PORPHYRIA IN SWEDEN AND SOUTH AFRICA

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The clinical and biochemical aspects of the diseases known as the porphyrias, in which disturbances of porphyrin metabolism are associated with a variety of clinical manifestations, have received increasing attention during the past two or three decades. It has been learned that these disorders are not so rare as was formerly believed and that they are, in fact, relatively common in some countries, e.g. Sweden[1] and South Africa.[2] Another important advance has been the elucidation of some of the stages in the biosynthesis of porphyrin pigments from glycine and acetate.[3, 4] From this have come methods for quantitative determination of porphobilinogen and δ-amino-laevulic acid,[5-7] precursors of porphyrins, which are sometimes excreted in quite considerable amounts in the urine. Application of these new methods has made it possible to study cases of porphyria in greater detail.

Early classifications were based on the varied associated clinical manifestations of the porphyrias. Gunther's scheme,[8] translated into modern terminology, provided for 3 groups:

1. Acute porphyria, usually characterized by episodes of acute abdominal pain and vomiting, often accompanied by psychotic manifestations and/or motor paralysis, and the passage of urine which was dark when fresh, or soon became so, and contained an excess of porphyrin. This was later divided into toxic and idiopathic forms but the distinction has lost its significance and has now been abandoned.

2. Chronic porphyria, in which porphyrin excretion and the development of skin lesions on exposed areas began in adult life.

3. Congenital porphyria, in which increased porphyrin excretion and skin lesions began in early childhood. Discolouration of the teeth by deposition of porphyrin was observed in these cases. The skin eruptions were more severe than in the chronic form and adult patients usually showed extensive scarring and even mutilation resulting from recurrent lesions. Congenital porphyria is a very rare condition now known to be essentially different from the chronic form though the two have frequently been

confused because of the marked similarity of their cutaneous manifestations.

In 1937 Waldenstrom[9] reported a large series of cases of acute porphyria in Sweden in whom skin sensitivity did not occur and showed that in addition to porphyrin the urines from these cases also contained porphobilinogen, a colourless substance which could be detected by means of Ehrlich's aldehyde reagent. Porphobilinogen was also found in the urines of patients who had recovered from acute attacks and in small amounts in the urine of some relations who had never suffered from porphyria.[21] A few of the latter later developed acute episodes and the test for porphobilinogen thus provided a valuable means for the detection of some of the latent cases. Waldenstrom proposed a classification of porphyria in which the congenital form remained as defined by Gunther and chronic porphyria was renamed porphyria cutanea tarda because of the late development of porphyrin excretion and photosensitivity, but he suggested that this condition, because of the occurrence of colic, might be related to acute porphyria.

A third classification based on pathogenesis was put forward by Watson *et al.*[10] on studies reported later by Schmid, Schwartz and Watson[11] and Schmid, Schwartz and Sundberg.[12] Congenital porphyria was renamed erythropoietic porphyria because in this type the presence of numerous fluorescent normoblasts in bone-marrow films indicated that the marrow was the site of the metabolic anomaly. Other forms were grouped as hepatic porphyria because excessive amounts of porphyrins or a precursor could be demonstrated in liver tissue from these cases. Though regarded as fundamentally a single entity this group was subdivided according to clinical manifestations into acute intermittent, cutanea tarda and mixed forms of porphyria. Rimington[13] dissents from this view and regards porphyria cutanea tarda as a separate entity and not a mixed form. He and his associates[14] have emphasized that raised stool porphyrins are characteristic of this condition.

Inheritance of Porphyria

Cases of erythropoietic porphyria have occurred in many widely separated countries and multiple occurrence in a sibship has been reported on several occasions. Cockayne[15] discusses the condition as an example of recessive inheritance.

The first indication of the familial incidence of acute porphyria was given by Barker and Estes.[16] While the diagnosis was established in the propositus by spectroscopic examination of her urine this was not done in other members of the family, in whom a provisional diagnosis of porphyria was suggested by clinical manifestations. Gunther[17] pointed out that many cases of porphyria occurred in persons with a peculiar psychological background, which suggested an hereditary constitution (porphyrism) as a basis for the disease. He was unable, however, to find other cases amongst relations of his own patients. The earlier indications for heredity and the difficulties of establishing this possibility are discussed by Waldenstrom,[9] who finally deduced from his extensive material that acute porphyria in Sweden was based on non-sex-linked inheritance of a Mendelian dominant type.

The studies of Dean and Barnes[2] disclosed a similar inheritance for the susceptibility to porphyria in the White population of South Africa and later investigation by Dean (unpublished) traced the inheritance to a pair of early settlers from Holland who married at the Cape in 1688. In these cases, however, symptomatology is mixed, acute attacks occur more frequently in women, cutaneous lesions are commoner and more severe in the men, and some cases show both acute and cutaneous symptoms. This supports Watson's contention that his three subgroups of hepatic porphyria are varied manifestations of the same underlying anomaly, but the findings in Sweden, where acute and cutaneous manifestations of porphyria do not overlap, are not in agreement with this hypothesis.

A comparative study of Swedish and South African cases was clearly indicated, and to this end Dean visited Sweden, where arrangements were made by Waldenstrom for him to see a number of cases, including a family containing several members who had suffered attacks of acute porphyria. Specimens of urine and faeces from these patients and some of their relations were screened for porphyrin metabolites by Dean, quantitative determinations of urinary porphobilinogen and δ-amino-laevulic acid were carried out by Dr. Haegar in Malmö, and the stools were sent to Barnes in Johannesburg for quantitative porphyrin analysis. Similar studies were carried out on two families in Holland with whom contact was provided by Prof. Formyne of the Wilhelmina Gasthuis, Amsterdam. These results and those obtained on excreta from a number of White South African cases are presented and discussed below.

Methods

The methods employed were as follows:

Urine. For screening purposes urine was examined in Wood's light from a portable mercury-vapour lamp for the red fluorescence characteristic of porphyrin. The apparatus described by Harrison[18] was used for spectroscopic detection of porphyrin in varying depths of urine before and after rendering acid to Congo red with hydrochloric acid.

Qualitative examination for porphobilinogen was made by the Watson-Schwartz[19] test with Ehrlich's aldehyde reagent. Porphobilinogen and δ-amino-laevulic acid were determined quantitatively by the procedure of Mauzerall and Granick;[5] amounts up to 1 mg. and 4 mg. per litre respectively were regarded as normal.

Stools. The screening test consisted of examining in Wood's light the extract obtained by rubbing a small fragment of faeces into 2 ml. of a mixture of equal parts of amyl alcohol, glacial acetic acid and ether. Coproporphyrin and protoporphyrin were quantitatively determined by the procedure outlined by Holti *et al.*[20] Coproporphyrin below 15 and protoporphyrin below 45 micrograms per g. dry wt. were regarded as normal. In this study and others somewhat raised stool porphyrins have occasionally been found in

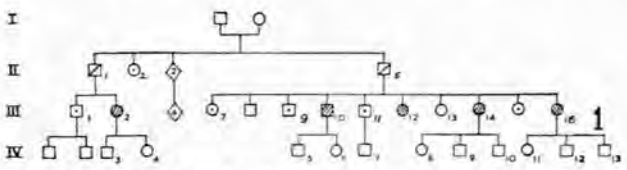

Fig. 1. A Swedish family with many cases of acute porphyria. Squares represent males and circles females. Hatched symbols represent living members with evidence of porphyria, a central dot indicates death with evidence of porphyria and a diagonal bar death without such evidence. See Table I.

TABLE I. (COMPARE FIG. 1)

Member	Acute Attacks	Screen Tests: Faeces porph.	Screen Tests: Urine porph.	Screen Tests: Watson-Schwartz	Urine Analysis: PBG (mg. per litre)	Urine Analysis: ALA (mg. per litre)	Stool Porphyrins: Copro. (μg. per g. dry wt.)	Stool Porphyrins: Proto. (μg. per g. dry wt.)
III/2	1938/52	+	++	++	33	26	22	25
III/10	several mild	neg.	neg.	neg.	2	4	14	15
III/12	mild	neg.	neg.	++	29	12	13	38
III/13	None	neg.	neg.	neg.	1	4	screen test neg.	
III/14	1951	neg.	+	++	42	29	15	24
III/16	1950/56	neg.	+	++	36	23	14	11
IV/3	None	neg.	neg.	neg.	1	4	20	16
IV/4	None	neg.	neg.	neg.			8	28
IV/5	None	neg.	neg.	neg.	1	2	screen test neg.	
IV/6	None	neg.	neg.	neg.	1	4	27	83
IV/7	None	neg.	neg.	neg.	1	4	screen test neg.	
IV/8	None	neg.	neg.	neg.	1	4	screen test neg.	
IV/9*	None	neg.	neg.	neg.	3	4	screen test neg.	
IV/10	None	neg.	neg.	neg.	1	3	screen test neg.	
IV/11	None	neg.	neg.	neg.	1	4	screen test neg.	
IV/12	None	neg.	neg.	neg.	1	4	screen test neg.	
IV/13	None	neg.	neg.	neg.	1	2	screen test neg.	

*The slightly raised urinary porphobilinogen suggests that this might be a latent case.

subjects who had not inherited porphyria, in these cases it is often a temporary phenomenon.

SWEDISH CASES

In this section are included particulars of an affected family and other cases which one of us (G.D.) investigated in Sweden.

The 5 members who had had acute attacks were all in remission when the tests were done, all but one showed pathological increases of porphobilinogen and δ-amino-laevulic acid in their urines, and none had significantly increased stool porphyrins.

Notes on Cases in Fig. 1 and Table I.

II/1 and II/5 were brothers not related to their wives otherwise than by marriage. Although many of their children were porphyrics they do not appear to have died from acute porphyria.

II/2 died in 1910 aged 60. She had suffered from recurrent attacks of abdominal pain. During her final illness she passed red-coloured urine and became paralysed.

III/1 died in 1946 aged 33. He developed severe abdominal pain and had a laparotomy. After the operation there were mental symptoms, he passed red urine, became paralysed and died.

III/2, F.44. She had attacks of acute porphyria in 1938, 1952, 1955 and 1957 after the taking of barbiturates. In some of these she was desperately ill.

III/7. In 1918, aged 20, she became desperately ill, became paralysed and died. She probably had acute porphyria.

III/9. In 1928, aged 30, he complained of abdominal pain and his abdomen was opened, he had fits, passed red urine, became paralysed, and died.

III/10 has had a number of minor attacks, during which he passed red urine.

III/11 died in 1938 aged 32. After taking sedatives he complained of abdominal pain and his abdomen was opened. After the operation he passed red urine, became paralysed, and died.

III/12. Minor attacks only.

III/14 had acute porphyria in 1951 but she made a good recovery.

III/15 died in 1938 aged 22. After taking sedatives she had severe abdominal pain and her abdomen was opened. After the operation she had mental symptoms, passed red urine, became paralysed and died.

III/16. After taking barbiturates in 1950 she developed an acute attack of porphyria. She made a good recovery but had another acute attack in 1956 after taking sleeping tablets.

Notes on Cases in Table Ia

Cases 1 and 1a. This brother and sister are examples of the type of porphyria seen in South Africa. The brother had developed blisters and sores on his hands late in life. Both he and his sister have raised faecal porphyrins. No case of acute porphyria is known as yet in this family.

Case 2. This woman has had a number of acute attacks and when seen still had residual peripheral neuritis. Nevertheless the increase in porphobilinogen was so slight that the Watson-Schwartz test was negative. Her twin sister had died from acute porphyria.

Case 3. This woman is a member of another large porphyric family. Although she was very well when seen, the Watson-Schwartz test was strongly positive.

Case 4. This woman was seen during an acute attack of porphyria. She did not have the marked electrolyte, calcium and potassium loss that usually occurs in South African cases in the acute phase.[27]

No skin lesions were observed in cases 2, 3 and 4. Stool porphyrins were raised in cases 1 and 1a (cutaneous) but not in 2 and 3 (quiescent acute), the increased values for case 4 may be related to the current acute episode. Urinary porphobilinogen and δ-amino-laevulic acid were abnormal in 2, 3 and 4.

While this paper was being prepared similar findings to the above were reported in a number of Swedish patients by Haeger.[26]

DUTCH CASES

In this section are included particulars of two affected families investigated by G.D. in Holland.

TABLE Ia. FINDINGS IN OTHER SWEDISH CASES SEEN BY G.D.

Case and Sex	Screen Tests: Faeces porph.	Screen Tests: Urine porph.	Screen Tests: Watson-Schwartz	Urine Analysis: PBG (mg. per litre)	Urine Analysis: ALA (mg. per litre)	Faeces Analysis: Copro. (μg. per g. dry wt.)	Faeces Analysis: Proto. (μg. per g. dry wt.)
1 M	++	++	neg.	specimen lost		152	55
1a F	++	neg.	neg.	1	2	173	180
2 F	neg.	tr.	neg.	2	7	15	31
3 F	neg.	+	++	19	37	26	25
4 F	+	+	++++	48	20	73	117

TABLE II. (COMPARE FIG. 2)

Member	Acute Attacks	Screen Tests: Faeces porph.	Screen Tests: Urine porph.	Screen Tests: Watson-Schwartz	Urine Analysis*: PBG (mg. per litre)	Urine Analysis*: ALA (mg. per litre)	Stool Porphyrins: Copro. (µg. per g. dry wt.)	Stool Porphyrins: Proto. (µg. per g. dry wt.)
II/1	No	neg.	+++	+		9	53	70
II/2	No	neg.	neg.	neg.			screen test neg.	
II/3	No	neg.	neg.	neg.			screen test neg.	
II/4	Could not be traced for examination or tests.							
II/5	No	?	neg.	neg.			9	13
III/6	Yes	++	+++	++		22	30	115
III/8	No	neg.	neg.	neg.			16	22
III/9	Yes	?	+++	++		16	26	22
IV/4		neg.					screen test neg.	
IV/5		neg.					screen test neg.	

*These urines were analysed by Dr. Haeger about 3 weeks after collection. Porphobilinogen is so unstable that results are not recorded; ALA is more stable and the raised figures recorded are significant.

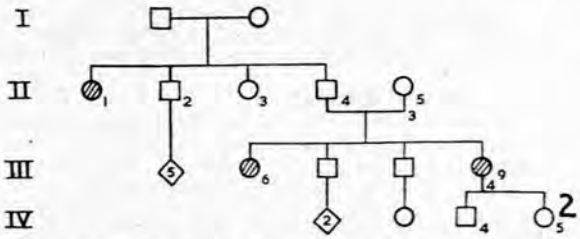

Fig. 2. A Dutch family with 3 cases of porphyria whose clinical manifestations and biochemical findings conform to the pattern seen in Swedish porphyrics. Compare Table II.

Notes on Cases in Fig. 2 *and Table II*

II/1. She has never had a definite attack of acute porphyria but on occasions has noted that her urine was slightly red in colour.

III/6. She has had 4 attacks of acute porphyria, the first when she was 18 years old in 1944 and the last in 1953. Each attack followed the taking of barbiturate sleeping tablets. During the attacks she had severe pain in her abdomen and back and passed red-coloured urine. She had marked weakness in her limbs for some weeks after the attacks. Since 1953 she has stopped all drugs and has remained well.

III/9. In 1951 she became acutely ill with severe pain in her back and legs after taking barbiturate sleeping tablets. She passed red urine and was in hospital for 6 weeks. In 1953 she complained of mild attacks of abdominal pain and underwent a laparotomy under thiopentone anaesthesia. A few days later she developed an acute attack of porphyria with mental symptoms and severe pains in her abdomen, back and limbs. She became paralysed from peripheral neuritis and was in hospital for 3 months. Since then she has taken no drugs and has remained well.

None of the patients in this family showed cutaneous manifestations. Their stool porphyrins are slightly raised but none is as high as is usual in South African porphyric patients.

Notes on Cases in Fig. 3 *and Table III*

II/3. He was a fit man aged 70 years who had never taken sedatives. His skin abraded easily if he knocked the back of his hand but he had no blisters, sores or scars.

II/5. She had suffered from an acute illness and passed dark urine after taking sedatives a few years previously but was otherwise well. The skin on the back of her hands abraded unduly easily.

III/2. She had suffered from recurrent mild attacks of abdominal pain and never felt really well. There were a few depigmented scars on her hands from previous sores and her skin abraded easily.

III/6. The propositus of this family study. He had taken a fair amount of alcohol during 1949, when the skin on the back of his hands started to blister and form small sores. He attributed this to his work as a baker. In 1950 he was in a very nervous state and could not sleep; he took veronal and phenobarbitone

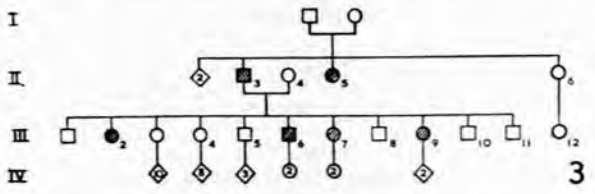

Fig. 3. A Dutch family with several cases of porphyria whose clinical manifestations and biochemical findings conform to the pattern seen in South African porphyrics. See Table III.

TABLE III (COMPARE FIG. 3)

Member	Screen Tests: Faeces porph.	Screen Tests: Urine porph.	Screen Tests: Watson-Schwartz	Stool Porphyrins: Copro. (µg. per g. dry wt.)	Stool Porphyrins: Proto. (µg. per g. dry wt.)
II/3	++	++	neg.	175	263
II/4	neg.	neg.	neg.	screen test negative	
II/5	++	+	neg.	146	192
II/6	neg.	neg.	neg.	screen test negative	
III/2	++	++	neg.	250	485
III/4	neg.	neg.	neg.	17	24
III/5	neg.	neg.	neg.	screen test negative	
III/6	+++	+++	neg.	620	564
III/7	++	+	neg.	730	504*
III/8	neg.	neg.	neg.	screen test negative	
III/9	++	+	neg.	383	645
III/10	neg.	neg.	neg.	45	68
III/11	neg.	neg.	neg.	screen test negative	
III/12	neg.	neg.	neg.	20	65

*This patient had emigrated to Canada and the stool analysis was done for us by Dr. L. A. Brunsting at the Mayo Clinic.

tablets and became acutely ill with mental symptoms and severe pain in his back, abdomen and limbs. His urine was red in colour. In hospital the urine was found to contain porphyrin and porphobilinogen in great excess. All drugs were stopped and he made a good recovery; the Watson-Schwartz test became negative before he left hospital.

III/7. She complains that she cannot sleep, is constipated and has frequent headaches. There has been no attack of acute porphyria but the skin on the back of her hands is unduly sensitive. Dr. Brunsting, of the Mayo Clinic, found high urinary and faecal porphyrin excretion.

III/9. This woman had an acute attack of porphyria in 1952 after taking barbiturates. During the attack the Watson-Schwartz test was positive but it became negative before she left hospital. When seen she was well but the skin on the back of her hands abraded easily.

WHITE SOUTH AFRICAN CASES

Many cases of porphyria have been detected in South Africa. The results in Tables IVa, IVb and IVc were all obtained on White patients of South African stock and those in Table IVd on 2 White patients who had no South African ancestors. The analyses of urine for δ-amino-laevulic acid and porphobilinogen were commenced within 1 hour of collection. A similar metabolic study on Bantu (African) patients is to be published shortly.[23]

Notes on Patients in Tables IVa, IVb, IVc *and* IVd

Case 1 (Table IVa). M28. Porphyria with cutaneous lesions was recognized in 1954. He developed a severe attack of acute porphyria in 1957. The results recorded were obtained on admission to hospital and again 5 weeks later when considerably improved but still far from recovered.

Case 2 (Table IVc). F35. Her skin has abraded easily for as long as she can remember but she has had no outspoken acute attack.

Case 3 (Table IVc). F41. Two attacks of severe abdominal pain with prostration were probably episodes of acute porphyria though not diagnosed at the time. She observed fragility of her skin during pregnancy but not at other times.

Case 4 (Table IVc). M54. Has never had acute porphyria but his skin was somewhat fragile between his 20th and 40th years.

TABLE IVa. SOUTH AFRICAN PATIENTS DURING ACUTE EPISODES

Case No.	Acute Attacks	Urine: Porphyrin	Urine: Watson-Schwartz	Urine: PBG (mg. per litre)	Urine: ALA (mg. per litre)	Stool Porphyrins: Copro. (μg. per g. dry wt.)	Stool Porphyrins: Proto. (μg. per g. dry wt.)
1.	Current	+++	+++	194	219	890	1,400
	5 wks. later	tr.	neg.	2	7	270	508
6.	Current	++	+	25	26	620	1,240
10.	Current	+	+++	99	45	not received	
11.	Current	tr.	++	40	41	805	810
13.	Current	+	++	138	81	623	805
14.	Recent	+	+	20	8	345	568
17.	Current	tr.	++	31	30	670	785

TABLE IVb. SOUTH AFRICAN PATIENTS IN THE SUB-ACUTE PHASE

Case No.	Acute Attacks	Urine: Porphyrin	Urine: Watson-Schwartz	Urine: PBG (mg. per litre)	Urine: ALA (mg. per litre)	Stool Porphyrins: Copro. (μg. per g. dry wt.)	Stool Porphyrins: Proto. (μg. per g. dry wt.)
7.	Subacute	tr.	neg.	3	3	363	266
8.	Subacute	tr.	neg.	8	5	477	930
13.	Recent	tr.	neg.	6	7	623	392
17.	Recent	+	?+*	24	81	580	890
20.	Subacute	tr.	neg.	6	11	630	760

*This urine contained a large amount of urobilinogen, which complicated the interpretation of the Watson-Schwartz test.

TABLE IVc. SOUTH AFRICAN PATIENTS, LATENT OR IN REMISSION

Case No.	Acute Attacks	Urine: Porphyrin	Urine: Watson-Schwartz	Urine: PBG (mg. per litre)	Urine: ALA (mg. per litre)	Stool Porphyrins: Copro. (μg. per g. dry wt.)	Stool Porphyrins: Proto. (μg. per g. dry wt.)
2	None	tr.	neg.	2	2	1,220	1,310
3	1940/41	neg.	neg.	1	2	54	145
4	None	neg.	neg.	1	5	106	186
5	None	neg.	neg.	0	1	70	165
9	1954	tr.	neg.	2	3	414	490
9a.	1953	tr.	neg.	2	5	315	348
10	Recent	neg.	?*	2	3	520	574
10a.		tr.	neg.	3	8	126	197
12	1957	tr.	?+	3	1	593	577
18	None	tr.	neg.	1	1	743	2,000
19	None	tr.	neg.	1	2	159	131

* This urine contained pyridium, which complicated the reading of the Watson-Schwartz test.

TABLE IVd. SOUTH AFRICAN PATIENTS WITH NO SOUTH AFRICAN ANCESTORS, IN REMISSION.

Case No.	Acute Attacks	Urine: Porphyrin	Urine: Watson-Schwartz	Urine: PBG (mg. per litre)	Urine: ALA (mg. per litre)	Stool Porphyrins: Copro. (μg. per g. dry wt.)	Stool Porphyrins: Proto. (μg. per g. dry wt.)
15	1945	++	++	76	47	36	64
16	1954/5	+++	+++	176	80	44	131

Case 5 (Table IVc). F. Traces of porphyrin were detected in urine in 1954 and stool contained 395 μg.of coproporphyrin and 740 μg. of protoporphyrin per g. dry wt. She has never had acute porphyria and the only indication of skin fragility was easy formation of blisters at the base of a thumb when playing tennis.

Cases 1, 2 and 3 are siblings and 4 and 5 are father and daughter.

Case 6 (Table IVa). F43. Had had cutaneous eruptions on exposed areas for the past 8 years. Scarring was marked and some active lesions were present. There had been bouts of intermittent epigastric discomfort, which had recently become worse. Gallbladder trouble was suspected but the findings recorded indicate mild acute porphyria.

Case 7 (Table IVb). M52. Porphyria with cutaneous lesions was recognized in 1954. Recent headaches and abdominal pain had largely subsided when the results recorded were obtained but suggest a subacute porphyric episode.

Case 8 (Table IVb). F39. Porphyria was first diagnosed in 1948 on admission to a neuropsychiatric hospital for investigation. She has had a recurrent rash of an eczematoid nature for some years rather than the characteristic bullous dermatosis. During exacerbations she feels weak and tired and headaches are sometimes severe. The results recorded were obtained on one of these occasions. She had no pain at the time but the findings suggest a subacute phase.

Case 9 (Table IVc). M29. There have been several mild recurrences of abdominal pain since his attack of acute porphyria. His skin is fragile and scars are present on exposed surfaces. When examined he had been free from acute symptoms for some years and was living an active life, participating in vigorous sport at week-ends.

Case 9a (Table IVc). F57. In 1953 a cold was treated with sulphadiazine. Abdominal pain occurred and a hysterectomy was performed. Paralysis of legs and arms developed within a month and lasted for about a year. Porphyria was not suspected, but after her son (case 9) had his acute attack examination of urine and faeces disclosed the presence of excessive amounts of porphyrin. No scarring was apparent on her arms or face.

Case 10 (Tables IVa and IVc). F47. This patient has never enjoyed good health and was frequently given sedatives by her doctors. From July 1956 a phenobarbitone preparation was used with no apparent ill-effects. She suffered a grave psychological trauma in August 1957 and soon afterwards acute porphyria commenced with gross peripheral neuritis. No cutaneous manifestations were observed. The results in Table IVa were obtained during the acute episode and those in IVc 3 months later, when the only residual sign was a mild contracture of the fingers of one hand.

Case 10a (Table IVc). F. Is a daughter of case 10. She accompanied her mother on the recent visit to the consulting physician for follow-up examination. Though not making any complaints at the time she followed the suggestion to send specimens for examination; these gave the results recorded.

Case 11 (Table IVa). M. Two laparotomies in the preceding 3 months afforded no relief of pain, constipation and sleeplessness. Porphyria was detected in time to prevent a third exploration. This patient is an exception to the common finding in South African male porphyrics in suffering an acute attack while presenting no evidence of skin lesions. He stated that a sister was troubled by cutaneous eruptions.

Case 12 (Table IVc). M31. Typical skin lesions have been present for many years. Meningitis in March 1957 was followed by acute porphyria with paralysis 3 months later. When the results recorded were obtained in January 1958 he complained only of slight weakness of the muscles of his right hand.

Case 13 (Tables IVa and IVb). F35. Ectopic pregnancy was suspected but the physical signs were inconclusive. Dark urine contained porphyrin and porphobilinogen. Hyperpigmentation and facial hirsuties were noted and she stated that her skin abraded easily. Three months elapsed between the two sets of analysis.

Case 14 (Table IVa). F. Symptoms attributable to acute porphyria began while she was on holiday; after she returned home porphyrin was detected in her urine but the porphobilinogen reaction was inconclusive because the specimen had been in transit for 48 hours. Three weeks later she was able to make the 200 mile journey to Johannesburg without difficulty and the results recorded were obtained. She then had a blister on one hand and showed numerous scars of previous lesions which began during pregnancy 9 years previously.

Case 15 (Table IVd). F54. This woman was first seen during an acute porphyric episode in 1945 and has fully recovered from the residual paresis of her left arm. There has been no recurrence of symptoms, even during an attack of infective hepatitis in 1952. There is no history or evidence of the cutaneous manifestations associated with porphyria, but she has complained of an intense irritation of the skin of her forearms during high summer.

Case 16 (Table IVd). F31. She is a daughter of case 15, has been hospitalized for 2 severe attacks of acute porphyria, and has had a third minor episode. She has never had any skin trouble.

Cases 15 and 16 are of British stock and have no South African ancestors. The clinical manifestations and biochemical findings conform to the pattern found in acute porphyria seen in Sweden.

Case 17 (Tables IVa and IVb). M29. Fragility of his skin was first noticed 8 years ago following burns of the forearms with hot porridge. He now has scarred forearms and hands. Temporal hirsutism was noted but there have been no lesions on his face. A tired feeling in his legs was followed by acute epigastric pain for which he was referred to a surgeon; the results in Table IVa were obtained at the time. Five months later, when apparently well, he came for follow-up tests (Table IVb). Porphobilinogen and δ-amino-laevulic acid were much higher than those of other patients in the same group and the urine contained a marked excess of urobilinogen. Further examinations will be carried out as opportunity presents.

Case 18 (Table IVc). F33. Her hands began to blister 7 years ago when they were subjected to frequent trauma during handling of motor spares. The lesions have been more or less continuous since and have spread to her arms, face, V-area of her chest, and ankles, which were badly scarred. Considerable facial hirsutism was noted. There was no history of neuritic or abdominal pains.

Case 19 (Table IVc). M49. Blisters following negligible trauma to hands began about 15 months ago and have recurred frequently since. He has had no abdominal pain or operations.

Case 20 (Table IVb). M23. For two or three years he has had lesions on his hands which commence as spontaneous blisters; he does not relate them to trauma. He has had no operations but states that when many lesions are present he loses appetite, experiences abdominal pain, and vomits after taking fatty food. This story and the slightly increased porphobilinogen and δ-amino-laevulic acid suggested the possibility of a smouldering sub-acute phase.

DISCUSSION

The results from this study given in detail in Tables I, Ia, IVa, IVb, IVc and IVd are summarized in Table V. These show that the differing clinical manifestations of porphyria in Sweden and South Africa are paralleled by differences in biochemical findings. The opportunity to study the condition in these two countries has been most instructive, for the differences stand out in high relief though some features are common to both. The similar mode of inheritance in the two countries has already been mentioned. Because the differences discussed below breed true in the two communities it is believed that the diseases depend on anomalies in different genes and are not varied manifestations of one underlying disorder. The occurrence of acute and cutaneous manifestations in separate families in Sweden and in the same family in South Africa does not support an earlier suggestion[2] that differences in climatic conditions such as the amount of solar irradiation play a significant role. When these genetic forms occur in the same community extensive investigation may be required to determine in which of the two any given patient belongs. The findings in the Dutch families (Figs. 2 and 3, Tables II and III) show that separation can be achieved.

As will be shown below the form of porphyria seen in the White South African patients does not fit comfortably into the existing classifications, and the name variegate porphyria (porphyria variegata) is proposed for the genetic disorder of pyrrole-porphyrin metabolism characterized clinically by acute attacks or cutaneous symptoms and not infrequently

TABLE V. SUMMARY OF FINDINGS IN TABLES I, Ia, IVa, IVb, IVc AND IVd

	No. of Cases	Urine: Porphyrin	Urine: Watson-Schwartz	Urine: PBG (mg. per litre)	Urine: ALA (mg. per litre)	Stool Porphyrins: Copro. (μg. per g. dry wt.)	Stool Porphyrins: Proto. (μg. per g. dry wt.)
Normal		neg.	neg.	less than 1	less than 4	0-15	0-45
Sweden							
Acute phase	1	+	+++	48	20	73	117
Remission	7	neg. to +	neg. to ++	2-42 (21)	4-37 (20)	13-26 (17)	11-38 (24)
Cutaneous cases	2	neg., ++	neg.	1	2	152; 73	55; 180
South Africa							
Acute phase	7	tr. to +++	+ to +++	20-194 (78)	8-219 (64)	345-890 (659)	568-1,400 (935)
Sub-acute	5	? to +	neg. to +	3-24 (9)	3-81 (21)	363-630 (535)	266-930 (648)
Latent and remission	11	neg. to tr.	neg to ?	0-3 (1·6)	1-8 (3·0)	54-1,220 (393)	131-2,000 (557)
Imported cases in remission	2	++, +++	++, +++	76; 176	47; 80	36; 44	64; 131

Watson-Schwartz = qualitative test for porphobilinogen
PBG = Porphobilinogen ALA = δ-amino-laevulic acid
Grossly pathological values are enclosed in rectangular frames.

by both. Acute porphyria, it is suggested, should cease to be the name for a clinical entity and should be restricted, in a descriptive sense, to the acute episodes of abdominal pain, neurological disorder or psychiatric disturbances which happen to constitute the main clinical picture of intermittent acute porphyria but are also a feature in many cases of variegate porphyria. Dissatisfaction has been expressed for the name intermittent acute porphyria on the grounds that the primary disturbance is at the precursor rather than the porphyrin stage and the occurrence of similar acute episodes in variegate porphyria makes for more confusion and renders it still less suitable. The name, is however, retained for the present to denote the condition exemplified by the Swedish group in which cutaneous lesions do not occur. These disorders are not restricted to the countries in which our cases have been found and it is hoped that study along the lines indicated will enable cases found elsewhere to be classified more exactly than has hitherto been possible.

In many respects porphyria variegata corresponds with the form known as porphyria cutanea tarda which Rimington and his associates[14] regard as a separate entity and not as mixed forms of the disease. For the condition seen in South Africa, however, porphyria cutanea tarda is an inapt name for two reasons: (*a*) a number of patients suffer acute episodes but present no cutaneous lesions whatever, and (*b*) some patients are known in whom skin lesions began in early childhood[22] and cannot, therefore, be regarded as delayed. The term mixed porphyria proposed by Watson is not a suitable alternative for variegate porphyria, because it is now clear that in this condition the varied clinical manifestations arise in patients who have inherited a single genetically determined constitutional anomaly, which is, however, different from the anomaly inherited in intermittent acute porphyria.

For some years it has been known that urinary porphobilinogen is increased during acute episodes in both intermittent acute and variegate porphyria. More recently it has been learned that this is also true of δ-amino-laevulic acid. The findings summarized in Table V show that, while excretion of these substances remains abnormal (sometimes for years) in patients in remission from intermittent acute porphyria, it returns to normal or nearly so during recovery from the acute episode in patients with variegate porphyria. The Watson-Schwartz test thus provides a valuable means for detecting quiescent cases of the former but is useless for this purpose in the latter since fresh specimens of urine consistently give negative results when acute symptoms are absent.

The outstanding constant feature of variegate porphyria is the increased excretion of copro- and protoporphyrin in the faeces. This is often marked irrespective of past or present acute episodes and has been observed[23] in some members of affected families, including young children, who have never presented either acute or cutaneous symptoms. Faecal excretion of these porphyrins by patients with intermittent acute porphyria, on the other hand, is almost always within normal limits. The simple screening procedure for stool porphyrins not only provides a method for detecting latent or quiescent variegate porphyria but also serves to distinguish this from the intermittent acute form. It must, however, be emphasized that increase in stool porphyrins, whilst strongly suggestive of porphyria when found in a member of a family known to be affected, cannot always be thus interpreted.[24]

Our experience in this connection has been limited to but one case of intermittent acute porphyria in an acute phase, who showed a slight increase in stool porphyrins. In this condition the fundamental metabolic disorder is the escape of precursors from the intracellular enzyme system responsible for their transformation into porphyrinogens. On these grounds no great increase in production and

excretion of these pigments would be expected. It is also pointed out that diminished faecal solids, resulting from reduced food intake during acute episodes, would lead to a slight increase of porphyrins when expressed in terms of dry or wet stool.

These biochemical findings indicate that in variegate porphyria the fundamental disturbance of porphyrin biosynthesis occurs at a later stage than in intermittent acute porphyria.[25] The precursors are satisfactorily transformed to the stage corresponding to copro- and protoporphyrin and only then escape from the intracellular enzyme system. This system is, however, sensitive to incidents such as the use of certain drugs which interfere at the δ-amino-laevulic acid and porphobilinogen stage and precipitate typical attacks of acute porphyria. It is strongly recommended that a conservative attitude should be adopted in the administration of drugs to patients in whom there is a possibility of porphyria and that barbiturates and sulphonamides should not be prescribed for them.

SUMMARY

Quantitative determinations of δ-amino-laevulic acid and porphobilinogen in urine and copro- and protoporphyrin in faeces have been carried out on excreta from porphyric patients in Holland and Sweden and amongst White members of the population of South Africa.

The results, which are discussed in relation to the clinical manifestations of the associated diseases, indicate that intermittent acute porphyria is a different genetic disorder from the condition which presents with acute episodes or cutaneous lesions and sometimes with both. The name variegate porphyria (porphyria variegata) is proposed for the latter.

The main features whereby these two forms can be differentiated are:

1. Cutaneous manifestations, which are common in variegate porphyria, are never seen in affected members of families with the intermittent acute form.

2. In the latter, excretion of porphobilinogen and δ-amino-laevulic acid continues at a high level, sometimes for years, after the attack has subsided, but in variegate porphyria it returns to normal or virtually normal levels as the patient recovers.

3. Raised stool copro- and protoporphyrin are characteristic of variegate porphyria even during remission from acute episodes and of latent cases without clinical manifestations. In intermittent acute porphyria stool porphyrins may be slightly raised during the acute attack but are otherwise normal or nearly so.

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REFERENCES

1. Waldenstrom, J. (1957): Amer. J. Med., **22**, 758.
2. Dean, G. and Barnes, H. D. (1955): Brit. Med. J., **2**, 89.
3. Rimington, C. (1956): *Ibid.*, **2**, 189.
4. Shemin, D. (1956): *Currents in Biochemical Research*. New York: Interscience Publishers.
5. Mauzerall, D. and Granick, S. (1956): J. Biol. Chem., **219**, 435.
6. Shuster, L. (1956): Biochem. J., **64**, 101.
7. Rimington, C., Krol, S. and Tooth, B. (1956): Scand. J. Clin. Lab. Invest., **8**, 251.
8. Gunther, H. (1911): Arch. Klin. Med., **105**, 89.
9. Waldenstrom, J. (1937): Acta med. scand., suppl., **82**.
10. Watson, C. J. *et al.* (1951): Trans. Assoc. Amer. Phys., **64**, 345.
11. Schmid, R., Schwartz, S. and Watson, C. J. (1954): Arch. Intern. Med., **93**, 167.
12. Schmid, R., Schwartz, S. and Sundberg, R. D. (1955): Blood, **10**, 416.
13. Rimington, C. (1955): Endeavour, **14**, 126.
14. References in Rimington, C. (1957): Ann. Rev. Biochem., **26**, 574.
15. Cockayne, E. A. (1933): *Inherited Abnormalities of the Skin and its Appendages*. London: Oxford University Press.
16. Barker, L. F. and Estes, W. L. (1912): J. Amer. Med. Assoc., **59**, 718.
17. Gunther, H. (1922): Ergebn. allg. Path. path. Anat., **20**, 607.
18. Harrison, G. A. (1947): *Chemical Methods in Clinical Medicine*, 3rd ed. London: Churchill.
19. Watson, C. J. and Schwartz, S. (1941): Proc. Soc. Exp. Biol. (N.Y.), **47**, 393
20. Holti, G., Rimington, C., Tate, B. C. and Thomas, G. (1958): Quart. J. Med., **27**, 1.
21. Waldenstrom, J. and Vahlquist, B. (1944): Acta med. scand., **117**, 1.
22. Barnes, H. D., Frootko, J. and Parnell, J. L. (1958): S. Afr. Med. J., **31**, 342
23. Barnes, H. D. (1959): *Ibid.*, in the press.
24. Dean, G. and Barnes, H. D. (1958): Brit. Med. J., **1**, 298.
25. Barnes, H. D. (1956): Ph.D. thesis, University of London.
26. Haeger, B. (1958): Lancet, **2**, 606.
27. Dean, G. (1958): Sem. Höp. Paris, **34**, 140.