of the same birth weights born in hospital or transferred there within two months of birth. Both measures show a considerable variation between different parts of the country (Table V). The experience of the Midlands region was the most favourable (all infants 0.89%, "hospital" infants 1.04%), and the highest incidence occurred in the North-western region (all infants 2.74%, "hospital" infants 3.07%).

Neither of these crude measures of incidence makes any allowance for possible differences in the sex and birth-weight distribution of infant populations in the different regions. The pattern of variation displayed by the crude rates can, however, be confirmed by a measure of incidence which makes adjustment for such differences. Thus the sex and birth-weight specific incidence rates for the whole country ("hospital" infants) were applied to the "hospital" infants of each region to give the number of infants "expected" to have developed the disease had there been no regional variation. Expressing the number of cases observed as a proportion of the "expected" number provides an index making appropriate allowance for differing sex and birth-weight distributions of the populations (Table VI). The wide

TABLE VI.—*Incidence in Each Region Compared with Incidence in England and Wales as a Whole (Based on Infants Born in or Transferred to Hospital or Nursing-home Within Two Months)*

Region	Relation Between Incidence and that of All E. and W.
Midlands	52% lower
East and West Ridings	43% ,,
London	25% ,,
Eastern	16% ,,
Southern	14% ,,
Northern	6% ,,
North Midlands	2% ,,
South-eastern	16% higher
South-western	27% ,,
Wales	60% ,,
North-western	65% ,,

variation between different regions was again apparent, with an incidence ranging from about 50% lower to more than 50% higher than that experienced over the whole of England and Wales. All three measures of incidence showed the rates to be highest in the North-western and Welsh regions and lowest in the Midlands and East and West Riding regions.

Summary

Particulars have been obtained from all local authorities in England and Wales of infants born in 1951 having a birth weight of 4 lb. 6 oz. (2,000 g.) or less and surviving at least two months. Of 6,926 such infants, 1.83% had retrolental fibroplasia. No case was found amongst the 797 infants born at home and never transferred to hospital. The incidence was closely related to birth weight, declining steeply with increasing birth weight. The incidence was higher in males than in females, but this difference may be due to male babies being less mature than female babies of the same weight. Twin babies showed the same incidence as single babies. Considerable regional variability was observed, with relatively high rates in Wales and the North-western counties and low rates in the Midlands and East and West Ridings of Yorkshire.

We are grateful to Professor A. Bradford Hill for helpful advice and criticism in the planning of the survey and in the preparation of this report. We are also deeply indebted to the medical officers of health, whose assistance enabled the survey to comprise the whole of England and Wales, to the many health visitors who compiled the detailed returns, and to the ophthalmologists who so readily co-operated.

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HEREDITARY COPROPORPHYRIA

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In 1936 Dobriner reported a case in which a woman excreted large amounts of coproporphyrin (probably series III) and traces of uroporphyrin in the urine, and also large amounts of coproporphyrin (series I and III) and protoporphyrin in the stool. Although this woman was then a patient in a psychiatric ward, there were no apparent symptoms associated with the abnormal porphyrin excretion. Watson *et al.* (1949) described the cases of two men who excreted large amounts of coproporphyrin III in the urine and stools, unaccompanied by symptoms. They stated that this condition, which they called "idiopathic coproporphyrinuria," represented an "inborn error of metabolism," although they could not find evidence for any hereditary association of the abnormality.

The present paper describes the occurrence of a similar pigment disturbance in a Swiss boy, in his mother and father (who are first cousins), and also in his paternal aunt. The boy excretes much higher quantities of coproporphyrin in his urine and faeces than the others and also passes traces of uroporphyrin I in his urine. He has suffered from rickets, noted for the first time at 3½ years, as well as from riboflavine deficiency. An unusual amino-acid excretion pattern was obtained by paper chromatography in three of these four subjects. The term "hereditary coproporphyria" has been used for this condition, because of the genetic significance of these findings and because the porphyrins are excreted in the faeces as well as in the urine, principally in the faeces.

Methods

Porphyrins.—Quantitative determinations of porphyrins and porphobilinogen in the urine and stools were carried out as in a previous study (Goldberg, 1954). Since initial investigation had shown that the excess porphyrins were entirely ether-soluble, the isolation and identification were done as under "ether-soluble porphyrins."

Urinary amino-acids were identified by paper chromatography (Dent, 1951).

Riboflavine determinations were carried out by means of microbiological assay, using *Lactobacillus casei*, or fluorimetrically.

Case Report

This patient was born in 1944 after a normal labour. His mother had hyperemesis during pregnancy. Birth weight, 3 kg. He was breast-fed until the age of 7 months, then was given breast milk and vegetables until 1 year, when he was put on a mixed diet. His first tooth erupted at 1 year and he completed his primary dentition by the end of his second year. He started walking at 1½ years and spoke his first word at 2. About the age of 1½ years he had a generalized skin rash, which disappeared when milk was discontinued. About this time he also had diarrhoea, which was treated in the out-patient department of the Jenner-Kinderspital, Berne, Switzerland. At 3½ years he had a severe middle-ear infection, which later was complicated by a throat and lung infection. He recovered from

this, but one month later developed gastro-enteritis with marked dehydration. At this time his family doctor noted that he had rickets and gave him calcium and vitamin preparations without benefit. At 4 years his mother observed that some of his nails were cracked and heaped up and that there was "eczema" between his fingers, where infection was common. There was also some cracking and irritation of the buccal mucous membrane and at the angles of the mouth. His mother believed that when he drank milk his mouth and hands got worse. His skin had never been affected adversely by the sun.

On September 22, 1952, he was admitted to the Jenner-Kinderspital under the care of Professor Ed. Glanzmann because of further attacks of diarrhoea and also for treatment of his rickets, mouth, and nails. It was during this admission that an investigation of the urine disclosed the incidental presence of excessive porphyrins.

FIG. 1

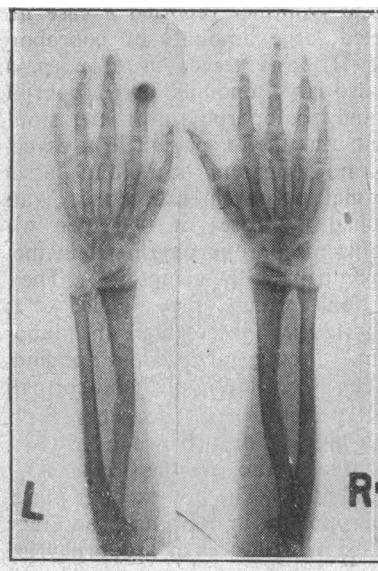


FIG. 2

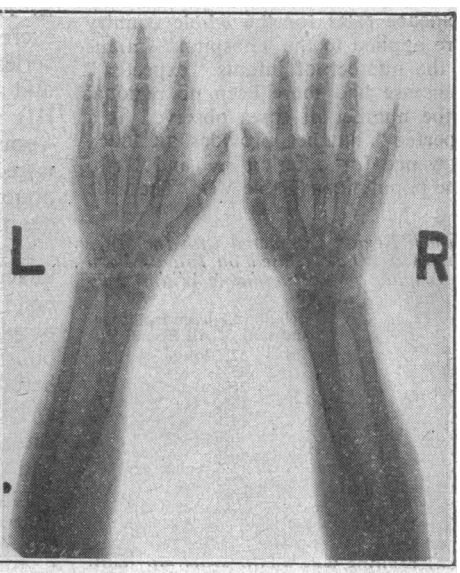


FIG. 3

FIG. 1.—The patient, showing presence of rickets. FIG. 2.—Forearms and hands of patient before treatment. FIG. 3.—Forearms and hands after one year of treatment.

Physical examination showed a normally intelligent boy with rickets (Fig. 1), undersized and underweight for his age. He was 108 cm. in height, 18.5 kg. in weight, while the standard height and weight for his age were 123 cm. and 24.4 kg. respectively. There was slight hypertelorism. The thorax was funnel-shaped, with a marked rachitic rosary. There was thickening of the epiphysial ends of the long bones, shortening and bowing of the femur, and antero-lateral bending of the tibiae. There was marked cheilosis and the tongue was red, shiny, and without papillae. His skin was generally dry, scaly, and hyperkeratotic, and there was also hyperkeratosis of the nails. Examination of his eyes showed a bilateral granular and flocculent cataract, denser centrally and finer more peripherally. He was hypermetropic. There was no further abnormality on physical examination; in particular, the liver and spleen were not enlarged. His blood pressure was 125/60. Chvostek's and Trousseau's signs were negative.

Tests

Peripheral Blood.—Hb 78%; R.B.C., 4,000,000 per c.mm., reticulocytes, 0.6%; platelets, 150,000 per c.mm. W.B.C., 5,000 per c.mm. (neutrophil polymorphs 57%, lymphocytes 29.5%, monocytes 8.5%, eosinophils 4%, basophils 1%). Bleeding, clotting, and prothrombin times were normal. E.S.R. (Westergren), 18 mm. in one hour. Bone-marrow examination, normal. Serum calcium, 9.7 mg./100 ml.; serum phosphorus, 2.86 mg./100 ml.; plasma phosphatase, 16 units (Bodansky). Total protein, 7.50 g.% (albumin 4.90 g., globulin 2.60 g.). Total cholesterol, 134 mg./100 ml. Plasma alkali reserve, 44 vols.%. Blood urea, 28.8 mg./100 ml. W.R. negative. Moro, Pirquet, and Mantoux reactions (1/10,000 to 1/100), negative.

Urine occasionally showed traces of protein. A water concentration and dilution test was normal (S.G. 1026 to 1000). Porphyrin investigations are reported below.

Liver Function Tests.—Takata-Ara and cadmium, normal; Weltmann, 0.35% $CaCl_2$ (normal, 0.4–0.5); serum bilirubin, 0.83 mg./100 ml. A fat balance was not done.

Progress

The patient was treated with large doses of vitamin D orally and B_2 (riboflavine) orally or intravenously. During the period September 22 to December 24 (94 days) he received a total of 1,458,000 I.U. of vitamin D and 4,675 mg. of riboflavine, with additional vitamins A, C, and B complex. The general condition of the child improved. His rickets improved greatly and his mouth and tongue were better. During this period of treatment several serum and urinary determinations were carried out on the patient and on a control of approximately the same age and weight. The serum and urinary riboflavine levels rose from 3.07 and 62.2 μg./100 ml. on September 24 to 97.0 and 4,062 μg./100 ml. respectively on October 30. The initial serum and urinary riboflavine levels were well below those of the control, which were 25–32 and 164–784 μg./100 ml. respectively. He was readmitted for further investigation in September, 1953. In the 15 months since his previous admission he had grown to 114 cm. in height. His measurements were: crown to pubis, 58 cm.; pubis to heel, 56 cm.; arm span 116 cm. He was still slightly bow-legged, but the *x*-ray film of his hands and forearms showed marked improvement of his rickets (Figs. 2 and 3). There was also considerable improvement of the cataract. Marked porphyrin fluorescence was noted in his upper incisor and molar teeth, but not in his lower incisors. There was no fluorescence elsewhere, except in the circumanal region, and this was due to faecal contamination. His blood plasma did not fluoresce in ultra-violet light. His urine and faeces still contained very large amounts of porphyrin (Table I).

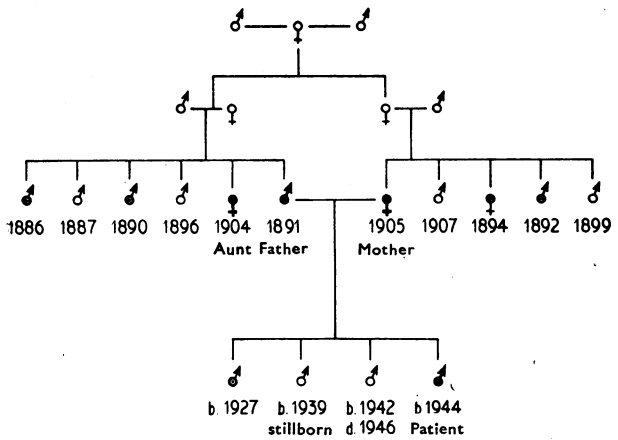
TABLE I.—*Quantitative Determinations. Urinary and Faecal Porphyrins*

	Urine			Faeces		
	Porphobilinogen	Uroporphyrin	Coproporphyrin (μg./l.)	Uroporphyrin	Coproporphyrin (μg./g. Dry Weight)	Protoporphyrin (μg./g. Dry Weight)
Normal (maximal)	Negative	Negative	100	Negative	15	30
Patient ..	,,	Negative*	5,719	,,	2,082	56·8
Mother ..	,,	Negative	500	,,	525	23
Father ..	,,	,,	775	,,	862	44
Aunt ..	,,	,,	295			

* Small amounts detected by chromatographic methods.

Family History

The patient's mother and father are aged 48 and 62 years respectively. Both are healthy and have never had any skin disease, deformity, or growth abnormality. The father is a farmer, and the general diet of the family is undoubtedly satisfactory. The patient has one living brother, aged 26 years, who is normally grown and healthy. Two other brothers are dead. One was stillborn at the sixth month of pregnancy, and the other died at 4 years from pneumonia. The latter was said to have had a brain injury during his birth and suffered from recurrent epilepsy (grand mal). The patient's paternal aunt, aged 59, is alive and well. There is no relevant disease in other relatives, so far as could be ascertained. The family tree is reproduced in Fig. 4.



Family tree. The mothers of the patient's father and mother were stepsisters.
○ Urine and stool not examined.
⊙ Urine only examined. Normal coproporphyrin excretion.
● Increased porphyrin output in stool and urine. (Stool of the aunt not examined.)

FIG. 4

Further Investigations

Porphyrins.—Tables I and II summarize the results of the urinary and faecal porphyrin investigations. There are marked increases in the coproporphyrin III excretion in the four cases. In the mother there is a fivefold and 35-fold increase of urinary and faecal coproporphyrin respectively; in the father an eightfold and 64-fold increase above maximal normal values. The urinary coproporphyrin of the aunt is increased threefold. The urinary and faecal coproporphyrins in the child are particularly high, and are more than 50 and 100 times the maximal normal values respectively. Uroporphyrin I was isolated from his urine in crystalline form as its methyl ester. A porphyrin, which behaved consistently as pentacarboxylic by paper chromatographic methods, was isolated. Although its α band in chloroform and its behaviour both as an ester and as the free porphyrin were distinctive, yet its crystalline appearance and melting-point were very similar to those of coproporphyrin III. Evidence was also obtained by alumina and paper chromatography of the presence of a pentacarboxylic porphyrin in the urine of the mother and aunt, and of a hexacarboxylic porphyrin in the stool of the patient and in the stool and urine of his father.

The urinary amino-acids of the patient and his mother and father, investigated by paper chromatography, showed in each case a "super-glycine pattern." This term is being currently used by Dent (private communication) and his collaborators to describe the pattern shown on a standard urine chromatogram (280 μg. total N) when the amino-acid excretion is comparatively normal except for a large excess of glycine. Those workers have encountered several individuals who appear to excrete amino-acids constantly in this manner. Its pathological significance is still under investigation. Urine from the aunt or other members of the family could not be obtained for this investigation.

The Sulkowitch test in the urines of the patient, mother, and father showed each to have a very high calcium concentration. In the case of the patient the urine was given this test before and after vitamin D treatment had begun.

Discussion

The condition in the four members of the family described above is similar, as regards the disturbances of porphyrin metabolism, to that described by Dobriner (1936) and Watson *et al.* (1949). The pigment excretion in Dobriner's case, in which traces of uroporphyrin were found in the urine along with greatly increased ether-soluble porphyrins, would seem to correspond closely to that of our patient. The demonstration, however, of this abnormal porphyrin excretion as a hereditary trait, less severe in the parents and the paternal aunt, and much more severe in the child, gives the present group of cases a significance which is important. The diseases of porphyrin metabolism have long been described as "inborn errors of metabolism" (Garrod). Congenital porphyria is accepted as being transferred as a Mendelian recessive, while there is strong evidence that acute porphyria occurs as a Mendelian dominant. The inheritance of porphyria cutanea tarda is still in doubt. The condition described above neither clinically nor biochemically corresponds exactly to any of these three diseases. The evidence presented suggests that the genetic pattern of the dyscrasia is heterozygous in the parents and paternal aunt, and is homozygous in the child.

The association of rickets and riboflavine deficiency with excessive porphyrin excretion in our patient is of interest. Rickets has never hitherto been reported in association

TABLE II.—*Chemical Identification of Porphyrins in Urine and Faeces*

		Free Porphyrin		Porphyrin Ester (Paper Chromatography)	M.P. of Crystals (°C.)	Summary
		No. of COOH Groups	α Band in $CHCl_3$ (mμ)			
Patient	Urine	4	621·5	Copro III	140–143, 166–167	Coproporphyrin III
		5	623·0	Between copro I and III	154, 172–178	Pentacarboxylic porphyrin
		8	625·3	Mainly uroporphyrin series I	291	Uroporphyrin I
	Faeces	4	621·3	Copro III	142, 162–166	Coproporphyrin III
		6	623·0			Hexacarboxylic porphyrin
Mother	Urine	4	621·5	Copro III	138–142, 164–168	Coproporphyrin III
		5	622·9			Pentacarboxylic porphyrin
	Faeces	4	621·5	,, ,,	141–143, 164–168	Coproporphyrin III
Father	Urine	4	621·6	,, ,,	143	Coproporphyrin III
		6	622·9			
		4	621·5	,, ,,	140, 164–166	Coproporphyrin III
	Faeces	6	623·3			Hexacarboxylic porphyrin
Aunt	Urine	4				Mainly coproporphyrin (trace pentacarboxylic porphyrin)
		Trace				
		5				

with a porphyrin disorder. The aetiology of the rickets is a matter of question. The bony deformities were noted only at the age of 3½ years. Since the age of 1½ years the mother considered that milk aggravated his skin condition. It is therefore possible that the withholding of milk over a long period contributed to the rickets in a patient whose disease predisposed him to it. On the other hand, renal acidosis or some defect in the renal tubular reabsorptive mechanism, or even steatorrhoea, has not been fully excluded. The fact that the improvement in the bone condition was not accompanied by any marked change in the porphyrin excretion suggests that the association of the rickets and excessive porphyrin excretion is not a close one.

Some relationship may exist between the porphyrin disorder and a predisposition to riboflavine deficiency, since an accidental association of these two excessively rare disorders is most unlikely. It is of interest that Stich (1952) has suggested that riboflavine acts as a regulator of biological porphyrin synthesis, directing it to the formation of the series III porphyrin isomers rather than series I, which, he claims, accumulate excessively when this vitamin is deficient. He based this hypothesis on experimental studies with yeast cultures and supported it with apparently successful therapeutic trials of riboflavine in cases of porphyria. This form of therapy had also previously been advocated by Vannotti (1937), and has also been used by Weingarten (1950) and Lups and Van Dijk (1950). The evidence obtained so far in the present case does not lend support to Stich's hypothesis, since most of the excessive porphyrin excreted is of the III series and only a small amount is excreted as uroporphyrin I. Since the completion of the present studies Antener and Berger (1955) have found that after the administration of 60 mg. of riboflavine daily to our patient, and after periods without riboflavine, the urinary excretions of porphyrin and riboflavine showed an inverse relationship. Thus high levels of urinary porphyrin excretion were associated with low levels of riboflavine excretion, and vice versa. The interpretation of these findings and their possible relation to Stich's hypothesis will be discussed by these authors.

The absence of symptoms, such as abdominal colic or constipation, in every case supports the findings of Goldberg, Paton, and Thompson (1954), that the known porphyrins have no pharmacological action. Our patient has shown no sign of photosensitivity, despite a high daily excretion of coproporphyrin. It has been suggested (Fischer and Zerweck, 1924) that the phototoxic action of the porphyrins is directly proportional to the number of carboxyl groups in the porphyrin molecule; thus coproporphyrin, the main excretion product in this case, would be less active in this respect than uroporphyrin, which is excreted in congenital porphyria and generally in porphyria cutanea tarda. The absence of plasma fluorescence would also suggest a very rapid clearance of coproporphyrin from the circulation, which would prevent an effective concentration of photosensitizing porphyrin in the skin. Watson *et al.* (1949) failed to find raised blood porphyrin levels in their cases. Both these factors—the presence of coproporphyrin rather than uroporphyrin and the efficient elimination of the porphyrin mainly by the faeces—might explain the lack of photosensitization.

The mechanism of the excessive porphyrin production is of interest. In the present case the absence of anaemia, despite the loss of approximately 50 mg. of coproporphyrin daily for several years, would suggest an overproduction of these pigments (Goldberg and Rimington, 1955). The porphyrin is greatly overproduced in the homozygote (the boy), only moderately so in the heterozygotes. This quantitative regulation of the pigments is thus apparently controlled genetically. The main route of excretion of the excess coproporphyrin is via the faeces, which renders unlikely any "renal leak" mechanism. The site of production of these excess pigments is probably the liver or the bone marrow, since one or other of these tissues contains large quantities of porphyrins in the main porphyria diseases. Further work is required to clarify this point. Hoffbauer, Watson, and Schwartz (1953) found that coproporphyrin III, given orally to the rat, was not absorbed from the gut. If this finding is applicable to the human it would make unlikely any theory of gut synthesis of coproporphyrin in this condition. No trial with chlortetracycline has been made so far.

Summary

Four cases of coproporphyria have been described in a single family—a boy aged 10, his mother and father (first cousins), and his paternal aunt. The symptoms of porphyria, such as photosensitivity, abdominal colic, constipation, and paralysis, were absent. The adults excreted moderately high quantities of coproporphyrin III in the urine and stool, whereas the boy excreted very large quantities of coproporphyrin III in the urine and stool, with a trace of uroporphyrin I in the urine. Intermediate porphyrins were also identified—a pentacarboxylic porphyrin in some urines and a hexacarboxylic porphyrin in some stools. In all cases examined the main route of porphyrin excretion was via the stool. The genetic significance of this hereditary porphyrin disorder has been discussed.

The boy also suffered from rickets and riboflavine deficiency, both of which were improved by treatment.

Both the boy and his parents had an amino-aciduria of somewhat unusual character, which is discussed.

The significance of the symptomless nature of this condition and the mechanism of its production are considered.

We wish to thank Professor C. Rimington, F.R.S., and Professor Ed. Glanzmann for their help and encouragement in this work. Dr. C. E. Dent gave advice on amino-acid chromatography and valuable criticism. Dr. H. Harris advised on the genetical aspect of the investigation. We are grateful to Dr. I. Antener, Leiterin des Kontroll-Laboratoriums der Fa. Nestle, Vevey, Switzerland, for the riboflavine assays and to Frl. R. Wermuth and Miss A. Benson for technical assistance. A visit by one of us (A. G.) to Berne was assisted by a grant from the Rockefeller Research Fund of University College Hospital Medical School.

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The first issue of a new journal, *Acta Rheumatologica Scandinavica*, has just been published in Stockholm under the direction of an editorial team led by Dr. G. Edström, of Lund. It is the official organ of the Scandinavian Society for Rheumatology, will appear four times a year, and will publish papers in English, French, or German, with summaries in all three languages. Subscription rate is 72s. per annum, and the publisher's address is Drottninggatan 6, Stockholm C.