guinea-pigs, or to act in a more limited capacity—for example, as an exclusion test.

6. It can be assumed that the compatibility or incompatibility revealed by the N.L.T. test applies to organs other than skin.

7. The N.L.T. test is to be thought of as an *ad hoc* measure which may be useful until the adoption of methods analogous to those used in erythrocyte grouping provide a definitive solution of the typing problem.

General Considerations

The N.L.T. test is biologically interesting in two ways. It shows that blood lymphocytes are much more reactive than lymph-node cells—a discovery for which the work of Billingham, Silvers, and Wilson (1962) and of Gowans (1962) had already prepared us. Secondly, the inflammation raised in the N.L.T. test is almost the simplest imaginable outward sign that an immunological performance is in progress. The speed at which it develops is not surprising in the light of the evidence presented by Gowans (1962) and by Miller, Pierce, Martinez, and Good (1963). As a test of immunological competence—for which it is otherwise well suited—the N.L.T. reaction will of course be especially vulnerable to interference by the non-specific inflammation that may be provoked by the injection of damaged cells.

Summary

In guinea-pigs the intradermal injection of normal blood lymphocytes from the intended recipient of a homograft into each member of a panel of possible donors excites inflammatory reactions of delayed onset and unequal intensity. The intensity of this inflammatory response

provides an almost exact forecast of the intensity of the reaction which a homograft from each donor will elicit after transplantation to the future recipient. Where choice can be exercised, this “normal lymphocyte transfer” (N.L.T.) test may therefore be made the basis of an *ad hoc* method for choosing the homograft donor most compatible with a given recipient. Subject to certain safeguards, the N.L.T. test should be applicable to human beings.

REFERENCES

- Battisto, J. R. (1960). *Nature (Lond.)*, **187**, 69.
 — (1963). *Ibid.*, **198**, 598.
 Billingham, R. E., and Brent, L. (1957). *Transplant. Bull.*, **4**, 67.
 — (1959). *Phil. Trans. B*, **242**, 439.
 — and Medawar, P. B. (1951). *J. exp. Biol.*, **28**, 385.
 — Silvers, W. K., and Wilson, D. B. (1962). *Lancet*, **1**, 512.
 Brent, L., Brown, J. B., and Medawar, P. B. (1958). *Ibid.*, **2**, 561.
 — (1962). *Proc. roy. Soc. B*, **156**, 187.
 Cock, A. G., and Simonsen, M. (1958). *Immunology*, **1**, 103.
 Dvorak, H. F., Kosunen, T. U., and Waksman, B. H. (1963). *Lab. Invest.*, **12**, 58.
 Friedman, E. A., Retan, J. W., Marshall, D. C., Henry, L., and Merrill, J. P. (1961). *J. clin. Invest.*, **40**, 2162.
 Gowans, J. L. (1962). *Ann. N.Y. Acad. Sci.*, **99**, 432.
 — Gesner, B. M., and McGregor, D. D. (1961). In *Biological Activity of the Leucocyte*, edited by G. E. W. Wolstenholme and M. O'Connor, p. 32. Churchill, London.
 McKhann, C. F. (1962). *J. Immunol.*, **88**, 500.
 Mannick, J. A., and Egdahl, R. H. (1962). *Ann. Surg.*, **156**, 356.
 Martinez, C., Shapiro, F., Kelman, H., Onstad, T., and Good, R. A. (1960). *Proc. Soc. exp. Biol. (N.Y.)*, **103**, 266.
 Medawar, P. B. (1963). *Transplantation*, **1**, 21.
 Merrill, J. P., Friedman, E. A., Wilson, R. E., and Marshall, D. C. (1961). *J. clin. Invest.*, **40**, 631.
 Miller, J., Pierce, J. C., Martinez, C., and Good, R. A. (1963). *J. exp. Med.*, **117**, 863.
 Nowell, P. C. (1960). *Cancer Res.*, **20**, 462.
 Simonsen, M. (1957). *Acta path. microbiol. scand.*, **40**, 480.
 Terasaki, P. I. (1959). *J. Embryol. exp. Morph.*, **7**, 394.
 Walzer, M., Bowman, K. L., and Stroyman, S. (1957). *J. Allergy*, **28**, 206.

DIFFERENT PATTERNS OF HUMAN PORPHYRIA*

BY

JAN WALDENSTRÖM, M.D.

BIRGITTA HAEGER-ARONSEN, M.D.

From the Department of Medicine (University of Lund), General Hospital, Malmö, Sweden

The delimitation of natural disease entities is one of the real difficulties in scientific medicine. We may accept the infectious conditions caused by a known agent such as tuberculosis and syphilis as “good” diseases. Others, like diabetes mellitus, are probably heterogeneous even if recent studies of heredity speak in favour of one chief factor. When we come to such old-fashioned concepts as chronic “myocarditis” everybody should be aware that these are no more than words without much meaning. There is, however, one group of diseases with a genuine right to be regarded as having a well-defined and identical origin. They are the inborn errors of metabolism. This is especially true of all cases occurring in the same family, where one mutation—that is, the same change in the structure of the D.N.A. molecule—must be at work. It may be dangerous, however, to postulate that all members of different families supposed to have the same disease are really suffering from the results of the same mutation—that is, that they are absolutely identical. Haemophilia is an excellent example of this. There are many learned calculations using impeccable statistical techniques of the mutation frequency of “haemophilia.” We now know that haemophilia was diagnosed as one disease until clinical analysis (Koller, Krüsi, and Luchsinger, 1950) showed that there must exist

two entirely different haemophilias: true=haemophilia A with deficiency of factor VIII, and Christmas disease=haemophilia B with deficiency of factor IX.

Recent work in Malmö has shown that a number of men suffering from von Willebrand's disease have probably earlier been regarded as haemophiliacs (Nilsson, Blombäck, and Blombäck, 1959). This group of haemorrhagic diseases is probably genetically still more heterogeneous. Several authors (Brinkhous and Graham, 1954; Nilsson, 1960) have pointed out the fact that there seem to be different degrees of haemophilia that always remain true to type—that is, they are inherited either as severe or as intermittent or as mild. Among the true haemophilia families there seem to exist three degrees of severity. This would mean that there are at least six different mutations. Von Willebrand's disease is inherited autosomally and obviously has quite a different mechanism. Linkage studies in this condition will ultimately show if this disease picture is always the result of mutations in the same locus or not.

It seems evident that all discussions regarding mutation frequencies are without scientific value so long as these fundamental clinical principles have not been recognized as basic.

When one of us (J.W.) became interested in the porphyrias, Günther (1911, 1922), who was a great authority,

*This is a slightly enlarged Litchfield Lecture given in Oxford in 1962 by one of us (J.W.).

spoke about four different "types" of the same disease: congenital (cutaneous), chronic cutaneous, and acute and toxic haematoporphyria.

Clinical, biochemical, and genetic studies (Waldenström, 1937) showed that there must be at least three entirely different diseases: congenital porphyria, porphyria cutanea tarda, and acute porphyria. Waldenström (1957) suggested, more or less facetiously, that the latter disease should be called a pyrrolia as the pyrrole porphyrin precursor porphobilinogen (P.B.G.) is always found in increased amounts in the urine. Eales (1961) has taken up this suggestion and calls this disease pyrroloporphyria. It was shown (Waldenström and Vahlquist, 1944) that P.B.G. could condense to uroporphyrin if the solution was made acid. Barbiturates are dangerous in porphyria acuta intermittens (P.A.I.) and the so-called toxic type is therefore not really a "type" by itself, but arises in a person with P.A.I. who is treated with barbiturates.

Watson and his group (Watson, 1954; Schmid, Schwartz, and Watson, 1954; Schmid, Schwartz, and Sundberg, 1955) thoroughly investigated the disease that Günther called congenital haematoporphyria and gave it the name erythropoietic porphyria, thereby indicating that the site of porphyrin formation is the erythroblast. Schmid *et al.* (1955) demonstrated that this is an extremely rare condition and that many previously published cases with this diagnosis were really instances of porphyria cutanea tarda (P.C.T.) and therefore did not belong to the group with early onset and probably recessive inheritance.

According to our experience from Sweden, together with that from other countries, the following different porphyrias seem to be well-established entities (see Table I).

Porphyria Acuta Intermittens, or Pyrroloporphyria

P.A.I. is characterized by attacks of most severe abdominal colic with constipation, often related to the menstrual cycle. In Sweden about 60% of all manifest cases occur in females. Latent carriers, who never develop clinical symptoms, are not rare and may be detected genealogically and biochemically—urinary P.B.G. in increased amounts (Waldenström, 1937). P.A.I. is not very rare in Sweden and we now know of about 600 cases. In one big Swedish family, where the genealogy was worked out in

FIG. 1.—Urinary excretion of δ -aminolaevulinic acid (A.L.A.) and porphobilinogen (P.B.G.) in 26 patients with P.A.I., 13 with protocoproporphyria, 16 with porphyria variegata (protocoproporphyria) in subacute or latent phase (Dean and Barnes, 1959), 37 with P.C.T., 2 with porphyria congenita, and 5 with protoporphyria erythroietica. Inserted vertical and horizontal lines indicate upper limit of normal range of excretion of P.B.G. and A.L.A. respectively. Logarithmic scale.

great detail, it was found that 23% of the female and 29% of the male carriers of the trait were latent at the time of examination. Several latent cases became manifest at a later stage. They were "candidates" for the disease (Waldenström, 1937).

Some patients develop quite severe general symptoms: oliguria, azotaemia, hypertension, and even coma during a porphyric crisis. Sinus tachycardia indicates that the crisis is not yet overcome and is therefore prognostically important. Slight fever and leucocytosis may occur, making the differential diagnosis from an acute surgical abdomen very difficult. This is most important for the prognosis. If the porphyria is not diagnosed the patient will probably be operated upon in narcosis and given different sedatives of the barbiturate group. There are cases where an acute delirium or severe unrest may cause the administration of

FIG. 2.—Urinary excretion of coproporphyrin (C.P.) and uroporphyrin (U.P.) in 13 patients with protocoproporphyria, 37 with P.C.T., 3 with porphyria congenita, and 5 with protoporphyria erythroietica. Inserted vertical and horizontal lines indicate upper limit of normal range of excretion of U.P. and C.P. respectively. Logarithmic scale.

FIG. 3.—Faecal excretion of coproporphyrin (C.P.) and protoporphyria (P.P.) in 28 patients with P.A.I., 13 with protocoproporphyria, 16 with porphyria variegata (protocoproporphyria) in subacute or latent phase (Dean and Barnes, 1959), 32 with P.C.T., 2 with porphyria congenita, and 5 with protoporphyria erythroietica. Inserted vertical and horizontal lines indicate upper limit of normal range of excretion of P.P. and C.P. respectively. Logarithmic scale.

sedatives in large amounts. In both situations the result will be disastrous. The risks that the patient will develop widespread paralyses and die from respiratory failure are very great. During an attack the urine (especially if left standing) is usually very dark, but it may have a practically normal colour, a fact that is, of course, responsible for many diagnostic errors. Cutaneous symptoms never occur in P.A.I. families.

The biochemical findings are summarized in Figs. 1 and 3 and in Table I. It is clearly seen that neither human lead intoxication nor the experimental types of porphyrin disturbances mimic any of the known porphyrias in man.

TABLE I.—Concentration of δ -Aminolaevulinic Acid (A.L.A.), Porphobilinogen (P.B.G.), Uroporphyrin (U.P.), and Coproporphyrin (C.P.) in Urine, of C.P. and Protoporphyria (P.P.) in Faeces, of A.L.A. in Serum, and of P.P. in Red Blood Cells in Patients with Different Types of Porphyria and Lead-induced Porphyrinuria as well as in Animals with Experimental Porphyria

Type of Porphyria	Urine				Faeces		Serum	R.B.C.
	A.L.A.	P.B.G.	U.P.	C.P.	C.P.	P.P.	A.L.A.	P.P.
P.A.I.:								
Latent	(+)	++	+++*	+	+	+	(+)	N
Manifest	++	+++	+++*	++	+	+	+	N
Protocopro-								
porphyria (P. variegata):								
Latent	N	N	N	N	+++	++	N	—
Manifest	++	+++	+++*	++	+++	+++	+	—
P.C.T.:								
Latent	N	++	(+)	+++	++	+	N	N
Manifest	(+)	N	+++	++	++	+	N	N
Porphyria congenita	N	N	+++	+++	+++	(+)	—	+
Protoporphyria erythropoietica	N	N	N	N	(+)	(++)	N	+++
Lead-induced:	+++	N	N	++	N	N	++	+++
"Sedormid"-induced	+	+++	++*	+	+	++	(+)	N
Hexachlorobenzene-induced	++	+++	++*	+	+	+	—	N
"D.D.T.D."-induced	+	+++	+++*	+++	+	++	(+)	N

(+) to +++ = Increased. N = Normal. — = Information not available.
* Chiefly made *in vitro* from P.B.G.

Protocoprophyria, or Porphyria Variegata

There has been much discussion regarding the interrelation between P.A.I., or the "Swedish" porphyria, and protocoprophyria, or the "South African" porphyria. One of us (J.W.) has maintained that they are different as we have never seen any cutaneous symptoms among our patients with P.A.I. in Sweden. Dean was first of the opinion that they were identical but later became convinced of their differences (Dean and Barnes, 1959). Schmid *et al.* (1954) speak of mixed porphyria and believe that strong insolation may produce cutaneous symptoms in patients with P.A.I. We have reason to believe that absence of much irradiation may be a factor causing the skin sensitivity to remain latent in the South African disease, when it occurs in northern countries. Strong insolation may produce cutaneous symptoms in this group but never in the Swedish disease (P.A.I., pyrrolporphyria).

The clinical picture of the South African disease is chiefly known to us through publications, as very few of our own Swedish cases seem to belong to this group. It must be regretted that few detailed descriptions of the natural history of South African porphyria have been given. According to South African authors (Dean and Barnes, 1955, 1958, 1959; Eales, 1960) the skin is easily eroded mechanically (Nikolsky's sign). A certain number of these patients develop abdominal and nervous symptoms identical with those of Swedish P.A.I. It must be noted that there is increased P.B.G. in the urine during such attacks but not in remission or in the latent stage (Table I). It would

therefore seem very likely that disturbance of δ -aminolaevulinic acid (A.L.A.) and P.B.G. metabolism is responsible for the abdominal and neurological disturbances in both Swedish and South African porphyria. It has also been reported from South Africa (Dean, 1953, 1957) that barbiturates play a part in the development of the clinical symptoms. Barnes (1958) and Eales (1960) have stressed the importance of stool examinations for the correct diagnosis of this disease. They have shown that both protoporphyria and coproporphyria are always increased. Quantitative determinations of faecal porphyrins have usually been neglected and it may be supposed that many of these cases are never correctly diagnosed, especially in climates where the cutaneous symptoms do not develop.

Thus even if there are obvious parallels between the Swedish and South African types of porphyria, the experiences from Sweden, where extensive genetic studies have been made, seem to indicate that they are genetically entirely separate entities. This is also the present opinion of the South African workers in this field (Dean and Barnes, 1959).

In a previous paper Waldenström (1957) pointed out that there must be a special type of cutaneous porphyria that could not be called porphyria cutanea tarda because it occurred at a relatively early age. Excellent studies of this *protocoprophyria*, with increased quantities of protoporphyria and coproporphyria in the stools as the remaining sign that never disappeared, have been published in England. Wells and Rimington (1953) found this condition in a brother and sister, and Holti, Rimington, Tate, and Thomas (1958) discovered it in 10 members of a family. Tio (1956) has described an interesting family from Holland with dominant heredity through three generations and early development of cutaneous symptoms. It seems to us that all these cases fit in well with the name *protocoprophyria*, and it should perhaps be noted that the inheritance of

TABLE II.—Urinary Excretion of A.L.A., P.B.G., U.P., and C.P., and of Faecal C.P. and P.P. in 13 Patients with Protocoprophyria and 8 Unclassified Cases

Family	Case No.	Urine				Faeces		
		A.L.A.	P.B.G.	U.P.	C.P.	C.P.	P.P.	
		mg./100 ml.	mg./100 ml.	μg./100 ml.	μg. 100 ml.	μg. g. (dry weight)	μg. g. (dry weight)	
<i>Protocoprophyria (P. variegata)</i>								
Pa.	1	0.34	0.10	4	0	—	—	
		0.23	0.06	2	1	4	40	
	2	0.42	0.09	1	0	10	54	
		0.34	0.06	24	28	6	35	
G.	3	1.28	0.58	11	99	48	70	
		—	—	14	90	115	149	
L.	4	0.90	0.24	9	23	387	193	
		1.89	0.58	27	104	798	224	
	5	0.51	0.53	22	86	76	89	
	6	0.55	0.34	112	95	154	241	
	7	0.85	0.26	181	56	90	139	
S.	8	1.40	1.00	184	120	73	134	
	9	0.49	0.25	23	58	88	41	
	10	0.72	0.42	10	34	122	784	
		0.84	0.67	36	58	333	1,295	
	11	1.60	0.84	10	88	184	778	
	12	0.83	0.29	5	19	6	22	
	13	0.66	0.29	0	3	29	136	
<i>Unclassified Cases</i>								
P.	14	1.88	4.20	409	16	3	10	
	15	1.44	0.92	871	58	110	119	
	16	1.33	3.02	249	59	5	16	
	17	1.48	10.32	1,370	88	5	28	
	18	0.63	2.77	47	58	5	36	
	19	0.79	1.67	47	82	6	51	
	20	0.45	2.26	81	13	24	97	
	21	1.69	4.18	180	114	6	25	
		Normal values	≤0.57	≤0.20	≤11	≤15	≤6	≤39

porphyria in the white population of South Africa has been traced to a pair of early settlers from Holland (Dean, 1961).

During the past few years we have observed 13 cases of what we believe to be protocoproporphyria. They belong to four different families (Table II). Five patients (Cases 2, 5, 6, 9, and 13) were, at the time of investigation, latent with no clinical symptoms but increased amounts of faecal protoporphyrin and coproporphyrin.

Case Reports

Case 1.—The 16-year-old daughter of Case 2 had blisters on the face and hands on one occasion after exposure to sunlight seven years ago. The lesions healed slowly, leaving white scars. At that time and one year later the girl had colicky abdominal attacks, and, in association with these, increased excretion of urinary porphyrins. Since 1956 she has had no symptoms.

Case 2.—Man aged 49. No symptoms.

Case 3.—Woman aged 33. In the summer of 1959 she developed blisters on the backs of her hands and on her face. The lesions healed very slowly. Since then the skin has been unduly fragile. She had her first abdominal attack at the same time as the cutaneous lesions and has since had one attack every year. She often has headache of migraine type. Her mother had died with severe porphyric symptoms at a young age. She also had typical cutaneous manifestations and her urine contained large quantities of porphyrins.

Case 4.—Man aged 42, brother of Cases 5, 6, 7, 8, and 9, had his first abdominal attack in 1957, and six severe attacks since. Often obstipated. Nervous. He is "light sensitive" but never develops blisters on exposure to sunshine.

Case 5.—Man aged 46. No symptoms.

Case 6.—Man aged 51. No symptoms.

Case 7.—Man aged 45. Has often been obstipated during the past 10 years. Sometimes dark urine. No skin lesions.

Case 8.—Man aged 48. Subject to intermittent attacks of intestinal colic during the past 20 years. Often obstipated. No skin lesions.

Case 9.—Woman aged 49. No symptoms.

Case 10.—Man aged 59, father of Cases 11, 12, and 13, had frequent abdominal attacks during the past 30 years. Very often obstipation and dark urine. Uncharacteristic skin lesions on his face during summer of 1953.

Case 11.—Man aged 27. Frequent colicky abdominal attacks during past three years. Dark urine sometimes observed.

Case 12.—Woman aged 25 suffered from obstipation all her life. Sometimes dark urine. Nervous. Thin. No skin lesions.

Case 13.—Woman aged 21. No symptoms.

Comment

It may be asked why only Cases 1, 3, and perhaps 10 show cutaneous symptoms when all these patients (Cases 1-13) are supposed to have protocoporphyria (porphyria variegata). Our answer would be that we believe protocoporphyria patients need strong exposure to sunlight in order to develop skin sensitivity. This they seldom get in Sweden.

We have never found any genetic connexions between these four protocoporphyria families and known P.A.I. families in spite of the fact that they have been followed back for several generations.

One family (P., Cases 14-21) is difficult to classify (Table II). Two members (Cases 15 and 20) have had pathologically increased faecal coproporphyrin and protoporphyrin values. Case 15 has had skin symptoms in the face that have not been observed by any doctor. They are said not to have been vesicular and to occur in the summer. There was no mechanical fragility of the skin when tested by us. The patient is an alcoholic.

B

Reports of Unclassified Cases

Case 14.—Man aged 69. Father of Cases 16, 17, 18, 19; uncle of Case 15, and half-brother of Case 20. No symptoms.

Case 15.—Man aged 49. Frequent attacks of abdominal pain for 20 years. Often obstipated and excreting dark urine. Nervous.

Case 16.—Woman aged 47. Attacks of abdominal pain and vomiting for more than 20 years. Often obstipated. No neurological symptoms or skin lesions.

Case 17.—Man aged 45. Often very nervous. Thin. Frequent attacks of abdominal pain. He has often seen dark urine.

Case 18.—Woman aged 41 had frequent attacks of abdominal colic since the age of 25. Almost always dark urine. Backache. She gets worse during menstruation. Sometimes, and not connected with exposure to sunlight, uncharacteristic skin lesions on back of hands; they heal without scars.

Case 19.—Man aged 37 has suffered from frequent attacks of abdominal pain for about 20 years. Always obstipated. Nervous. Thin. Backache. Dark urine. No skin lesions.

Case 20.—Woman aged 39, aunt of Case 21, has been very nervous for about 20 years. Obstipated since childhood. Frequent attacks of abdominal pain. Then often hallucinations. No skin lesions.

Case 21.—Man aged 29. No symptoms.

Porphyria Cutanea Tarda

This is a different cutaneous disease but is also caused by the light-sensitizing effects of porphyrins. It is commonly accepted that alcohol plays a large part in the development of this condition. Waldenström and Haeger (1960) have discussed the condition of the liver in these patients. Signs of slight fibrosis are common on liver biopsy and bromsulphthalein excretion is impaired. We were able to follow these patients during periods of clinical and biochemical improvement and it was obvious that the bromsulphthalein excretion also improved, but we have never seen it become normal even when the skin symptoms disappeared. We are convinced that there are a few cases where alcoholism could not be the explanation of the skin symptoms. In most cases, however, the patients have ultimately been found to have taken alcohol in larger quantities than normal.

It is evident that only a very small number of all alcoholics will show any signs of porphyria and we have therefore wondered if this condition might also develop on a constitutional basis. Our efforts to investigate relatives of these patients have not been very successful owing to several circumstances. One is the fact that these alcoholics are mostly elderly, often not married or with derangements of their family life.

We have been able to follow one patient (Case III, Fig. 4) and investigate 13 of her relatives. She had her first symptoms of P.C.T. in 1956. After stopping her alcohol intake her light sensitivity disappeared, and, what was more remarkable, her porphyrin excretion came down to normal values on examination in 1962 (see Table III). If this is a familial genetic trait, and the fact that two brothers (Cases I and II, Fig. 4) of the patient have abnormal porphyrin

FIG. 4.—Family B. Squares represent males and circles females. Solid symbols indicate manifest cases of P.C.T.; semi-solid symbols, latent cases; hollow symbols, healthy members.

excretion (Table III) would strongly support such an assumption, we are obviously not able to detect all carriers by biochemical observation.

TABLE III.—*Urinary Excretion of U.P. and C.P. and of Faecal C.P. and P.P. in 2 Cases (Nos. III and IV) of Manifest and 5 Cases (Nos. I, II, V, VI, and VII) of Latent P.C.T.*

Case No.	Date	Urine		Faeces	
		U.P.	C.P.	C.P.	P.P.
		µg./100 ml.	µg./100 ml.	µg./g. (dry weight)	µg./g. (dry weight)
I	Sept., 1958	9	14	—	—
	Mar., 1960	7	12	16	54
II	Sept., 1958	22	14	—	—
	Mar., 1960	24	17	10	52
III	Oct., 1957	4,913	1,087	—	—
	Oct., 1957	4,978	660	—	—
	Mar., 1958	49	18	—	—
	Sept., 1959	5	4	—	—
	Oct., 1959	13	7	—	—
	June, 1960	31	4	3	0
	Feb., 1962	6	3	5	24
IV	Sept., 1957	1,750	213	—	—
	Apr., 1958	106	12	—	—
	Sept., 1958	178	8	—	—
	June, 1960	133	5	19	0
	Sept., 1960	101	8	8	23
	Mar., 1961	67	9	5	16
	Mar., 1961	—	—	—	—
V	Oct., 1957	0	94	—	—
	Apr., 1958	10	8	—	—
	Mar., 1961	22	34	—	—
VI	Oct., 1957	12	17	—	—
	Apr., 1958	10	26	—	—
	Sept., 1958	16	20	—	—
	Mar., 1961	13	17	—	—
	Feb., 1962	—	—	1	11
VII	Oct., 1957	10	35	—	—
	Apr., 1958	10	22	—	—
	Mar., 1961	12	19	—	—
	Feb., 1962	—	—	14	40

Another family (Fig. 5) is interesting in so far as only one member (Case IV), who is a very keen yachtsman, has the fully developed disease with cutaneous symptoms, whereas his brother (Case V), who is not interested in sailing, has no skin lesions but is definitely not normal biochemically (Table III). One son of each of these brothers also has a disturbance of porphyrin metabolism (Cases VI and VII, Table III). There seems to be convincing evidence that the patient himself has not been using alcohol.

FIG. 5.—Family L

The question of the genetics of P.C.T. is not easy to solve. One thing seems certain, however: no family connexions have been established between our 40 P.C.T. cases, where the ancestry has been investigated in detail, and our families with P.A.I. It should also be

pointed out that none of our patients with P.C.T. have had any abdominal or nervous symptoms indicating protocoproporphyrin, nor have they ever had cutaneous symptoms as juveniles.

In our opinion the most intriguing case of porphyria that has ever been published (Tio, 1956; Tio, Leijnse, Jarrett, and Rimington, 1957) occurred in a woman aged 80, who had suffered for a short time from typical P.C.T. It was found that she had a big tumour of the liver and this tumour was extirpated. The histological diagnosis was liver-cell adenoma. It contained large amounts of uroporphyrin and was obviously the source of the porphyrins, as her "porphyria" disappeared after removal of the tumour. This could be a "somatic mutation," where the tumour

cells have lost part of their capacity to decarboxylate uroporphyrin. The family was investigated in detail and there were no other instances of P.C.T.

Porphyria Congenita

No cases have been observed in Sweden.

Protoporphyrin Erythropoietica

Quite recently one of us (B.H.-A.) found a Swedish family with a "new" type of disturbed porphyrin metabolism that had been earlier described from Germany (Kosenow and Treibs, 1953; Kosenow, 1954) and England (Magnus, Jarrett, Prankerd, and Rimington, 1961). The proband, a man aged 39, and his two daughters of 14 and 8 years all suffer from light sensitivity (erythema, oedema, and itching of the exposed parts of the skin, but no blisters, scars, pigmentation, or hypertrichosis) since childhood. They have a very high content of protoporphyrin in their erythrocytes and numerous fluorescing normoblasts in the bone-marrow. In the mother and sister of the proband the concentration of protoporphyrin in the erythrocytes was significantly increased. As they never suffered from hypersensitivity to sunshine they were regarded as latent cases. The disease was thus traced through three generations of a family and appears to be transmitted by a dominant gene (Haeger-Aronsen, 1962, 1963).

Conclusion

This paper deals with the patterns found in the different types of porphyria in humans. It seems clear that they are on the whole characteristic even if some patients cannot be classified with certainty. The data seem to indicate that there are at least five genetically determined types of inborn error of porphyrin metabolism and the pattern within one family remains true to type.

REFERENCES

- Barnes, H. D. (1958). *S. Afr. med. J.*, **32**, 680.
 Brinkhous, K. M., and Graham, J. B. (1954). *Blood*, **9**, 254.
 Dean, G. (1953). *Brit. med. J.*, **2**, 1291.
 — (1957). *Sci. Amer.*, **196**, 133.
 — (1961). *Current Therapy*, edited by H. F. Conn, p. 317. Saunders, Philadelphia and London.
 — and Barnes, H. D. (1955). *Brit. med. J.*, **2**, 89.
 — (1958). *Ibid.*, **1**, 298.
 — (1959). *S. Afr. med. J.*, **33**, 246.
 Eales, L. (1960). *S. Afr. J. Lab. clin. Med.*, **6**, 63.
 — (1961). *Ann. Rev. Med.*, **12**, 251.
 Günther, H. (1911). *Disch. Arch. klin. Med.*, **105**, 89.
 — (1922). *Ergebn. allg. Path. path. Anat.*, **20**, 607.
 Haeger-Aronsen, B. (1962). *Lancet*, **1**, 1073.
 — (1963). *Amer. J. Med.* In press.
 Holti, G., Rimington, C., Tate, B. C., and Thomas, G. (1958). *Quart. J. Med.*, **27**, 1.
 Koller, F., Krüsi, G., and Luchsinger, P. (1950). *Schweiz. med. Wschr.*, **80**, 1101.
 Kosenow, W. (1954). *Med. Klin.*, **49**, 1099.
 — and Treibs, A. (1953). *Z. Kinderheilk.*, **73**, 82.
 Magnus, I. A., Jarrett, A., Prankerd, T. A. J., and Rimington, C. (1961). *Lancet*, **2**, 448.
 Nilsson, I. M. (1960). *Troisième Symposium de la Fondation Valentino Baldacci*. Omnia Medica, Pisa.
 — Blombäck, M., and Blombäck, B. (1959). *Acta med. scand.*, **164**, 263.
 Schmid, R., Schwartz, S., and Sundberg, R. D. (1955). *Blood*, **10**, 416.
 — and Watson, C. J. (1954). *Arch. intern. Med.*, **93**, 167.
 Tio, T. H. (1956). M.D. thesis, University of Amsterdam.
 — Leijnse, B., Jarrett, A., and Rimington, C. (1957). *Clin. Sci.*, **16**, 517.
 Waldenström, J. (1937). *Acta med. scand.*, Suppl. 82.
 — (1957). *Amer. J. Med.*, **22**, 758.
 — and Haeger, B. (1960). *Ann. intern. Med.*, **53**, 286.
 — and Vahlquist, B. (1944). *Acta med. scand.*, **117**, 1.
 Watson, C. J. (1954). *Advanc. intern. Med.*, **6**, 235.
 Wells, G. C., and Rimington, C. (1953). *Brit. J. Derm.*, **65**, 337.