PORPHYRIA IN SOUTH AFRICA: THE FAECAL EXCRETION OF PORPHYRIN

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In comparison with the numerous detailed examinations of urine from cases of porphyria relatively little attention has been paid to the excretion of porphyrins in the faeces in these diseases, although it was noted by Gunther (1911) that excessive amounts of porphyrin were present in the stools of chronic and acute cases. Studies by Dobriner (1937), Dobriner, Strain and Localio (1937), Heising (1940), Localio, Schwartz and Gannon (1941) and Nesbitt and Snell (1942) indicated that the normal faecal excretion of coproporphyrin was in the range 200-400 μg. per day; that patients with diseases involving increased haemopoiesis excreted from 2 to 3 times as much; and that excretion by this route was diminished in patients with liver diseases. Dobriner found no evidence of the presence of haemato- or mesoporphyrin in normal or pathological stools.

A few quantitative analyses have been reported on stools from cases of porphyria. Prunty (1946) found 1·33 mg. of coproporphyrin per 100 g. in faeces obtained post-mortem from a case of acute porphyria. Watson (1954) tabulated faecal analyses in 13 cases of the acute intermittent and cutanea tarda types during remission; increased amounts of copro- and protoporphyrin were found. Both these workers recorded finding increased amounts of uroporphyrin in the faeces of their patients. Rimington and his associates [Gray, Rimington and Thomson (1948), Macgregor, Nicholas and Rimington (1952 and Wells and Rimington (1953)] described cases of porphyria cutanea tarda and emphasized the importance of quantitative determination of stool porphyrins in this disorder. They regard high faecal values with normal or only slightly increased urinary values as characteristic of the cutanea tarda form.

Porphyria is common in the White and Bantu races in South Africa and the faecal excretion of porphyrins has been studied in patients and in some of their relations. The clinical manifestations shown by White cases vary even within a single family unit. Cutaneous eruptions and scarring are commonest in males, who rarely suffer episodes of acute porphyria, which occur more frequently in females, in whom the skin lesions are usually milder and often cannot be detected. Both pictures are sometimes demonstrable in the same individual. In family studies occasional members have been found who excrete excessive amounts of porphyrin in their stools but have not shown clinical symptoms—these are regarded as cases of latent porphyria. Porphobilinogen is not increased in the urine of these White patients except in association with symptoms suggestive of an episode of acute porphyria; recent observations show that this is also true of δ-aminolaevulic acid.

Considered individually these patients can be allocated to one or other of the acute intermittent, cutanea tarda or mixed sub-groups of Watson's porphyria hepatica. It is, nevertheless, possible that all these cases are genetically homogeneous, since genealogical studies by Dean (personal communication), based on a number of affected families, indicate a convergence of ancestry to a pair of immigrants from Holland who married in the Cape of Good Hope settlement in 1688. On this basis these South African cases, despite their varied clinical features, would properly belong to one group, which should be differentiated from pure acute intermittent porphyria, in which skin eruptions do not occur.

The Bantu cases of porphyria have already been described elsewhere (Barnes 1955). The great majority of these show skin lesions as the only clinical manifestation of the disorder. Acute porphyria is rare in these people and no case of this type presented during the course of the present study. Confirmation of the clinical diagnosis was readily obtained by the detection of porphyrin in the urine but, as will be shown later, their stool porphyrins were not so markedly increased as those of the White cases and were, in fact, sometimes within normal limits. For this reason it is difficult to fit them into the cutanea tarda group as defined by Rimington.

Our findings on the stools of 4 cases of erythropoietic (congenital) porphyria are also presented in this paper.

Many of the subjects were well and following their ordinary occupations, so that continuous collection of stools to obtain reliable figures for daily excretion, which is the ideal in metabolic experiments, was not practicable and it was decided to analyse casual specimens. As will be seen later, faecal excretion was so markedly increased in many instances that this simplification is justified, but in borderline cases interpretation is difficult. Since the solid content of stools varies considerably, from 4·6 to 38% according to Fowweather (1926), the results were determined in terms of the dry weight of the stools. Ether-soluble porphyrins only were determined by a method eliminating porphyrins derived from chlorophyll and designated coproporphyrin (removed from the ether extract by 0·1 N hydrochloric acid) and protoporphyrin (removed from the ether extract by subsequent shaking with 1·5 N hydrochloric acid). Fuller details are given by Holti *et al.* (1958). It is known that the latter fraction includes the deuteroporphyrin present in the faeces and Watson (personal communication) states that in his experience coproporphyrin, for reasons not immediately apparent, is not always completely removed from the ether extracts of faeces by 0·1 N hydrochloric acid. By his more elaborate procedure results for coproporphyrin in some specimens are higher and for protoporphyrin are lower than by the method used in this study.

RESULTS

Normal Bantu. Stools from 18 Bantu adults convalescing from minor operations or under observation for mild disorders were analysed. These persons were free from signs or symptoms of diseases known to be associated with disturbances of porphyrin metabolism. The results obtained are recorded in Table I. These will be discussed later in relation to the normal range adopted.

TABLE I. PORPHYRINS IN STOOLS OF NORMAL BANTU

	*Coproporphyrin**	*Protoporphyrin**
Minimum	less than 1	less than 1
Maximum	11	37
Mean	7	16

* μg. per g. dry weight.

Adult Porphyrics. These comprised 27 Whites and 19 Bantu. The White subjects were mainly members of the

family described by Dean and Barnes (1955). Many showed active cutaneous eruptions or scars of past lesions and several of the women had had acute episodes. Porphyrins had been detected in the urine of all of them at some time. The Bantu were partly new cases seen currently at clinics and partly old patients who were traced for this study. Skin lesions were not active in all of the latter but an excess of porphyrin was still present in their urine. None of these cases was known to have had acute porphyria.

TABLE II. PORPHYRINS IN STOOLS OF ADULT PORPHYRICS

		White	*Bantu*
No.		27	19
Corproporphyrin*	Min.	23	6
	Max.	800	161
	Mean	242	58
Protoporphyrin*	Min.	103	11
	Max.	1,280	134
	Mean	487	45

* μg. per g. dry weight.

Children of Porphyric Parents. Stools were obtained from White and Bantu children under 20 years of age, one of whose parents was known to be affected. The White families were all of South African stock. We have not yet encountered a family in which both parents were porphyric. The results of porphyrin determinations on the stools of these children are classified in Table III.

TABLE III. PORPHYRINS IN STOOLS OF CHILDREN OF AFFECTED PARENTS

	White			*Bantu*
	Normal	*Doubtful**	*Abnormal*	*Normal†*
No.	21	2	14	13
Coproporphyrin‡				
Min.	0	9	16	1
Max.	14	10	158	11
Mean	7	9·5	52	5
Protoporphyrin‡				
Min.	5	47	51	3
Max.	42	51	212	27
Mean	17	49	116	10

* This group is defined in the discussion.
† All the specimens from Bantu children gave results within normal limits.
‡ μg. per g. dry weight.

Erythropoietic (congenital) Porphyria. Data are available from 4 cases of this rare condition and from some of their relations. A and B are 2 Sudanese siblings (male and female); fuller details are given by Townsend-Coles and Barnes (1957). C is a Bantu female, first reported by Findlay and Barnes (1950), with whom contact has since been maintained. D is a second Bantu female case discovered by Baxter (1958) at the Jane Furse Memorial Hospital in the Eastern Transvaal. Stools from these 4 patients gave the results recorded in Table IV. The parents of A and B and two younger siblings were healthy. Specimens of urine and faeces from these 4 relations, the paternal grandmother and 4 of the mother's 5 brothers were examined and none was found to contain excessive amounts of porphyrin. The father of case C deserted his family soon after the child was born and was never examined. Her mother had no skin lesions, urine has been negative for porphyrins on several occasions, and 2 stools were normal with respect to porphyrin. No excess of these pigments was detected in urine or stool from 2 of the patient's half-brothers. Case D was about 3 years old when the diagnosis was made. Urines and stools from her paternal grandmother, both parents and 4 of her 5 brothers were all normal in porphyrin content.

TABLE IV. STOOL PORPHYRINS IN CASES OF ERYTHROPOIETIC PORPHYRIA

Case	*Coproporphyrin**	*Protoporphyrin**
A	643	79
B	644	17
C	3,000	76
D before splenectomy		
6 specimens	740-1,550	26-113
1 specimen	43	8
after operation		
4 specimens	83-220	29-103

* μg. per g. dry weight.

A complete White family. The diagnosis of porphyria in the adult White subjects referred to above were established on clinical and laboratory findings. Subsequently another family was studied in which every member provided faeces for analysis (Fig. 1).

DISCUSSION

Normal values

Brugsch (1952) determined the copro and non-copro fractions of the ether-soluble porphyrins in stools from a number of healthy subjects, using analytical procedures similar to ours. His non-copro type corresponds to our protoporphyrin. The results were tabulated according to the benzidine test for occult blood given by the specimens; the mean values calculated from his tables are given in Table V. If it is assumed that an average stool contained 80% of water it can be calculated from the over-all means of these groups that the faeces of healthy persons on mixed diet would contain on the average 4·4 μg. of copro- and 11·7 μg. of protoporphyrin per g. dry weight. The upper limits for these pigments in this group were 13 and 37 μg. respectively.

TABLE V. PORPHYRIN CONTENT OF NORMAL STOOLS (BRUGSCH 1952)

Benzidine reaction	*No.*	*Copro type**	*Non-copro type**
Negative	16	104	187
Positive	7†	90	484
Doubtful	13	70	173

* μg. per 100 g. of wet stool.
† One result, much higher than the others, has been excluded.

In a recent investigation of porphyria cutanea tarda Holti, Rimington, Tate and Thomas (1958) regard 20 and 30 μg. per g. dry wt. as the upper limits for copro- and protoporphyrin respectively in the stools of normal English subjects. In this present study 15 and 45 μg. per g. dry wt. have been adopted as the upper normal limits and the results considered doubtful if either pigment exceeded its norm but the total porphyrin was below 75 μg.

The results on the group of 'normal' Bantu subjects on hospital diet fell within these provisional limits, suggesting that there is no marked essential racial difference between these people and Caucasians with respect to porphyrin production and excretion. The diets of the Bantu, however, vary considerably according to their circumstances and the amount of roughage influences the composition of their stools. Analyses by A. R. P. Walker show that the dry solids of faeces, which vary from 15 to 30 g. per day for White South Africans on mixed diet containing white bread,

are from 40 to 60 g. for urban Bantu on a partly europeanized diet and may be as high as 80-100 g. per day for rural Bantu on their primitive diets. Faecal porphyrins of Bantu subjects, expressed in terms of dry stool weight, may thus be low because of dilution by high faecal solids.

Abnormal values in conditions other than porphyria

It is known that stool porphyrin concentration may be influenced by conditions not related to porphyria. Since these must be kept in mind when interpreting results they are here summarized briefly. In blood diseases involving increased haemopoiesis the faecal output of coproporphyrin is increased. The figures given by Brugsch show that the haem ingested on a mixed diet does not affect the copro- but raises the protoporphyrin twofold or threefold. Bleeding in the upper gastro-intestinal tract will have a similar effect; protoporphyrin of 100-120 μg. per g. dry weight has been found in melaena stools. In liver diseases coproporphyrin may be raised in the urine and diminished in the faeces. This is regarded as a diversion of excretion from bile to urine (Watson 1952). Though no example has been encountered it is possible for the stool porphyrin per g. of dry solids to be raised in a person on a small intake of low-residue food, e.g. a faddist or a patient on invalid diet.

Findings in adult porphyrics

The stool porphyrins of all the adult White patients were abnormally high according to the criterion adopted and with one exception protoporphyrin exceeded coproporhyrin. Of the Bantu, 12 showed abnormally raised porphyrin excretion (but at distinctly lower level than the White group), 5 were doubtful, and 2 were within the normal range. In only 7 of these specimens, i.e. less than half, was protoporphyrin greater than coproporphyrin.

The Bantu patients were drawn from an urbanized population and if their stool porphyrin figures are doubled to compensate for dilution by roughage, as suggested by Walker's findings, the means for copro- and protoporphyrin become 116 and 90 μg. respectively, still far below the average values of 242 and 487 μg. found for the White group. The possibility that the difference could be ascribed to a degree of liver dysfunction in the Bantu could only be tested by fully controlled metabolic study of both groups with simultaneous analyses of urine and faeces.

The lower excretion of protoporphyrin relative to coproporphyrin observed in the Bantu patients is so large that it suggests different underlying metabolic disorders in the two groups. That difference in meat consumption is not an important factor is indicated by the similarity of the ratios of these two pigments found in the stools from normal Bantu and European subjects.

Findings in children

About two-fifths of the White children had abnormal stool porphyrins, though none showed clinical manifestations of porphyria. It seems reasonable to regard the children giving abnormal results as latent porphyrics who will become manifest in adult life and pass the affection on to about half of their children. The increases are not as large as those found in the adult group, but it is possible that with increasing age the degree of abnormality will become greater and that more of the children will show this evidence of affection.

No Bantu child showed clinical manifestations of porphyria, all their stool porphyrins were within the normal range, and none showed an excess of copro- over protoporphyrin as did many of the specimens from affected Bantu adults. The ages of these children ranged from infancy to 18 years, and, though the results from 4 of them become abnormal when multiplied by the factor used to compensate for dilution in the adult specimens, we do not know enough about the roughage in their diets to justify this procedure.

The findings in the White children can thus be reconciled with the established inheritance of susceptibility to porphyria in this section of the population. In the Bantu, however, this supporting evidence of heredity was not obtained and the alternative possibility, that the condition may be acquired in these people, remains open.

Findings in erythropoietic porphyria

All the specimens of faeces from this group of patients contained abnormal amounts of coproporphyrin; that from case C indicates how gross the increase can sometimes be in this condition. Protoporphyrin was only slightly raised in some specimens and within normal limits in others. It has been shown elsewhere (Barnes 1957) that, though very unusual, cutaneous lesions may occur in young children in White porphyric families and simulate very closely the picture of erythropoietic porphyria. Determination of the proportion of copro- to protoporphyrin in the stool may thus afford another means of distinguishing between these two forms of the malady.

Whilst case D was under observation before the splenectomy, her urine became very much paler for a few days and one stool analysed during this period contained only 43 μg. of coproporphyrin per g. dry weight. This is a remarkable spontaneous partial remission in a condition in which enhanced excretion of porphyrin is believed to be a constant phenomenon.

No disturbances of porphyrin excretion were disclosed in near relations of these patients by stool analysis.

Detection of latent porphyria

The custom has been adopted of advising patients with porphyria to inform their near relations that doctors should be told of its occurrence in the family. The detection of latent porphyria is very desirable because of the risk these people run of developing acute attacks when treated with certain sedatives, more particularly after surgical operations. To this end the Watson-Schwartz test for porphobilinogen in the urine has proved valuable in other countries but fails in South Africa since porphobilinogen is only found at the time of acute episodes. The findings presented above in White cases and their children suggest that stool examination for porphyrin should be useful in this respect and the results recorded in Fig. 1 on an entire family enable this possibility to be evaluated.

No stool analysis was available for the propositus (II. 6) but his clinical status and the presence of porphyrin and porphobilinogen in his urine shortly before death from a recurrent coronary thrombosis were compatible with an attack of acute porphyria. Characteristic lesions and scars on his hands and forearms indicated that the condition was of the type which is common in South Africa. His mother was alive and well, presenting no clinical features

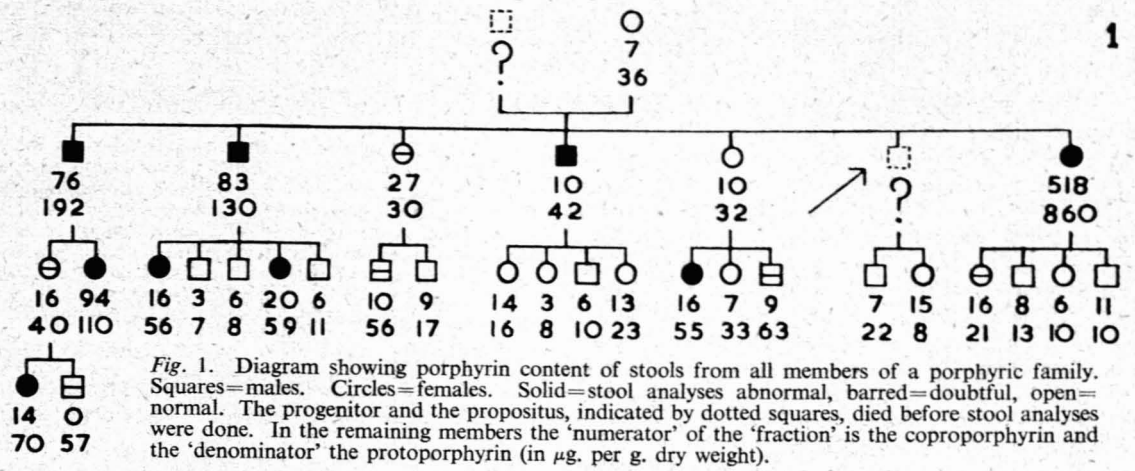

Fig. 1. Diagram showing porphyrin content of stools from all members of a porphyric family. Squares=males. Circles=females. Solid=stool analyses abnormal, barred=doubtful, open=normal. The progenitor and the propositus, indicated by dotted squares, died before stool analyses were done. In the remaining members the 'numerator' of the 'fraction' is the coproporphyrin and the 'denominator' the protoporphyrin (in μg. per g. dry weight).

of porphyria and her stool porphyrins were normal, but his father was a possible link with other affected South African families as he was stated to have had a fragile skin.

Three members of generation II had abnormal stool porphyrins and of these 1 and 7 showed slight scarring as evidence of skin fragility; the third did not, though he was subject to abrasions in his manual work as a fitter. The remaining 5 members who passed abnormal stools were all under 22 years of age and none showed any clinical manifestations. The finding of abnormal stools in some of the progeny of II 1 and II 2 is additional evidence that the two parents are affected. The stool of the eldest child of II 7 was doubtful and those from her 3 younger children were normal. It has already been suggested that the abnormality may be progressive and re-examination of this family in the future may show a different picture.

Stools classified as doubtful were obtained from 6 members, of whom 2 were adults. One of these (II 3) showed a little facial pigmentation but had no lesions and had had two abdominal operations with no complications during convalescence; the other adult and the 4 children presented no signs or symptoms. Interpretation of these doubtful results and, in particular, such groups as II 5 (stool normal) and her 3 children, one of whom fell into each category, requires more knowledge of the variations which may occur in stool porphyrin concentrations.

From these findings it is clear that some near relations of cases of porphyria pass abnormal amounts of porphyrin in their stools though other indications of the disease may be slight or even absent. It would seem wise, in the present state of our knowledge, to regard these people as probably having an inherited susceptibility to the affection. This should be taken into consideration when surgery or treatment with sedative drugs is contemplated.

SUMMARY

1. Copro- and protoporphyrin were determined in the stools of normal Bantu subjects and the findings compared with those reported in normal Europeans.

2. These pigments are increased, sometimes to a very marked degree, in the stools of adult porphyrics in the White population of South Africa. Some of the children of these patients, though free from clinical manifestations of porphyria, also excrete abnormal amounts of porphyrin in their stools. The presence of increased porphyrins in the stools from relations of patients with porphyria is suggestive of latent porphyria.

3. Less marked increases of pigment were found in stools from adult Bantu patients showing cutaneous manifestations of porphyria and the proportion of copro- to protoporphyrin differed from the ratio found in the specimens from White porphyrics. No definite evidence was obtained of increased porphyrins in faeces from children of Bantu porphyrics.

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