Toxic Porphyria

By ARIF I. CETINGIL AND MUHLIS A. ÖZEN

THE EXCESSIVE porphyrin excretion seen in idiopathic disturbances of porphyrin metabolism must be differentiated from the porphyrinuria that occurs in various diseases associated with alterations in porphyrin metabolism. Porphyrinuria can be observed in the course of various diseases and may result from the intake of various drugs and poisons.

It is well known that certain drugs and poisons can produce porphyrinuria. Coproporphyrinuria was observed by Garrod in 1849 and by Stokvis in 1895 following lead intoxication. The porphyrinogenic action of sulfonal and related compounds was described by Salkowsky in 1891. Brownlee noted the porphyrinogenic action of certain aromatic groups in rats. Porphyrinuria was observed in man treated with sulfanilamide and in rats fed with sulfanilamides, other sulfa drugs and anilin. Coproporphyrinuria occurs following methylchloride intoxication. Occasionally it has been observed after administration of arsphenamine, barbiturates, chloral, cinchophen and thiosinamine. The porphyrinogenic action of these drugs in man and animals usually consists in an increase of urinary and fecal coproporphyrin excretion.

In the toxemia produced by trional and sulfonal, Ellinger and Riesser (1916) found in the urine uro-type porphyrins which are insoluble in ether. Later Fischer and Duesberg detected traces of similar ether insoluble porphyrins in the urine of rabbits fed sulfonal. Waldenström and Wendt repeated these experiments with negative results.

During the last few years, a new classification of human porphyria has been proposed based on the work done in the laboratories of Watson, which is as follows:

1. Erythropoietic porphyria
2. Hepatic porphyria
   a. Intermittent acute
   b. cutanea tarda
   c. Mixed

This was in part supported by studies of experimental porphyria made in the same laboratories. Schmid et al. found an increase of coproporphyrin type III in the bone marrow and erythrocytes of lead intoxicated rabbits together with uro-type porphyrins. They were able to crystallize uroporphyrin type I from the bone marrow. "Experimental porphyria" was first produced by Schwartz et al. by intoxicating animals with phenylhydrazine and

From the 2nd Internal Clinic, Medical School of the Istanbul University, Turkey (Director: Prof. A. I. Cetingil).

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lead and exposing them to light. This "experimental porphyria" produced in rabbits resembled human erythropoietic porphyria, but from a chemical standpoint it exhibited features of all three types of porphyria (erythropoietic, hepatic cutanea tarda and intermittent acute). This disturbance was transitory in character. Schmid and Schwartz\textsuperscript{14} also produced an experimental porphyria in rabbits resembling human hepatic porphyria using Sedormid as the toxic agent. This disturbance is associated with a defect in catalase metabolism in the liver.\textsuperscript{15,16}

Talman et al.\textsuperscript{17} observed in embryonic tissues of chicks injected with Sedormid a brilliant red fluorescence under ultraviolet light. The liver of animals treated with Sedormid exhibited a greenish discoloration. These green porphyrins were found to differ from other porphyrins as well as "heme" of hemoglobin.\textsuperscript{18} Talman et al.\textsuperscript{17} also showed that Sedormid resulted in a decrease in catalase activity in chick livers. Despite the advances made in the study of experimental and idiopathic human porphyria, the situation of human toxic porphyria is still being discussed.

An opportunity to study human toxic porphyria presented itself to us when numerous cases of porphyria were discovered in south-eastern Turkey. Six of these cases were sent to our clinic. Similar cases had already been observed in 1956 by Cihat Cam, a dermatologist who was working in and around Diyarbakir. He has called attention to the outbreak of toxic porphyria.\textsuperscript{19} More than 400 cases have been reported in town and villages around Diyarbakir, Urfa, Mardin, Elazig, Sirt, Mus and Bingöl. The disease was found most commonly in children below the age of 15, boys being most frequently affected (169 boys and 48 girls). In adults it occurred less frequently (31 males and 6 females). Children under 4 were rarely involved. Cihat Cam noted that the disease occurred among people who had eaten the fungicide-treated seed wheat which was distributed by the Government. The disease was never observed in individuals who had eaten other cereals, including native wheat, other than the treated seed. Cam concluded that the disease most likely was produced by hexachlorobenzene, which was used as a fungicide to treat the wheat. Unfortunately he did not have the opportunity to study the disturbance in porphyrin metabolism in more detail.

The following 6 cases have been studied in our clinic.

**Case Reports**

Of the 6 cases who came from the town of Bismil in the District of Diyarbakir, 4 were children. All were males. If the disease was to be attributed to the poisoned wheat, toxic signs appeared at the earliest one month (case 6) and at the latest 3 years (case 2) after continuous consumption of the cereal (table 1).

In all cases the most remarkable clinical feature was the presence of signs and symptoms of "porphyria cutanea tarda." The "inborn error of metabolism," as Garrod had termed idiopathic porphyria, was seen here as an acquired defect, probably produced by a toxin.

In the affected children (cases 1–4) the first sign was the formation of bullae on face and extremities, i.e., on the parts exposed to sunlight. Occasionally some bullae were found on the chest. They varied in size from a pinhead to a pigeon's egg. Bullae also appeared after mechanical irritation of parts of skin not exposed to sunlight.

On admission to the clinic all four children had extensive pyodermic lesions on the
Table 1

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Initials</th>
<th>Age</th>
<th>Previous diseases</th>
<th>Intake of poisoned wheat for</th>
<th>First symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H. K.</td>
<td>6</td>
<td>Typhoid Fever</td>
<td>1 Year</td>
<td>Bullae on face and scalp, pyodermatitis</td>
</tr>
<tr>
<td>2</td>
<td>A. A.</td>
<td>11</td>
<td>—</td>
<td>3 Years</td>
<td>Bullae on face, pyodermatitis</td>
</tr>
<tr>
<td>3</td>
<td>N. G.</td>
<td>11</td>
<td>—</td>
<td>1 Year</td>
<td>Bullae on nose and right pollex, pyodermatitis</td>
</tr>
<tr>
<td>4</td>
<td>A. K.</td>
<td>8</td>
<td>—</td>
<td>1 Year</td>
<td>Bullae on fingers, pyodermatitis</td>
</tr>
<tr>
<td>5</td>
<td>C. K.</td>
<td>28</td>
<td>Rheumatic Fever, Gonorrhea</td>
<td>4 Years with Intervals</td>
<td>Orbital hypertrichosis and hyperpigmentation</td>
</tr>
<tr>
<td>6</td>
<td>M. D.</td>
<td>19</td>
<td>—</td>
<td>1 Month</td>
<td>Orbital hypertrichosis and hyperpigmentation</td>
</tr>
</tbody>
</table>

face, scalp, arms, neck, hands, legs and feet which were due to secondary infections of bullae (fig. 1). The new bullae which formed while in the hospital were treated aseptically and healed in 7 to 10 days without scarring. Infected lesions left white scars surrounded by a hyperpigmented area. In cases 2 and 4 the scalp lesion resulted in permanent alopecia. All of the children had atrophic nails which fell off easily. The skin of the hands (case 2 and 4) lost its pliability, becoming thin and adherent to the underlying tissue so that one had the impression of a scleroderma. One patient (case 2) was unable to flex his fingers into a fist.

All cases presented hyperpigmentation and hypertrichosis. In the two adults (cases 5 and 6), there were the first signs of the disturbance. Although case 6 exhibited a few bullae during his first days in hospital which disappeared without leaving a scar, case 5 had no bullae at all. The pigmentation was most prominent in the face around the eyes and over the cheeks. Hypertrichosis was present, particularly over the forehead and around the eyes. In severe cases it was found also over the cheeks, forearms, tibias, anterior chest, abdomen, arms and back. Hypertrichosis was more pronounced in children than in adults. In case 2, the arms and legs were covered with hair like that in an adult (fig. 2). This patient and case 1 had hair on the forehead. The skin over the entire body of both patients was dark in color.

Except for case 5 all of the patients showed malnutrition. The children had an almost cachectic appearance (fig. 3). This was especially noted in case 2, whose eyes were sunken and who had a monkey-like appearance due to the excessive hypertrichosis and hyperpigmentation.

Except for the enlarged liver in cases 1 and 2, the remainder of the physical examination was within normal limits.

**Laboratory Findings**

With the exception of case 5, all patients had a normochromic anemia. The leukocyte and differential counts were normal, and serologic tests for syphilis were negative. In all but case 5 the sedimentation rate was accelerated; this was probably due to the pyodermia, since treatment of the infectious process resulted in a normal sedimentation rate. The slight fever present in these patients disappeared as the infection subsided.

In all cases the urine was dark in color and became almost black when exposed to air. In case 3, urobilin was present and in cases 1 and 2, urobilinogen was present in the urine, but the porphobilinogen reaction was negative. In some of the cases the thymol turbidity, cadmium, zinc sulfate and Kunkel-phenol tests were positive. The hippuric acid test done in the two adults gave normal results. Takata-Ara and formol gel tests were negative in all patients.
Fig. 1.—Photosensitive skin lesions on face, hands and feet; hypertrichosis of legs.

It is noteworthy that in all patients total serum proteins were normal although the A G ratio was reversed. This was confirmed on paper electrophoresis. Glucose tolerance tests were normal, and there were no significant abnormalities in the lipogram.

Liver aspiration biopsy revealed advanced hydropic and granular degeneration of the parenchyma, increased number of mononuclear cells in capillaries and the presence of a yellow pigment within parenchymal cells.

Serum electrolytes, including sodium, chloride, potassium and phosphorus, were normal. Eosinophils and 17-ketosteroids showed adequate adrenal response to injection of ACTH. There was no evidence of hemorrhagic tendency. Serum bilirubin and reticulocyte counts were normal. The bone marrow revealed a slight normoblastic hyperplasia. X-ray examinations of the chest, heart, skull and long bones were normal. The electrocardiogram was normal. There was no decrease in the libido of the two adults.

Tests for porphobilinogen by the simple method of Watson and Schwartz was repeatedly negative in the urine of all patients. The "5 ml." method of Schwartz et al. was employed for estimation of the urinary coproporphyrin. Urinary uroporphyrin was determined by the following method: The combined aqueous extracts obtained during the
Fig. 2.—Case 2: hypertrichosis over back and buttocks.

determination of coproporphyrin were filtered through a column of aluminum oxide. After washing, the uroporphyrin was eluted with 1.5 N HCl and quantitated fluorometrically.13 Tissue porphyrins were estimated by the method of Schwartz and Wikoff.22 Uroporphyrin in tissues was determined by aluminum oxide chromatography as described above. As extraction of uroporphyrin I with ethylacetate/acetic acid is incomplete, a 19:1 mixture of methanol and sulfuric acid was used to extract the tissue residue following the previous extractions.23 In case 1, the copro- and uroporphyrin fractions obtained from feces and urine were esterified with 19:1 methyl alcohol/sulfuric acid and purified by means of calcium carbonate column chromatography. Porphyrins were extracted from the column with chloroform. After evaporation of the chloroform, the esters were crystallized from methyl alcohol. The results are given in table 2.

Urinary uroporphyrin crystals obtained by this method had a melting point of 289 C., and the fecal uroporphyrin of 282 C. which corresponds to the melting points of uroporphyrin I. The melting point of urinary coproporphyrin crystals was 153 C., and that of the fecal group 144 C., which corresponds to the melting points of coproporphyrin III.

In cases 1 and 6 fresh unstained smears of bone marrow exhibited no fluorescence when examined by fluorescence microscopy. The determination of porphyrins in bone marrow was performed by the method of Schmid et al.19: 1 ml. of marrow was placed in a heparin-containing centrifuge tube. After centrifugation, the cellular material was extracted as described above. The porphyrin content of bone marrow was found to be normal. The tissue obtained by needle biopsy of the liver was insufficient for porphyrin determination.

**DISCUSSION**

All cases of this series came from an area in which many inhabitants have the disease. Heredity could be ruled out as an etiologic factor because the
Fig. 3.—Cachexia, hypertrichosis over face and extremities. The white areas over the hands and feet are due to liniments for the pyoderma.

Disease occurred in hundreds of people at one time, and one of our cases was of Yugoslav extraction (case 3). Since not all of the members of a family that ingested the toxic wheat were affected, it is possible that individual susceptibility played a certain role. Children appeared to be more severely affected than adults, particularly with regard to photosensitivity and hypertrichosis.

None of the patients had evidence of abdominal, neurologic or psychic manifestations. Splenomegaly was not present. The red cells showed no signif-

Table 2.—Amount of Porphyrin in the Urine, Feces, Bone Marrow, Erythrocytes and Plasma of Patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Plasma A</th>
<th>Plasma B</th>
<th>Plasma C</th>
<th>Erythrocytes A</th>
<th>Erythrocytes B</th>
<th>Erythrocytes C</th>
<th>Bone marrow A</th>
<th>Bone marrow B</th>
<th>Bone marrow C</th>
<th>Feces A</th>
<th>Feces B</th>
<th>Feces C</th>
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<td>...</td>
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<td>...</td>
<td>1550</td>
<td>...</td>
<td>8673</td>
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<td>1.4</td>
<td>2208</td>
<td>1484</td>
<td>3764</td>
<td>721</td>
<td>0</td>
</tr>
</tbody>
</table>

*A, protoporphyrin, µg./100 ml.; B, uroporphyrin, µg./100 ml.; C, coproporphyrin, µg./100 ml.; D, porphobilinogen; tr., trace.
significant increase in porphyrin concentration, and no fluorescence was observed in fresh bone marrow preparations examined by fluorescence microscopy. Unfortunately, there was no opportunity to determine the porphyrin content of the liver. Needle biopsy showed abnormal hepatic histology, and liver disease was also suggested by the liver function tests. Hemolytic anemia was not present. All the features of these cases were compatible with the diagnosis of porphyria cutanea tarda.

Experimental Sedormid porphyria, as produced by Schmid and Schwartz, was characterized by gastrointestinal and neurologic signs and by excretion of uroporphyrin III. None of these patients exhibited any of these signs, nor did they resemble experimental porphyria as produced by Schwartz et al. with phenylhydrazine and lead followed by exposure to light. Our cases had neither increased porphyrin content of the bone marrow nor excessive urinary porphobilinogen excretion.

Coproporphyrinuria has been observed in heavy industry workers as evidence of industrial poisoning. Bernard et al. found porphyrinuria with excretion of coproporphyrin III in a group of marines exposed to lead. However, occurrence of massive porphyria has rarely been observed.

What was the toxic agent in these cases? Should buckwheat (Fagopyrum esculentum) be incriminated? We do not believe so as buckwheat intoxication is well known through its use in northern Europe, especially in Germany. This cereal is not grown in Turkey. The Ministry of Agriculture furnished information concerning the fungicides used in treating the wheat seed. Of the four chemicals used, two contained mercury, one was hexachlorobenzene and the fourth was a copper compound. The latter had not been used in the diseased area. These compounds had been added in a proportion of 0.2 percent to the wheat.

The possibility that the intoxicant was mercury is not convincing as mercury is not usually followed by porphyrinuria. Mercury was formerly used in great quantities as an antisyphilitic agent and is still used as a diuretic, but no complications suggestive of porphyria have ever been reported. It has been postulated that perhaps a porphyrinogenic effect could be produced by mercury bound to an organic radical. Hexachlorobenzol alone or in conjunction with mercury could be the etiologic factor. All of these possibilities will require investigation before a definite conclusion can be reached.

The mechanism of bullae formation is not clear in idiopathic porphyria, nor is it in our cases. Hypertrichosis and hyperpigmentation are probably not the result of cortical dysfunction as no abnormality of adrenal function was detected. In cases of idiopathic porphyria reported in the literature, cortical dysfunction has not been a feature.

What is the prognosis in these cases? We have no indication that this alteration of porphyrin metabolism will be completely reversible. In cases 1 to 4, in which the bullae disappeared after a few days of hospitalization.

*Phenylmercuric urea 1.09 per cent Hg; phenylmercuric acetate 1.5 per cent Hg; hexachlorobenzene 10 per cent.
urinary porphyrin excretion was still greatly increased at the time of the patients’ departure from the clinic. Photosensitivity had perhaps decreased because the patients were exposed to less sunlight than was the case on their farms. Case 5 had no bullae even on admission to the hospital, but when he left the hospital his urinary porphyrin still was very high. Case 6 remained at the clinic for six months; at the end of this period he was asymptomatic but still was excreting large amounts of porphyrins. It is probable that in these cases severe chronic liver disease is present.

TREATMENT

Pyodermia was treated locally and responded well to treatment. All patients were given a high calorie, high protein diet. In addition, liver extract plus vitamins, including B\textsubscript{12}, were given parenterally. During their stay in the hospital all patients gained weight, and the cutaneous manifestation, disappeared. Partial clearing of hyperpigmentation was observed, but this may have been due to better hygienic care. The lesions on the hands and fingers remained unaltered. The massive urinary excretion of porphyrins was not influenced by treatment.

CONCLUSION AND SUMMARY

1. Numerous cases of porphyria of the “cutanea tarda” type were observed recently in the southeastern districts of Turkey. The toxic agents appear to have been fungicides, including two mercury compounds together with hexachlorobenzol which were added to seed wheat. The disease did not appear in peasants who did not consume this seed wheat. There were no indications of buckwheat toxicity; furthermore, this seed is not cultivated in Turkey.

   Six of the affected patients were treated in our clinic.

2. Clinically the patients presented cachexia, bullae, hyperpigmentation and hypertrichosis, i.e., skin lesions of the cutanea tarda type of porphyria. There were no cases of splenomegaly, and no abdominal or neurologic signs.

3. The patients were found to have an organic and functional liver disease. No suprarenal cortical dysfunction was recorded. X-rays of the bones were normal. No signs of hemolysis were present. Bone marrow studies revealed slight normoblastic hyperplasia.

4. Urinary porphobilinogen was repeatedly found to be negative. Urinary and fecal uroporphyrin 1 and coproporphyrin II1 were present in excess. The fecal excretion of coproporphyrin III was greater than that of uroporphyrin 1, whereas in the urine the relation was reversed. The bone marrow content of porphyrin was not increased. No fluorescence was recorded in the fresh unstained blood smears by fluorescence microscopy.

5. Our cases had the clinical and laboratory findings consistent with the cutanea tarda type of porphyria.

6. The advanced and severe alteration of our patients’ porphyrin metabolism may not be reversible. Although the bullae disappeared during their hospital residence, the excessive porphyrin excretion was still present on their departure from the clinic.
7. For therapy, the patients were given a high caloric diet of protein rich food and treated with liver extracts, vitamin B₁, B₂, B₁₂ and whole B-complex preparations. We can express no opinion as to the value of this treatment.

**Summario in Interlingua**

1. Grande numeros de casos de porphyria del typo “cutanee tardive” esseva observate recentemente in le districtos del sud-est de Turchia. Le agentes del toxicitate esseva apparentemente fungicides, incluse duo compositos de mercurio e hexachlorobenzol que esseva addite a frumento semine. Le morbo non appareva in fermeros qui non habeva consumite iste frumento semine. Toxicitate per grano saracen es excludite proque Turchia non lo produce.—Sex del patientes esseva tractate a nostre clinica.

2. Clinicamente le patientes exhibiva cachexia, bullas, hyperpigmentation, e hypertrichosis, i.e. lesiones del pelle del typo cutanee tardive de porphyria. Splenomegalia non esseva presente in ulle de nostre casos. Nulle signos abdominal o neurologic esseva trovate.


4. Examines pro porphobilinogeno urinari esseva repetitemente negative. Uroporphyrina I e coproporphyrina III esseva presente in excesso in le urina e le feces. Le excretion fecal de coproporphyrina III esseva plus alte que illo de uroporphyrina I. In le urina, le relation esseva revertite. Le contento de porphyrina in le medulla non esseva augmentate. Microscopia fluorescential non revelava ulle fluorescentia in fresc e non-tincturate frottis de sanguine.


6. Le avantiate e sever alteration del metabolismo de porphyrina in nostre patientes es possibilemente in ultra de lo que es revertible. Ben que le bullas dispareva durante le hospitalisation, le excesso del excretion de porphyrina persisteva quando le patientes quitava le hospital.

7. Como therapia, le patientes recipeva un dieta a alte contento caloric e ric in proteina. In plus, illes esseva tractate con extracto de hepate, vitamina B₁, B₂, B₁₂, e preparatos del complete complexo B. Quanto al efficacia de iste tractamento, nos non pote exprimer un opinion.

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Toxic Porphyria

ARIF I. CETINGIL and MUHLIS A. ÖZEN