH, ROUTINE TESTS: 5,647 (1,929 MALES, 3,718 FEMALES) (Cont'd.)

No.	Sex	Age	Initial	Diagnosis on admission	Screening faeces	Screening urine	Watson-Schwartz test	Skin sensitive	Treatment instituted	If routine stool test	Analysis/porphyrin stool dry weight		Porphyrics found in family	Outcome
											Copro µg.%	Proto µg.%		
17	M	55	F	Admitted for correction of squint	+	++	−	+	Conservative	Yes. Repeated after 3 months	96 102	97 119	1	Recovered
18	M	26	M	Admitted for reduction of dislocated shoulder	+++	+	−	−	Gas, oxygen, ether	Yes. Known porphyric	−	−	16	Recovered
19	F	60	F	Admitted for hysterectomy	−	+	−	−	As stool test was 'negative' given 0·35 g. of pentothal for hysterectomy. Made good recovery.	Yes	72	92	9	Recovered
			Sister	Known porphyric, retested	+++	++	−	+						
			Daughter	Known porphyric with a very sensitive skin, retested	++++	+++	−	+++	Her daughter and sister were known porphyrics. She had formerly refused to send a specimen for testing. Ten years previously she collapsed 10 days after cholecystectomy and took 10 weeks to recover					
20	M	53	C	Admitted as ?coronary thrombosis	++++	Trace	−	++	Conservative. Although not previously tested, a member of a porphyric group already investigated	Yes	395	343	29	Recovered
21	F	19	N	Abdominal pain during pregnancy	++++	−	−	+++	Conservative	Yes	372	645	1	Recovered
22	F	48	K	Admitted for treatment severe backache	++++	++	−	+++	Back manipulated under gas and oxygen anaesthetic	Yes. House doctor diagnosed porphyria	1,000	875		Recovered
23	F	58	B	Carcinoma of cervix	++++	++	−	+	Gas, oxygen, ether. This patient was found to belong to a large clan of porphyrics from the Ladismith area	Yes	1,010	870	29	Recovered from operation
ST. JOSEPH'S HOSPITAL, PORT ELIZABETH, ROUTINE TESTS 811 (257 MALES, 554 FEMALES)														
24	M	27	R	Took sonergan (butobarbitone) 2 at night for 5 days. Developed severe abdominal pain, vomiting and constipation. Two enemas, no result; so stool not routine tested for porphyrin. Urine not tested. Given 0·35 g. of pentothal. Laparotomy and caecostomy. Acute porphyria recognized 2 days later	++++	++++	+++	+−	Delirious, attacked and injured anaesthetist a few days later. Fed intravenously. Saline, calcium, potassium, etc. Had convulsions, tetany. Became partly paralysed; knee jerks absent. Died, sudden cardiac collapse	Routine test missed	1,220	615	2	Died
25	F	41	M	Admitted for removal of ovary. Was to have pentothal anaesthetic	++++	++	−	+	Gas, oxygen, ether	Yes	875	590	−	Recovered
26	F	47	N	Admitted for hysterectomy (fibroids)	++++	+	−	−	Gas, oxygen, ether	Yes. Known porphyric	−	−	11	Recovered
27	F	31	L	Admitted for hysterectomy (fibroids)	++++	−	−	+	Gas, oxygen, ether. Had pentothal for previous operation 6 years previously. Good recovery, but skin of hands abraded easily since	Yes	2,060	1,270		Recovered
28	M	62	L	Admitted for laparotomy. Deeply jaundiced	− Clay colour	+ Bile ++	−	−	Gas, oxygen, ether. Neoplasm of pancreas found. Cholecystenterostomy	Yes. Known porphyric	very low		31	Recovered from operation
29	F	14	vR	Admitted for tonsillectomy	+++	−	−	−	Mother had acute porphyria after pentothal 1952. Recovered	Yes	250	395	31	Recovered

to the bile the stool test for porphyrin will inevitably be negative.

THE INCIDENCE OF PORPHYRIA VARIEGATA IN THE EASTERN CAPE

During the 12-month period 23 porphyrics were found at the Provincial Hospital out of 5,647 cases on routine testing in adults (17 female and 6 male). Children were not tested. More women are admitted than men, and this no doubt accounts for the higher incidence amongst the women. The fact that more women are given barbiturates and have operations is, in my opinion, the chief reason for the higher incidence of acute porphyria in women. Fifty-three further undiagnosed cases of porphyrics were found on investigating the families. During the 12-month period about 10,900 adult patients were admitted to the two hospitals, excluding readmissions, and 60% of these were tested for porphyria. Many of the older patients, who were not admitted for operation and not given barbiturates, were not tested. No doubt a number of these patients also carried the gene for porphyria. During the present year we are endeavouring to test all admissions to hospital. A stamp has been placed on the outside of the hospital folders marked 'porphyria positive' or 'porphyria negative' and, as the patients are tested, the result of the test is clearly marked on the folder. At St. Joseph's Hospital 811 routine tests were carried out and 6 patients were found to have porphyria. At both hospitals the only patient who died was one whose routine test had been missed. At the Provincial Hospital the incidence of porphyria was 1 out of 246 routine tests. Taking the two hospitals together the incidence was 1 out of 223 routine tests. In round figures the incidence of porphyria variegata among hospital admissions in Port Elizabeth appears to be at least 1 in 250. The hospital admissions represent a good cross-section of the community, but have a higher incidence of porphyria than the healthy population, since some patients are admitted to hospital because of their porphyria. Nevertheless, from the number of porphyrics I have detected and the number of healthy porphyrics admitted to hospital, I estimate the incidence of porphyria variegata among the White population of the Eastern Cape to be about 1 in 350.

The incidence of porphyria variegata can be estimated by the following indirect method: Patients with porphyria variegata in South Africa can be traced back to one original family, that of Gerrit Jansz (van Deventer) who married Ariaantje Adriansse at the Cape in 1688.[16] Gerrit had 8 children and porphyric families can be traced back to 4 of them. The first daughter, Jacomintje, married the first van Rooyen to come to South Africa, Cornelis, who came from Gorkum in 1713. Four of Cornelis van Rooyen's 11 children were sons who carried on the family name. Porphyric groups can be traced back to 5 of the 11 children, who, therefore, inherited the gene for porphyria from Jacomintje. Another daughter of Gerrit Jansz married one of the first Nels. Yet another daughter married twice and had porphyric descendents by both marriages. She first married Phillipus Snyman, and then Jan Hendrik Debes. The fourth porphyric child of Gerrit was a son and he had 12 children — the van Deventer family. At least 10 of the grandchildren of the first porphyric in South Africa appear to have carried the gene for porphyria.

Prof. S. Pauw[16] has shown that one million of the White population of South Africa hold 40 original family names and are descendants of 40 original burghers and their wives. The males among them inherit their Y-chromosomes from 40 original free burghers. For instance, except for illegitimacy and an occasional recent immigrant, the male van Rooyens inherit their Y-chromosomes from Cornelis van Rooyen. Male sex is inherited according to the same Mendelian dominant law as porphyria, i.e. on an average about half the children inherit the Y-chromosome and male sex. Therefore, the incidence of the name van Rooyen in a community should run roughly parallel to the incidence of porphyria. In the past, porphyric families were just as large as the other families in South Africa and it is only recently, since the introduction of barbiturates, that the gene for porphyria has become a potentially lethal gene. The names of 6 common porphyric families in the Eastern Cape are van Rooyen, Barnard, Potgieter, van Niekerk, Nel and Ferreira. These are not the commonest names. Table II shows the number of patients with these

TABLE II. A SUGGESTED METHOD OF OBTAINING A ROUGH GUIDE OF THE INCIDENCE OF PORPHYRIA VARIEGATA IN A HOSPITAL OR COMMUNITY IN SOUTHERN AFRICA—WITH EXAMPLES (ADULTS ONLY)

	Two Port Elizabeth hospitals, April 1959 - March 1960		Hospital admissions, 1959, excluding readmissions in same year				
Name	*Patients tested*	*Patients admitted*	*Pretoria General*	*Karl Bremer*	*Groote Schuur*	*Johannesburg General*	*Addington*
van Rooyen	43	66	85	16	13	38	26
Barnard	50	91	72	20	15	30	10
van Niekerk	28	44	101	31	27	80	26
Potgieter	43	62	111	10	6	45	13
Nel	55	91	131	38	28	91	13
Ferreira	60	80	47	11	4	26	12
Average of names	46·7	73·7	91·7	21·0	16·5	51·7	16·7
¾ of van Rooyens	32	49	64	12	10	29	20
¾ of average of all 6 names	35	55	68	15	12	39	13
Totals, excluding readmissions ..	6,458	10,900	23,082	4,678	7,490	17,433	12,287
Porphyrics detected	29						
Approximate incidence estimated ..	1/250	1/250	1/400	1/400	1/750	1/600	1/1,000

names who were given routine tests at the Provincial Hospital, Port Elizabeth and St. Joseph's Hospital, and the total number of admissions with these family names at these two hospitals, excluding readmissions.

The number of porphyrics in a large South African community should on an average be at least equal to the number of male van Rooyens, who can themselves be averaged by taking half the total van Rooyens in a group. In fact the first van Rooyen married one of the 4 porphyric children of Gerrit Jansz; however, she was the eldest, and 5 of the 10 known porphyric grandchildren of Gerrit Jansz belong to this family. In my experience about two-thirds of all South African porphyrics can be traced back to the van Rooyen clan, although most of them do not hold the van Rooyen name today. Therefore I suggest the number of porphyrics in a South African community can be roughly estimated by taking three quarters (a half plus a quarter) of all the van Rooyens, male and female. This estimate can be checked by averaging the 6 common names mentioned above and multiplying by three quarters. Table II shows a rough estimate of the expected number of porphyrics at Port Elizabeth hospitals and other large South African hospitals using these two methods.

By analogy other hospitals in Southern Africa can make a rough estimate of the number of porphyrics admitted during the previous 12-month period by adding up the van Rooyens who have been admitted in that period and multiplying by three quarters, checked, in case the name van Rooyen is disproportionately common, by averaging the 6 names mentioned above and multiplying by three quarters.

It is early to estimate the total number who have inherited the gene for porphyria variegata from Gerrit or his wife Ariaantje. Port Elizabeth is known as the 'City of the 1820 settlers' and yet in this predominantly English-speaking city the incidence of porphyria appears to be about 1 in 250. Porphyria is common among the descendants of trekboer families, i.e. boer families that trekked eastwards to the Eastern Cape and went on the Great Trek to the Transvaal and Natal. It seems probable that the incidence of porphyria is lower in Johannesburg, Durban and Cape Town where there have been a large number of more recent immigrants, and this is confirmed by the estimations made in Table II. Nevertheless, there are 15,000 van Rooyens in the country of whom half have inherited their Y-chromosomes from Cornelis van Rooyen, and Cornelis' wife was only one of Gerrit's 4 porphyric children. If I were to make an estimate, which will be confirmed or refuted by posterity, of the number of persons who have inherited the gene for porphyria variegata amongst our South African community, including the Rhodesias, I would say it is 8,000 $\pm$ 2,000, bearing in mind the fact that a number of porphyrics have inadvertently lost their lives through acute porphyria during the last 50 years. As far as is known they all inherited the gene from one ancestor who married at the Cape in 1688.

SUMMARY

It has been well established that the gene for porphyria variegata is very common among the White and Coloured populations of Southern Africa. These porphyric families descend from one original couple who married at the Cape in 1688.

If porphyrics are given barbiturates, and in particular a thiopentone anaesthetic, an attack of porphyria, which is highly dangerous to life, may be inadvertently precipitated. Porphyria variegata in the quiescent phase is not easily detected unless the diagnosis is suspected or a routine test of the stool is carried out. Therefore, in Port Elizabeth the routine testing of all admissions to hospital for porphyria variegata, before the administration of thiopentone and other barbiturates, was introduced. During the first 12-month period 29 porphyrics were found among the hospital admissions and 6,458 routine tests were carried out. It is estimated that the incidence of this gene among the hospital admissions is about 1 in 250 in the Eastern Cape and it is considered that this reflects the incidence of porphyria amongst the White population of the Eastern Cape.

A method is described for making a rough estimate of the expected number of persons with porphyria variegata in any large community or hospital in Southern Africa.

It is strongly recommended that routine testing be instituted in all hospitals in Southern Africa before the administration of barbiturates and especially before the administration of thiopentone anaesthetics. As porphyria variegata is generally easily detected by routine testing, the doctor in South Africa leaves himself open to criticism if a patient develops acute porphyria after the administration of thiopentone — if the test has not been done.

It is estimated that the total number of people who have inherited this gene in Southern Africa is about 10,000.

The institution of routine testing for porphyria variegata at the Provincial Hospital, Port Elizabeth and at St. Joseph's Hospital was made possible by the unstinting cooperation of Dr. J. H. McLean, Superintendent of the Provincial Hospital, and the hospital committee; the Reverend Mother and Sisters of St. Joseph's Hospital, and all the doctors who use the hospitals. I should particularly like to thank the anaesthetists who insisted on routine tests before the administration of thiopentone anaesthetics. I should like to thank the Director of the South African Institute for Medical Research, Johannesburg, who authorized the Institute in Port Elizabeth to carry out the routine tests free of charge for 1 year; Dr. W. C. Harington who provided facilities; and Mr. Welsh and his assistants who did the tests. Mrs. Basford and Mrs. Mitchell did the secretarial work. I should also like to thank Dr. H. D. Barnes, of the SAIMR, Johannesburg, for carrying out the quantitative analysis of stool porphyrin on 20 patients who were not known to have porphyria before the routine tests. I am indebted to the Medical Superintendents of the Groote Schuur, Johannesburg General, Pretoria General, Karl Bremer, and Addington Hospitals for providing statistical information for Table II. The South African Council for Scientific and Industrial Research made a grant in aid of the administrative expenses.

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