Porphyria Cutanea Tarda Associated with Chronic Granulocytic Leukemia Treated with Busulfan (Myleran)

By ROBERT A. KYLE* and WILLIAM DAMESHEK

MANY CASES of porphyria cutanea tarda have been reported since the term was introduced by Waldenström in 19371 to describe a type of porphyria occurring usually in adult patients and characterized by the presence of vesicles and bullae over areas exposed to the sun. Porphyria cutanea tarda may be on a genetic basis as seen frequently in the white population of South Africa,2–4 or it may be acquired. The latter group includes those patients with liver disease and alcoholism as described by Brunsting,5–7 the porphyria found among the Bantus of South Africa,6–12 and the recently described cutaneous porphyria in Turkey associated with the ingestion of hexachlorobenzene.13–15 In the case to be described, porphyria cutanea tarda occurred in association with chronic granulocytic leukemia and busulfan therapy. This association has not been previously reported.

CASE REPORT (H. M. NECH #131–509)

This 55-year-old white male oil company distributor was well until January, 1959, when he developed an acute febrile illness with malaise and generalized aching. This was followed by continued fatigue, left upper quadrant fullness, night sweats, anorexia, loss of weight and petechiae. An unexplained leukocytosis was found and because of this he was hospitalized at the New England Center Hospital for further study. Examination revealed a light-complexioned man whose liver and spleen extended 9 cm. and 11 cm. below their respective costal margins. There were no other abnormal physical findings. The blood findings revealed: hemoglobin 8.3 Gm. per 100 ml., white cell count 435,500 with a differential count and bone marrow aspiration compatible with chronic granulocytic leukemia. Laboratory studies included normal values for blood urea nitrogen, serum cholesterol, serum albumin, serum globulin, bilirubin concentrations, serum alkaline phosphatase activity, thymol turbidity, cephalin flocculation, SGOT and SGPT. The prothrombin time was 30 per cent (17 seconds) and the serum uric acid 7.5 mg. per cent. Two blood transfusions were given and busulfan therapy was instituted in a dosage of 12 mg. daily. Sodium bicarbonate 1.2 Gm. 4 times daily and Diamox 250 mg. once daily at night were given to alkalinize the urine. Busulfan was discontinued in mid-March, 1960, when the white cell count reached 17,350. At that time the patient was asymptomatic, the spleen had decreased in size and the hemoglobin was normal. Busulfan therapy was re-instituted in April, 1960, when the leukocytes increased, but the patient continued to work and felt well.

In October, 1960, the patient noted afternoon fatigue. The hemoglobin was 12.7 Gm./100 ml. and the white cells were 39,000, but no myeloblasts were seen. He developed a productive cough, marked weakness, anorexia, increased weight loss and left upper quadrant distress which required hospitalization in February, 1961. Busulfan was discontinued; at
Fig. 1.—Hyperpigmentation of face, neck and nipples in patient with porphyria cutanea tarda.

This time he had received a total dosage of 1320 mg. Physical examination revealed a generalized, dirty-brown pigmentation, especially marked on the face, neck, nipples and upper extremities (fig. 1). The oral mucous membrane and palmar creases did not reveal unusual pigmentation. The blood pressure was 110/60, while the liver extended 6 cm. below the costal margin and the spleen reached the iliac crest. The hemoglobin was 5.8 Gm./100 ml, white cell count 46,000 with neutrophils 8, bands 11, lymphocytes 16, monocytes 1, eosinophils 14, basophils 14, metamyelocytes 3, myelocytes 11, promyelocytes 3, and myeloblasts 19. The platelets were 382,800 per cu. mm. Bone marrow aspiration revealed a dry tap but a biopsy obtained using a Vim-Silverman needle showed increased fibrosis and many myeloblasts. It was thought that the patient had developed a reaction to busulfan, previously described, and characterized by hyperpigmentation, weakness, fatigue, anorexia, nausea and weight loss, or a myeloblast crisis. Numerous studies were then performed in order to evaluate the pigmentation and other possible metabolic abnormalities. The 2-hour post-prandial blood sugar, blood urea nitrogen, creatinine, calcium, phosphorus, bilirubin, serum alkaline phosphatase, uric acid, thymol turbidity, cephalin flocculation, SGOT and SGPT values were normal. Other studies included serum albumin 2.6 Gm. per cent, serum globulin 2.6 Gm. per cent.
per cent and 10 per cent in 45 minutes on two occasions (normal less than 10 per cent), serum carotene 30 μg. per 100 ml. (this increased to 84 μg. per cent after oral carotene in oil for 3 days), xylose tolerance 2.6 Gm. in the urine collected during a 5-hour period, serum iron 125 μg. per cent and fecal urobilinogen 153 mg. per 24 hours. The protein-bound iodine, serum ascorbic acid level and glutathione content of the red cells were within normal limits. No lead was found in a 24-hour urine specimen and a test for urinary 5-hydroxyindolacteic acid was negative. A chromium53 red cell survival time was normal (T½ = 27 days).

Roentgenographic studies of the chest, skull, upper gastrointestinal tract and small bowel were not remarkable. There was a moderate decrease in prothrombin, factors V, VII and X, interpreted as compatible with liver disease. The direct Coombs' test was negative. Since the urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids before and after ACTH stimulation was normal, adrenal cortical insufficiency was felt to be excluded. Biopsy of the skin revealed a marked increase of pigment in the basal layer of the epidermis. The dopa reaction was strongly positive indicating that the pigment was melanin. The pigment did not show a positive stain for iron. A split thickness skin biopsy revealed very active melanocytes with a fast dopa reaction, but no evidence of neoplastic change.

The urine appeared dark and reddish brown; the porphyrins were markedly increased. These were determined quantitatively by the methods of Rimington17 (table 1). Several fresh specimens of urine gave a negative Watson-Schwartz18 reaction for porphobilinogen. Fresh, unstained bone marrow and peripheral blood smears showed no red fluorescence characteristic of porphyrins, and there was no red fluorescence of the patient's skin, nails or mucous membranes, but both his serum and urine exhibited red fluorescence. Dermatologic lesions had not appeared during or prior to his illness except that his skin had been rather easily traumatized for several months in 1959. He had never developed vesicles or bullae upon exposure to the sun, but he had had an indoor job and his exposure was not great. The patient had never had abdominal colic, neurologic signs or symptoms, hirsutism or had passed dark brown or red urine in the past. He denied any excessive intake of alcohol or history of liver disease or jaundice. There was no history of skin lesions, hyperpigmentation, red urine, abdominal colic, neurologic symptoms or leukemia in any members of his family. Unfortunately, none of his family was available for study.

The patient was diagnosed as having the myeloblastic crisis of chronic granulocytic leukemia, hyperpigmentation of continued busulfan therapy and porphyria of either coincidental origin or related to the disease or secondary to drug administration. He was given three units of blood and 150 mg. of 6-mercaptopurine daily. This had to be discontinued after 6 days because of severe diarrhea and increased nausea. Another short trial of this drug resulted in diarrhea and it again had to be discontinued. The skin became much darker during observation. The Nikolsky sign19 was present because the skin rubbed off during shaving, but no bullae formed. His hair turned almost black and became wavy, whereas it had previously been white and straight. He had lost 37 pounds since October, 1960.

When last seen on April 24, 1961, he was still troubled with anorexia, nausea, extreme weakness and discomfort from splenomegaly. The liver and spleen were enlarged as before and the hemoglobin had fallen to 5.5 Gm. per 100 ml., in spite of two blood transfusions. The white cell count was 304,000 with 26 per cent myeloblasts. The marked urinary excretion of porphyrins persisted (table 1). He died suddenly at home on May 8, 1961.

At post-mortem examination, the liver was markedly infiltrated by primitive leukocytes, especially in the portal areas. The parenchymal cells contained a large amount of brown pigment which stained positively for iron. The splenic architecture was totally disrupted from leukemic infiltration. There were some leukemic infiltrates in the heart and kidney.

*We are indebted to Drs. W. J. Mitus and C. Szabo for these studies.
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Table 1.—Quantitative Porphyrin Excretion

<table>
<thead>
<tr>
<th></th>
<th>Urine</th>
<th>Stool</th>
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<tr>
<td></td>
<td>Coproporphyrin</td>
<td>Uroporphyrin</td>
</tr>
<tr>
<td></td>
<td>μg./L. 24 hr.</td>
<td>μg./L. 24 hr.</td>
</tr>
<tr>
<td>Normal (17)</td>
<td>&lt;210</td>
<td>5-30</td>
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<tr>
<td>3-26-61</td>
<td>170</td>
<td>271</td>
</tr>
<tr>
<td>3-27-61</td>
<td>196</td>
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<td>3-28-61</td>
<td>314</td>
<td>486</td>
</tr>
<tr>
<td>3-29-61</td>
<td>271</td>
<td>401</td>
</tr>
<tr>
<td>4-24-61</td>
<td>167</td>
<td>107</td>
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Unfortunately, the patient had been embalmed prior to pathologic examination and it is almost certain that this accounted for the absence of fluorescence of the liver.

Summary of Case History

This 55-year-old man developed chronic granulocytic leukemia, which was treated with busulfan, and entered the acute phase a year later. Marked hyperpigmentation, weight loss of 35 pounds and extreme weakness and fatigue occurred. He was found to be excreting large amounts of uroporphyrin in the urine with only small increases in urinary coproporphyrin and fecal porphyrins. At post-mortem examination there was leukemic infiltration, especially in the portal areas of the liver.

Discussion

Review of Literature

Excellent reviews of the biosynthesis and metabolism of porphyrins are presented by Schmid,2 Watson,21 Harper,22 Gray,23 Goldberg and Rimmington24 and Eales.25

Normal human urine contains less than 300 μg. of coproporphyrin per 24 hours,26 but this is commonly increased in liver disease,11-27 after alcohol ingestion,31 during fever and infections,29,30 following poisoning with lead and other heavy metals or chemicals;21,30 less frequently it is elevated in anemia21,29,30,32 (pernicious, hemolytic or aplastic), hemorrhage,29,30 leukemia29,30,35 Hodgkin’s disease,21,36 pellagra29 and skin diseases.29,30

Urinary uroporphyrin excretion is less than 30 μg. daily but may be increased in lead poisoning or cirrhosis.21 With and Petersen37 have reported elevation of urinary uroporphyrins in such diverse conditions as carcinomatosis, cirrhosis, barbiturate intoxication, Hodgkin’s disease, lymphatic leukemia, rheumatoid arthritis, subacute bacterial endocarditis and hereditary spherocytosis. According to these authors, the excretion of ether-insoluble urotype porphyrins in the urine is always less than 600 μg. per 24 hours which is considerably below the values usually found in the porphyrias.

Small amounts of porphobilinogen are present in all urine but in amounts insufficient to produce a positive Watson-Schwartz reaction. Occasionally this test may yield positive results in liver disease, malignancy and infectious or nervous diseases.38 Another author reported no false positive tests in 1000 general hospital cases.38
Porphyria was first classified by Günther in 1911 into hematoporphyria acuta, H. acuta toxica, H. chronica and H. congenita.\textsuperscript{39} In 1937, the term porphyria cutanea tarda was introduced by Waldenström.\textsuperscript{1} Watson and associates\textsuperscript{40-42} described two major types of porphyria based on the site of excessive porphyrin formation. Porphyria erythropoietica corresponds to the older congenital porphyria in which the porphyrins are formed in normoblasts of the bone marrow; porphyria hepatica includes acute intermittent porphyria and porphyria cutanea tarda in which the metabolic defect is in the liver where large amounts of porphyrin precursors or porphyrins are formed.

Porphyria cutanea tarda (PCT)\textsuperscript{20,21,24} occurs in the fourth to the sixth decade and is characterized by hyperpigmentation, increased photo- and mechanical sensitivity of the skin, and is often associated with liver disease or alcoholism. The urine contains increased uroporphyrins and coproporphyrins while the fecal output of these substances is variable. No excess of porphobilinogen is found unless the patient has a combination of porphyria cutanea tarda and acute intermittent porphyria.

Brunsting and associates\textsuperscript{57} have described a total of 34 cases of porphyria cutanea tarda in adults which were characterized by formation of vesicles and bullae on light-exposed areas, hyperpigmentation of skin and hair, hypertrichosis, milia and ruddy complexion with occasional abdominal pains and nervous symptoms. Abnormal liver function studies and alcoholism were common features. There were increased amounts of urinary uroporphyrin and coproporphyrin as well as fecal porphyrins. Seven had increased amounts of porphobilinogen in the urine.

In South Africa, porphyria cutanea tarda in the white population has been designated variegate porphyria and is characterized by vesicles or bullae of the skin, which is sensitive to light or trauma (the skin lesions are particularly prominent in males), and occasional abdominal colic or neurologic symptoms which are often precipitated by drugs (more common in females).\textsuperscript{24} The most striking finding is an increase in coproporphyrin and protoporphyrin excretion in the feces in these patients and in almost one-half of their offspring.\textsuperscript{9} During an acute attack, porphobilinogen, delta-amino levulinic acid and porphyrins are excreted in the urine, but these usually return to normal levels when the acute episode subsides. A non-sex linked Mendelian dominant type of inheritance has been demonstrated by Dean and Barnes\textsuperscript{2} in a study of 13 families with porphyria. One of these families was traced as far back as 1688.

The Bantus of South Africa evidently have a type of porphyria which is quite different from the variegate type found in Europeans.\textsuperscript{8-12} Skin manifestations consisting of bullae in sun-exposed areas are commonly found, but acute attacks of abdominal colic or nervous symptoms are not part of the syndrome. The presence of hepatomegaly and abnormal liver function tests are common. Urinary excretion of porphyrins is elevated, but fecal porphyrin levels are normal or only slightly elevated. Excessive excretion of porphobilinogen and delta amino-levulinic acid in the urine are rarely, if ever, found. There is no
evidence of an hereditary element, the porphyria being presumably acquired. The cause of the porphyria of the Bantus is unknown although malnutrition and the drinking of adulterated alcoholic beverages have been incriminated. Recently, an outbreak of cutaneous porphyria has been reported from Turkey. It is characterized by blistering of the skin (which is sensitive to both sun and trauma) on exposed parts of the body. There is hyperpigmentation especially around the face, hypertrichosis and frequent malnutrition, but no abdominal pains or neurologic symptoms. The urine is dark in color, fluoresces in Wood’s light and contains large amounts of uroporphyrin and coproporphyrin. The stool also contains an increased amount of porphyrin. Some patients have shown abnormal liver function tests. There is no increase of urinary porphobilinogen excretion or fluorescence of the bone marrow. The porphyria is believed to result from ingestion of seed wheat treated with hexachlorobenzene. Ockner and Schmid have reported increased urinary excretion of uroporphyrin, coproporphyrin, porphobilinogen and delta aminolevulinic acid and slight to moderate increased fecal excretion of coproporphyrin and protoporphyrin in rats given hexachlorobenzene in their food. There was liver cell degeneration as well as an increased porphyrin content of this organ. This study presented strong evidence that hexachlorobenzene was responsible for the cutaneous porphyria in Turkey although elevations of urinary porphobilinogen or fecal protoporphyrin were not noted in the Turkish cases.

This hexachlorobenzene-induced porphyria is the first evidence of a purely acquired form. De Matteis and Rimington have produced experimental porphyria in some strains of mice by adding griseofulvin to the diet.

The appearance of porphyria following the use of various drugs has been reported occasionally. Thus, chloroquine has been stated to aggravate porphyria in a number of instances while tolbutamide has also been incriminated. Watson and associates have seen porphyria appear in seven patients during the ingestion of stilbestrol or chlorotrianisene (TACE). Neither busulfan nor any of the alkylating agents have thus far been associated with porphyria, although we have reported pigmentation and an Addisonian-like syndrome. We have studied the latter condition intensively and in none of the four Addisonian-like cases previously reported or in several others seen subsequently has a porphyria been discovered.

A remarkable case of porphyria cutanea tarda which disappeared after removal of a hepatic adenoma containing uroporphyrin, coproporphyrin and protoporphyrin has been reported. Elevation of the urinary coproporphyrins has been reported in leukemia but Watson and Thiel found normal urinary porphyrin levels in myeloid leukemia. With and Petersen reported on a patient with monocytic leukemia treated with busulfan who excreted 319 µg per 24 hours of 3- and 4-carboxyl porphyrins and another with chronic lymphatic leukemia with a daily excretion of 525 µg of 4-, 5- and 8-carboxyl porphyrins. We were not able to find any cases of chronic granulocytic leukemia in the literature with a uroporphyria comparable in degree to that shown by our patient.
Some Remarks as to Type and Pathogenesis of the Porphyrias

This patient had a well-documented chronic granulocytic leukemia which terminated in a "blast crisis" or acute phase. His past history was not suggestive of porphyria of any type except for a short period when his skin was easily traumatized. There was no history of sun sensitivity, alcoholism, liver disease, abdominal pain and neuropsychiatric abnormality nor was there a family history of any of these. The presence of porphyria erythropoietica (congenital porphyria) can be easily excluded by the lack of symptoms early in life, absence of bullae, red teeth, and of fluorescence of the normoblasts of the bone marrow and the patient's relatively normal excretion of fecal porphyrins. Acute intermittent porphyria was also excluded by the absence of abdominal colic and neuropsychiatric symptoms, as well as by the normal excretion of porphobilinogen. The present case of porphyria resembled porphyria cutanea tarda in that it occurred later in life and porphobilinogen was not increased. However, there was no increased sensitivity of the skin to sunlight or trauma.

A disturbance of the liver was present despite the many normal liver function tests as indicated by low serum albumin, decreased coagulation factors which are synthesized by the liver and the presence of marked leukemic infiltration of that organ. The excessive amount of iron within the hepatic parenchymal cells is hard to explain—a history of malnutrition or alcoholism was lacking and only 13 blood transfusions were given. Hemochromatosis was excluded by the absence of cirrhosis of the liver, absence of diabetes mellitus and normal serum iron.

Biochemically, porphyrin excretion in both the urine and stool of our case was very similar to that in the South African Bantus and in the Turkish group except that in the former the fecal coproporphyrins were not increased. Clinically, cutaneous manifestations were prominent features of both the Bantu and Turkish groups in contrast to our patient.

The etiology of the porphyria in our patient is difficult to establish with certainty. A genetic defect of porphyrin metabolism is possible, and this is supported by the history of cutaneous fragility. He had not taken sulfonamides, griseofulvin, Sedormid and barbiturates nor had he been exposed to lead, Rose Bengal, aniline dyes or excessive ultra-violet radiation. There was no history of chloroquine, tolbutamide or hexachlorobenzene ingestion. On the other hand, it is conceivable that busulfan, a potent sulfur-containing alkylating agent, may have precipitated the porphyria. This idea is enhanced by the striking urinary findings in the Turkish hexachlorobenzene cases which were similar to those found in the present case. The continued long-term study of patients treated with busulfan indicates that many reactions may occur with the use of this drug (interstitial pulmonary fibrosis, ovarian and testicular dysfunction, pigmentation, hyperuricemia with renal stones and an Addisonian-like state). These various reactions indicate that the drug is a profound metabolic poison; like hexachlorobenzene in the Turkish cases, it may well have been responsible for the porphyria and skin pigmentation in the present case. The role of the leukemia is unclear but it is unlikely that it was of importance except for its part in producing hepatic dysfunction by infiltration. Whether or not the patient had an occult genetic defect which was triggered
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either by the leukemia or more likely by the chemical busulfan can only be speculated upon.

SUMMARY

A patient with chronic granulocytic leukemia terminating in "blast crisis" and marked porphyria is presented. Quantitative porphyrin studies revealed: urinary uroporphyrin 8894 to 11,453 \( \mu g/24 \) hours, urinary coproporphyrin 107-486 \( \mu g/24 \) hours, fecal coproporphyrin 55-116 \( \mu g/\) Gm. dry weight and fecal protoporphyrin 22-38 \( \mu g/\) Gm. dry weight. A review of the clinical aspects of porphyria is briefly presented, together with some speculation as to the etiology of the porphyria in the present case. The possibility is present that the busulfan therapy either initiated the disorder or triggered its development from a previously occult state. If so, this would be another manifestation of busulfan toxicity, of which pigmentation is the most common.

SUMMARY IN INTERLINGUA

Es presentate un patiente con chronic leucemia granulocytic que se terminava in un crise myeloblastic e un marcate porphyria. Studios quantitative del porphyrina revelava: Uroporphyrina urinari, 8.894 a 11.453 \( \mu g \) per 24 horas; coproporphyrina urinari, 107 a 486 \( \mu g \) per 24 horas, coproporphyrina fecal, 55 a 116 \( \mu g \) per g de peso sic; e protoporphyrina fecal, 22 a 38 \( \mu g \) per g de peso sic. Es presentate un breve revista del aspectos clinic de porphyria, insimul con speculationes in re le etiologia del porphyria. Es signalate le possibilitate que le therapia a bulsulfan initiava le disordine o precipitava su disveloppamento ab un previemente occulte stato. Si isto es correcte, nos ha hic un nove genere de manifestation del toxicitate de busulfan. Pigmentation es le manifestation le plus commun.

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