THE EXCRETION OF PORPHYRINS AND PORPHYRIN PRECURSORS BY BANTU CASES OF PORPHYRIA

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It has recently been shown[1] that Swedish patients with intermittent acute porphyria and White South African patients with variegate porphyria, who may present either cutaneous manifestations or acute symptoms and not infrequently both, differ markedly from each other in their patterns of excretion of porphyrins and porphyrin precursors. Many hundreds of cases of porphyria have been seen in the Bantu of South Africa in recent years and the pattern of excretion in some of these has been determined for comparison with those of the two groups mentioned above.

The patients were seen by doctors in hospitals and clinics in and around Johannesburg, and the provisional diagnosis of porphyria, based on the observation of characteristic skin lesions, was confirmed by the detection of an excess of porphyrin in the urine. Arrangements were then made for fresh specimens of urine and faeces, passed at about the same time, to be collected and delivered promptly for analysis. The results in 15 adult patients (10 females and 5 males) are recorded in Table I. The means and ranges of these figures are given in Table II for comparison with those from 7 Swedish and 11 White South African patients[1] obtained during remission from acute symptoms.

The methods employed in the analysis were as follows:

Urine. Total porphyrin was determined directly on a suitably diluted specimen by the spectrophotometric method

of Sveinsson, Rimington and Barnes,[2] and δ-amino-laevulic acid and porphobilinogen by the method of Mauzerall and Granick.[3] Because of the lability of the latter substance all these analyses were commenced within 2 hours of collection, and mostly within 1 hour.

Stools were screened for porphyrin by examining in Wood's light an acetic acid and ether extract of a small fragment; coproporphyrin and protoporphyrin were determined quantitatively as described by Holti *et al.*[4]

TABLE I. PORPHYRINS AND PORPHYRIN PRECURSORS IN URINE AND FAECES FROM BANTU CASES OF PORPHYRIA

Case No. and Sex	Urine			Faeces	
	ALA	*PBG*	*Porphyrin*	*Copro.*	*Proto.*
	mg./litre		*μg./100 ml.*	*μg./g. dry wt.*	
1 F ..	44	16	2,360	20	11
2 F ..	8	0	1,710	31	11
3 F ..	5	2	1,490	91	25
4 M ..	1	1	98	52	74
5 M ..	2	1	335	37	35
6 M ..	6	2	594	32	53
7 F ..	6	1	392	60	46
8 F ..	4	2	75	23	38
9 F ..	14	11	1,460	29	23
10 F ..	10	2	716	38	19
11 M ..	0	0	560	90	57
12 F ..	47	11	2,220	11	13
13 M ..	3	1	445	89	51
14 F ..	6	1	1,140	screen test normal	
15 F ..	8	1	1,790	50	71

TABLE II. MEAN VALUES AND RANGES OF THE FIGURES RECORDED IN TABLE I COMPARED WITH SIMILAR FINDINGS IN SWEDISH AND WHITE SOUTH AFRICAN PORPHYRICS IN REMISSION

		Urine			Faeces	
		ALA	*PBG*	*Porphyrin*	*Copro.*	*Proto.*
		mg./litre		*μg./100 ml.*	*μg./g. dry wt.*	
Bantu	Mean	11	3·5	1026	47	38
	Range	0-47	0-16	75-2360	11-91	11-74
Swedish	Mean	20	23	—	17	24
	Range	4-37	2-42		13-26	11-38
White S. African						
	Mean	3·0	1·6	—	393	557
	Range	1-8	0-3		54-1220	131-2000

The numbers of observations are small and in several of the groups the distributions are markedly skewed so that the validity of the conventional *t* test is questionable. Professor Kerrich suggested using distribution free methods[5] to assess the confidence limits of the medians in order to gauge the significance of the differences between the findings in the three populations. The 90 per cent confidence range for each group was obtained by linear interpolation between the pairs of observations at either end of the ranked series which bracketed the upper and lower limits of this range and are given in Table III together with the corresponding medians. The judgments of significance at this level (S) or non-significance (N) of differences between pairs of medians are shown in Table IV.

TABLE III. MEDIANS AND 90 PER CENT CONFIDENCE RANGES DETERMINED BY DISTRIBUTION FREE METHODS ON THE DATA IN TABLE II

	ALA	*PBG*	*Copro.*	*Proto.*
Bantu	6	1	37·5	36·5
	3·2-9·4	1-2	28-65	18-54
Swedish	23	29	15	25
	5·4-31	2-40	13-25	13-35
White	2	2	315	348
	1-5	1-2·2	95-630	160-754

TABLE IV. ASSESSMENT OF SIGNIFICANCE (S) OR NON-SIGNIFICANCE (N) OF THE DIFFERENCES BETWEEN THE MEDIANS TAKEN IN PAIRS

	ALA	*PBG*	*Copro.*	*Proto.*
Swedish-White ..	S	S (?)	S	S
Bantu-Swedish ..	N	S	S	N
Bantu-White ..	N	N	S	S

DISCUSSION

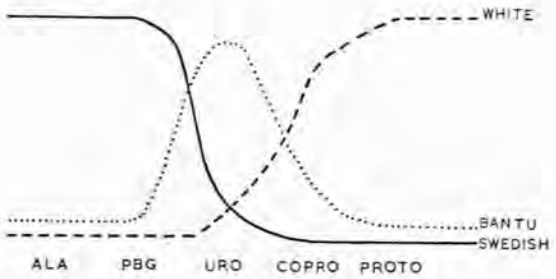
It is known that excretion of δ-amino-laevulic acid and porphobilinogen increases markedly during acute porphyric episodes both in Swedish and in White South African patients. These attacks are very rare in the Bantu and were not known to have occurred in any of the patients in the present group. In order to avoid the disturbances associated with these episodes the findings during quiescent phases only have been compared.

Inspection of Table II shows that the Swedish and White South African groups differ in that the urinary excretion of precursors is high in the former and virtually normal in the latter, while the converse is true of the faecal excretion of porphyrins. Except for a very slight overlap of the confidence ranges for the median values for porphobilinogen (Table III) the differences between these two are significant at the 5 per cent level. The findings in the Bantu group occupy intermediate positions, differing significantly from the Swedish in excretion of porphobilinogen and faecal coproporphyrin and from the White South African with respect to both fractions of faecal porphyrin.

The urinary porphyrins of the Bantu group (Table II), determined on fresh urine, are all abnormally high as this was the finding used to substantiate the provisional diagnosis of porphyria. Corresponding figures are not available for the other two groups but it has been pointed out elsewhere[6] that urinary porphyrins in White South African patients during remission from acute attacks, while often slightly increased, may sometimes not be detectable on direct spectroscopic examination, i.e. would be less than about 50 μg. per 100 ml. None of the urines from the 11 White patients in this group showed a marked excess of porphyrin on spectroscopic examination. It is our common experience that examination of urine is the better test for detection of porphyria in the Bantu and examination of faeces in quiescent White cases. Assessment is more difficult in the Swedish patients since once the urine becomes acid in the renal tubules non-enzymatic transformation of porphobilinogen into uroporphyrin commences and the amount of the latter in the urine when voided has been artifactually increased. None of these urines was regarded as containing a gross excess of porphyrin when screened by Dr. Dean in ultraviolet light. On these grounds it seems justifiable to infer that freshly voided urine from Bantu patients contains more preformed porphyrin than that from the other two groups.

It is visualized that the successive reactions in the biosynthesis of protoporphyrin are catalysed by a series of intracellular enzymes. The findings here presented support the hypothesis that in these three groups of patients the fundamental disturbances which result in the release of the various metabolites from their normal sites to escape

from the cells and become available for excretion occur at different stages of the process. The degree of divergence from normal may be diagrammatically represented as follows:



The suggestion that the primary metabolic error in intermittent acute porphyria lies at the precursor level is not new. It has been put forward by others on the grounds that the uroporphyrin found in the urine of these patients arises from spontaneous transformation of porphobilinogen during the interval between secretion and excretion mentioned above. It is further supported by the finding that faecal porphyrins are virtually normal in this condition. Localization of the error at the later copro-protoporphyrin stage in White porphyrics in South Africa was first discussed by Barnes[7] and amply confirmed by subsequent studies. The deduction from the findings on the Bantu is put forward tentatively in the hope of confirmation by the discovery of similar cases elsewhere.

The relationship of the porphyria seen in the Bantu to other forms of the disease presents several problems for discussion. This is of an involved nature because of the confusion which exists in current classification and nomenclature.

Latency. The Bantu cases considered in this study all showed active cutaneous eruptions or scars of old lesions which directed the clinician's attention to porphyria. It is quite likely that disturbed porphyrin metabolism may exist in other patients prior to clinical manifestations. These have not been sought by surveys of random urine specimens. Mentz[8] found varying increases of coproporphyrin only in the urine of the majority of a number of patients with liver disease, but 3 patients, who had no stigmata of porphyria, also showed 290, 880 and 930 μg. of uroporphyrin in 24-hour specimens of urine. For lack of further evidence the question of latent porphyria in these patients was left open.

Duration. Few of the Bantu patients gave reliable information about the duration of their skin lesions, and statements that these had been present for a few months only could not always be accepted. Though a great many cases have been found in the past 10 years, little or nothing can be done for them by way of treatment, so that there is no incentive for patients to maintain contact with the clinic and follow-up studies are difficult. In a few instances in which the same patient has been seen again after an interval of several months or years, some still had active lesions but in others these had ceased though the scars of former eruptions were still evident. Nevertheless, persistence of the metabolic anomaly was confirmed by appropriate tests. The evidence, though slender, is thus that the anomaly in these patients is not a transient disturbance.

Heredity. The great majority of the Bantu patients fall into the middle years of the life span. Our records include only 3 under the age of 20, and 2 of these were under 10 years old. Of the latter two cases, the mother and a sibling of one provided no clinical or laboratory evidence of affection but the father refused to be examined; family studies were not carried out in the other. A few examples of multiple occurrence in a family unit have been found, but these cases were all adults. Eighteen children with a porphyric parent have been examined and no clinical or metabolic evidence of porphyria was detected in any of them. There is thus, as yet, no conclusive indication of a hereditary factor in the aetiology of porphyria in the Bantu, a marked contrast to the convincing evidence of a Mendelian dominant inheritance for susceptibility to acute intermittent porphyria in the Swedish[9] and variegate porphyria in the White South African[6] groups. While this gap may be filled in the future the possibility must be maintained for the present that porphyria may be an acquired disease in the Bantu. I have never accepted the suggestion put forward in a recent paper[19] that the name porphyria should be restricted to the genetically conditioned disturbances of porphyrin metabolism and hereby disclaim agreement with it.

Precipitating incident. A mechanism whereby the disturbance may be acquired has already been suggested,[7] viz. that a liver, weakened in some way by infantile malnutrition, which is common amongst the Bantu, breaks down under stress in adult life and that this form of porphyria is one of its manifestations. For practical purposes all these cases have occurred in urbanized communities, since most of the very few first detected in rural clinics have acknowledged a period of residence in an urban township. Rural Bantu meet their need for alcohol, which is considered to be an important aetiological factor in cutaneous porphyria, with comparatively innocuous home-brewed fermented drinks. On the other hand, the preparation and sale of a variety of adulterated and often toxic concoctions is a major illicit industry in the townships. No statement has been found that kwashiorkor is commoner in urban than in rural areas, but it is well known that infant morbidity is high in large semi-sophisticated urban communities and much of it is ascribed to malnutrition. Severe malnutrition in infancy does not, of itself, provoke disturbances of porphyrin metabolism, for excreta from 10 infants hospitalized for severe malnutrition did not contain excessive amounts of porphyrin. While these observations are purely speculative it is felt that the occurrence of possible predisposing and precipitating factors in a community where porphyria is not uncommon points a way to further studies.

Though the remarkable patient described by Tio[10] does not indicate an actual precipitating incident it provides evidence that erstwhile normal liver cells can acquire a disordered porphyrin metabolism. This elderly woman first showed skin lesions and excreted excessive amounts of porphyrin when she developed a hepatic adenoma, which was found to be richly infiltrated with porphyrin. No evidence of porphyria was found in relations and at her death some years later no fluorescence was observed in the internal organs. It is suggested that a similar deviation of pigment synthesis of diffuse distribution and without the neoplastic tendency might account for the findings in the Bantu.

Hepatic impairment as a modifying factor. Disturbances

of liver function are widespread in the Bantu and excess of urobilinogen, sometimes gross, is seen more frequently in the urine from these patients than in specimens from White cases. Mentz[3] has shown that increased urinary coproporphyrin in Bantu subjects is related to impairment of liver function. The question then arises, might the porphyria in these two groups be the same condition and the differences in excretion be ascribed to hepatic impairment in the Bantu? On this supposition the urine of the Bantu cases should contain the marked excesses of coproporphyrin and protoporphyrin excreted by the Whites in their stools. This is not supported by the available evidence, since many analyses and recovery experiments have demonstrated that the urinary porphyrin from Bantu patients is predominantly uroporphyrin. Coproporphyrin is often increased but of the numerous paper chromatograms on total recovered porphyrin none has ever suggested the presence of protoporphyrin.

Classification. The name porphyria cutanea tarda has been used in various ways. When it was coined by Waldenstrom[11] the statement was made that colics (cause?) occurred in these patients. Watson,[12] in subdividing cases of hepatic porphyria, reserved this name for the cases with cutaneous manifestations only and introduced a mixed or intermediate category for those presenting both acute and cutaneous features. Holti *et al.*,[4] discussing affected members in the family of an English patient with porphyria cutanea tarda, state, '... in this condition abdominal and neurological manifestations may be the most prominent features, while the skin may be insignificantly affected, or indeed appear quite normal'. This is also true of many South African White patients and it is almost certain that many similar patients have been erroneously regarded as cases of intermittent acute or purely cutaneous porphyria, according to the predominating symptom complex.

Rimington[13] and his associates have frequently stressed the importance of high faecal porphyrins as a diagnostic feature of porphyria cutanea tarda. On this basis the Bantu cannot be included in this group, since stool porphyrins are relatively slightly increased and, indeed, are sometimes within normal limits. The White patients, on the other hand, conform to this requirement, but many are entirely free from cutaneous manifestations, while on the other hand these have been observed in several young children in affected White families in addition to the case reported by Barnes *et al.*,[14] in whom they began at 6 months of age and have persisted ever since.

The present situation points to the necessity for distinguishing two groups of cutaneous porphyria in addition to the erythropoietic (congenital) form. This is discussed at some length by Tio,[15] who culled many cases from the literature and pointed out that the mixed cases (with cutaneous and acute features) tended to commence earlier in adult life and to give family histories more frequently than purely cutaneous cases, who began later in life and were more often solitary. The latter he designated as porphyria cutanea tarda SS (sensu strictiori). Waldenstrom[11] has recently proposed hereditary and symptomatic sub-groups of porphyria cutanea tarda.

Mixed porphyria in Watson's sense has not been encountered in Bantu patients; very few have presented with acute manifestations and none of these has had conspicuous skin lesions (Woods and Barnes[16]). None has been available recently for full metabolic study. In one acute case elective appendicectomy was performed and he recovered completely despite an exacerbation of acute symptoms during convalescence. In several large hospitals in this vicinity, no other instance is known of acute porphyria following surgery or medical treatment in a Bantu. Cutaneous porphyria in the Bantu might, therefore, be equated with Tio's porphyria cutanea tarda SS or Waldenstrom's symptomatic sub-group. Against the former, however, is the fact that many cases have occurred as early as the third decade of life, while the admittedly slender evidence already presented that the condition is not transient is rather against the latter.

Metabolic studies along the lines indicated herein will help to overcome some of the difficulties of classification and more thorough family studies are clearly important.

It is noteworthy that the Bantu cases, who on metabolic findings seem to lie between the Swedish and White South Africans, on the basis of clinical manifestations would be placed at the opposite extreme to the Swedish with the White South African group intermediate. This leads to the inference that Watson's hypothesis that the clinical findings in hepatic porphyria are varied manifestations of a single underlying metabolic anomaly, though true of the White South African patients, cannot be extended to cover all three of these groups.

It has been observed that skin sensitivity to solar radiation in humans[17] and to ultraviolet light in albino rats[18] is enhanced after administration of δ-amino-laevulic acid. Cutaneous reactions in the patients under discussion cannot be harmonized with this finding, since the Swedish patients, who would presumably have the highest concentrations of this metabolite in the circulating blood, have no skin lesions such as are present in many patients in the other two groups.

SUMMARY

The excretion of porphyrins and porphyrin precursors by 15 adult Bantu patients with a cutaneous type of porphyria is reported and shown to differ from corresponding findings in patients with intermittent acute and variegate forms of porphyria.

The implications of this observation in relation to the aetiology and classification of the porphyria in Bantu patients are discussed.

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