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THE EXCRETION OF PORPHYRINS IN CONGENITAL PORPHYRIA

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In 1915 Hans Fischer identified the kinds and types of porphyrins excreted in congenital porphyria (1, 2, 3), and since that time 8 cases of this rare disease have been studied by qualitative, chemical methods (4 to 11). No quantitative studies of the total excretion of porphyrins in this condition have been made, however, and although reports of the therapeutic effect of liver extract on acute porphyria are recorded in the literature (12, 13, 14), complete detailed observations have not been published. In this communication qualitative studies of the types and kinds of porphyrins excreted in 3 cases of congenital porphyria are recorded, together with quantitative studies of the coproporphyrin excretion and the effect of liver extract therapy on that excretion in 2 of the cases.

The methods used for the qualitative and quantitative determinations of the urinary and fecal porphyrins, except uroporphyrin, are those previously reported (15, 16). Uroporphyrin was isolated by the method of Fischer and Duesberg (11), but because of the lack of a suitable method it was not measured quantitatively. In all instances a thorough search for isomeric and hitherto undescribed porphyrins was made.

The clinical material studied was as follows: Case I (Rochester) (20). A clinical report has been published (29). Case II (Baltimore), Hospital record number 98673, Harriet Lane Home, Johns Hopkins Hospital. Case III (San Francisco). A preliminary report concerning the photosensitivity in this child has already been published by Blum and Hardgrave (17).

RESULTS

Qualitative

In all 3 cases both coproporphyrin and uroporphyrin were present in large amounts in the urine. Much coproporphyrin was present in the

feces, as well as relatively small amounts of protoporphyrin and deuteroporphyrin. In Table I the results of the melting point determinations

TABLE I
Melting points in ° C. of the porphyrin methyl esters

Case number	Urine		Feces. Copro I	Free coproporphyrin of natural ester
	Copro I	Uro I		
I (Rochester).....	250	286	249	251
II (Baltimore).....	251	285	250	
III (San Francisco)...	249	279		

are given. In Case I relatively large amounts of a natural coproporphyrin ester (15b) were present both in the urine and in the feces, but it was not found constantly. This natural ester had an HCl number of 0.3 to 0.5 per cent HCl, and was easily extracted from this HCl concentration with chloroform. It could be saponified with 20 per cent NaOH. After saponification the porphyrin was no longer soluble in chloroform and showed all the properties of coproporphyrin. Spectroscopically it was identical with coproporphyrin. Although the esterifying group could not be established definitely, certain qualities suggested that it was of a lipoidal nature. The Liebermann-Burchard reaction was negative. After saponification the porphyrin was esterified and the methyl ester was identified by melting point determinations as coproporphyrin I (M. P. 251° C.).

Quantitative

In Cases I and II quantitative determinations of coproporphyrin excretion in the urine and feces could be made during control periods and during periods of intensive intramuscular liver extract therapy.

Case I (Rochester) Figure 1. A 3-year-old, female child was admitted to the Strong Memorial

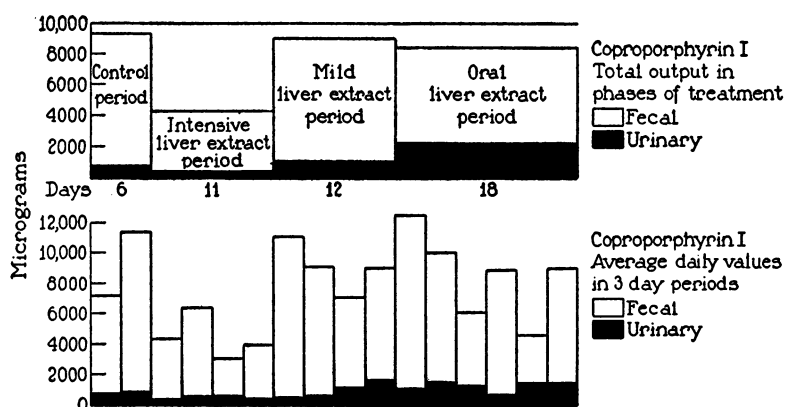


FIG. 1. CASE I

Hospital, Rochester, New York, in August, 1936, and was maintained on a meat free diet during the study. Quantitative studies of coproporphyrin were made both of the urine and feces on 3-day collections. A control period of 6 days was followed by a period of 11 days, during which 5 cc. of concentrated liver extract (Eli Lilly and Co.) was injected intramuscularly each day. In a subsequent period of 12 days, 5 cc. of liver extract was administered twice weekly, and in a final period of 18 days 10 to 30 grams of liver extract (Lilly) was administered daily by mouth.

The total excretion of coproporphyrin during the control period was about 50 times the normal average for a child. The average daily total output was 9380 micrograms, of which 870 micrograms were excreted in the urine. Following daily injections of liver extract the total coproporphyrin output decreased to an average of 4450 micrograms a day, of which 550 micrograms were in the urine. In the third period the excretion of coproporphyrin increased rapidly, approaching the levels present before treatment. The total coproporphyrin output during this period averaged 9250 micrograms, of which 1060 micrograms were excreted in the urine. In a fourth period, of 18 days' duration, the patient received from 10 to 30 grams daily of liver extract by mouth, and 2 injections of intramuscular liver extract weekly. The coproporphyrin output in this period averaged 8890 micrograms of which 1240 micrograms were excreted in the urine. During the period of intensive liver extract therapy the uroporphyrin excretion decreased, and the natural porphyrin ester excreted during the control

period could no longer be detected. Clinical improvement was manifested by the disappearance of the vesicular eruption.

Case II (Baltimore) Figure 2. The patient was a 4-year-old girl observed from 1936 to 1938 in the Harriet Lane Home and maintained on a constant diet. The urine and feces were collected in 3-day periods and studied at the Hospital of the Rockefeller Institute. In the control period of 15 days the child excreted an average of 5600 micrograms of coproporphyrin daily, of which 1535 micrograms were excreted in the urine. In the treatment period of 12 days the patient received 5 cc. of liver extract (Lederle) intramuscularly each day. The total coproporphyrin excretion decreased to 1650 micrograms daily, of which 520 micrograms were in the urine. In a second control period of 12 days the total average coproporphyrin output rose to 6030 micrograms daily, of which 1670 micrograms were in the urine.

DISCUSSION

The 3 cases reported showed a mass excretion of coproporphyrin I and uroporphyrin I similar to the 6 cases of congenital porphyria previously described in the literature (1 to 8). Two cases of congenital porphyria with a mass excretion of coproporphyrin III also have been described elsewhere (9, 10, 11). Fischer and Hofmann (18) recently reported that in a restudy of the uroporphyrin fraction of the famous case, Petry, small amounts of uroporphyrin III were isolated from the large uroporphyrin I fraction. Uroporphyrin I was excreted by the cases here re-

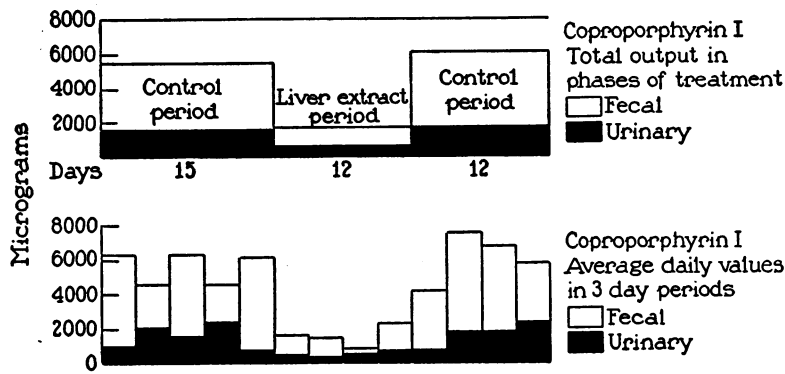


FIG. 2. CASE II

ported, but small amounts of uroporphyrin III may also be present. Work on this phase of the problem is still in progress. The coproporphyrin methyl ester fraction was separated by a method previously described (15, 19) and in no instance was coproporphyrin III obtained from the large amounts of coproporphyrin I present.

A working hypothesis which has been outlined previously (16, 20, 21, 22, 23, 24) is derived from the *in vitro* synthesis of the porphyrins and is supported by clinical and experimental evidence. The hypothesis postulates the simultaneous construction of Types III and I porphyrins in nature. Under normal conditions there appears to be a relatively constant ratio between the amounts of the 2 types formed.

In congenital porphyria (20) with mass production and excretion of Type I porphyrins the normal ratio between the construction of Type III and Type I compounds is disturbed and a disproportional or disorderly type of synthesis in favor of Type I occurs. In recent publications Rimington independently has come to similar conclusions (25, 26). From these studies, together with those previously reported, it appears that the disturbance of porphyrin metabolism which characterizes congenital porphyria is quite unlike that seen in pernicious anemia (23), in pellagra (27), or in refractory anemia (28).

SUMMARY

1. In 3 cases of congenital porphyria in children qualitative porphyrin studies revealed a mass excretion of coproporphyrin Type I and uroporphyrin Type I. In 1 case of the 3 a natural coproporphyrin I ester was excreted.

2. Quantitative studies in 2 of the 3 cases suggest that the porphyrin excretion in this disease is influenced by daily injections of liver extract.

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