Liver - Porph

THE CLINICAL PORPHYRIAS

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THE CLINICAL PORPHYRIAS

The clinical porphyrias are a family of clinically heterogeneous diseases which have in common the excessive excretion of one or more of the porphyrins or porphyrin precursors. Although the porphyrias appear to be uncommon in clinical practice, they are probably much more prevalent than is recognized. This is so because: (a) The diseases are often present in a latent form; (b) Many of the clinical symptoms in overt cases are non-specific, leading to frequent misdiagnosis; and, (c) The diagnosis can only be made with assurance by quantitation of excessive excretion of porphyrins and their precursors. These tests are often not readily available and may not be performed properly.

The clinical porphyrias will be reviewed, including recent advances in the biochemical mechanisms resulting in disordered porphyrin and heme biosynthesis which characterize each of the porphyrias. Although it is undoubtedly an oversimplification, the primary thesis which will be advanced is that at least some of these disorders can be biochemically understood in terms of specific defects in the porphyrin and heme biosynthetic pathway.

Before discussing the classification of the porphyrias and each disorder, it is necessary to review briefly porphyrin and heme biosynthesis since a superficial knowledge of this pathway is essential for an understanding of the porphyrias.

I. Biochemical Considerations

A. Heme biosynthesis. Figure 1 is a diagrammatic representation of the heme biosynthetic pathway. Although all cells are capable of synthesizing heme, the bone marrow and the liver account for most of the heme synthesis in the body. About 2/3 of the heme is synthesized in bone marrow and about 1/3 in the liver. Heme synthesis is initiated in the mitochondrion by the condensation of glycine and succinyl CoA to form the aminoketone, δ-aminolevulinic acid (ALA). This rate limiting step is catalyzed by δ-aminolevulinic acid synthetase (ALA-synthetase). ALA-synthetase is synthesized on the rough endoplasmic reticulum and is then transported into the mitochondrial matrix where it is catalytically active. ALA which is formed diffuses into the cytosol where it is converted to the pyrrole, porphobilinogen (PBG). PBG is the intermediate which is identified by the Watson-Schwartz test. Four moles of PBG are then polymerized into a cyclic intermediate, uroporphyrinogen III by two enzymes, uroporphyrinogen I synthetase and uroporphyrinogen III cosynthetase. Uroporphyrinogen I synthetase removes an amino group and uroporphyrinogen III cosynthetase (in the presence of the synthetase) flips over the fourth pyrrole ring to form the III isomer which is the isomer type capable of being converted to heme. Uroporphyrinogen contains 8 carboxyl groups and is decarboxylated to the 4 carboxyl intermediate, coproporphyrinogen. Coproporphyrinogen then moves into the mitochondrion where it is oxidized and decarboxylated to the 2 carboxyl intermediate, protoporphyrin. Iron is inserted into the protoporphyrin ring under the influence of ferrochelatase to form the end produce, heme.

Heme then combines with various apoproteins to form hemoglobin, myoglobin, mitochondrial and microsomal respiratory chain cytochromes (including cytochrome P-450, the important drug hydroxylating mixed function oxygenase), catalase, and tryptophane pyrrolase. Considering the essential functions of the various hemoproteins, it is quite obvious that abnormalities of heme biosynthesis could result in severe functional disturbance.

B. Regulation of heme biosynthesis.

1. Enzymatic. As already mentioned, heme synthesis is normally regulated by the activity of ALA-synthetase. This enzyme in turn is regulated in three important ways: (a) It is subject to end product repression by heme. This provides a closed negative feedback loop so that when heme synthesis is excessive, ALA-synthetase is repressed, and when heme synthesis is sufficiently impaired, ALA-synthetase is induced; (b) ALA-synthetase is inducible. A large number of drugs, some of which are in common clinical use, and certain steroids can induce ALA-synthetase; and, (c) ALA-synthetase induction by these drugs and steroids can be prevented by carbohydrate feeding.

Although ALA-synthetase regulates the rate of heme synthesis under normal circumstances, the activity of other enzymes in the pathway may become rate limiting. In disease states in which certain enzymes are deficient the activity of the defective enzyme may control the overall rate of heme synthesis. As will be discussed, this appears to be the case in certain types of porphyria.

2. Other factors may also be important in regulating the rate of heme synthesis:

a. Supply of substrate
b. Presence of inhibitors or activators of enzymatic activity at various steps
c. Induction or repression of enzyme activity at enzymatic steps other than ALA-synthetase
d. Transport of ALA, coproporphyrinogen, and heme across the mitochondrial membrane

C. Additional features of heme biosynthesis.

1. The porphyrinogens are colorless, non-fluorescing molecules. It is only when the hexahydroporphyrins are oxidized to the corresponding porphyrins that they acquire a pink color in the visible spectrum and become intensely fluorescent when exposed to light at about 400 nM. The intense fluorescence of the porphyrins enables their quantitation in 10^{-11} M concentrations.

2. The number of carboxyl groups on the porphyrinogens determines their polarity and their route of excretion. The highly polar and water soluble 8 carboxyl uroporphyrinogen is excreted almost exclusively in the urine, 4 carboxyl coproporphyrinogen is excreted both in urine and feces, and 2 carboxyl protoporphyrin is excreted solely in feces. ALA and PBG are excreted in the urine.

3. The pathway is normally extremely efficient so that of the approximately 500 mg of heme synthesized each day only a few mg of intermediates in the pathway are excreted each day. Normal daily excretion values for these intermediates are as follows: ALA (0-4 mg/liter), PBG (0-1.8 mg/liter), uroporphyrin (10-50 µg/liter), coproporphyrin (20-250 µg/liter of urine and 0-40 µg/gram dry weight of stool), and protoporphyrin 0-100 µg/gram dry weight of stool).

II. Classification of the Porphyrias

A current classification of the clinical porphyrias is based on whether the bone marrow or the liver is the primary site of excessive porphyrin and/or precursor production and is shown in Figure 2. The only porphyria which is clearly erythropoietic is congenital erythropoietic porphyria which has a counterpart in a similar genetic disorder in cattle. The last porphyria listed, protoporphyria, is usually called erythropoietic protoporphyria. Recent evidence indicates that excessive porphyrin production arises from both bone marrow and liver in this disease. Hence a new name, erythrohepatic protoporphyria has been proposed. The remainder of the porphyrias are classified as hepatic. Acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria are genetically determined whereas porphyria cutanea tarda appears to be acquired in most instances. The only example of toxic porphyria in man is the well documented epidemic of a cutaneous type of porphyria in Turkey in the early 1950's traced to hexachlorobenzene contamination of wheat. Not listed are a group of secondary porphyrinurias, which will be discussed.

Each of these diseases has been characterized in terms of genetics, clinical features, and abnormal excretion of intermediates in the heme biosynthetic pathway.

III. The Human Porphyrias

A. Congenital Erythropoietic Porphyria

1. Clinical Features. Although this was historically the first type of porphyria to be recognized, less than 100 cases have been reported in the literature. It is inherited as an autosomal recessive and is expressed chemically by excessive excretion of uroporphyrin I. It usually becomes clinically apparent in the first few years of life when the

children began to excrete red colored urine and develop extremely severe photosensitivity. Sun exposure produces large bullous lesions which ulcerate, heal slowly, and often produce scarring and disfiguration. Hypertrichosis and hyperpigmentation may also be present but are not limited to sun exposed areas. Porphyrin deposition in the teeth and bones causes a brown or pink discoloration of bones and teeth which fluoresce under UV light. During childhood most of these patients develop hemolytic anemia, ineffective erythropoiesis and splenomegaly.

The presence of porphyrin in the skin is responsible for the photosensitivity in congenital erythropoietic porphyria as well as other forms of porphyria associated with photosensitivity. Absorption of radiant energy is thought to result in excitation of the porphyrin molecule with consequent energy release, with formation of free radicals which attack lipid membranes, resulting in their destruction and release of lysosomal enzymes. Although porphyrins appear to be related to the hypertrichosis and hemolysis, the mechanisms have not been elucidated.

Treatment is symptomatic. Splenectomy may be helpful in patients with severe hemolytic anemia. Protection against sunlight is essential. Watson recommends a lawsone-dihydroxyacetone combination which combines with superficial layers of the skin and effectively filters out light for several days. The skin then desquamates and the application is repeated. Usual sun screen creams do not help since they do not block 400 nM light.

Few of the patients have survived past 40. The cause of death is variable, usually relating to the hemolytic anemia and complications of therapy.

2. Diagnosis. This is rarely a problem in a disease with as distinctive a clinical syndrome as the one I have described. Chemical confirmation includes demonstration of markedly increased bone marrow, red cell, and urine uroporphyrin. Isomer analysis will show that the uroporphyrin is predominantly of the I type.

3. Nature of metabolic defect. As previously mentioned, uroporphyrinogen I synthetase converts PBG only to uroporphyrinogen I, whereas formation of uroporphyrinogen III requires the combined action of uroporphyrinogen I synthetase and uroporphyrinogen III cosynthetase. Activity of the cosynthetase is almost absent in red cell hemolysates and cultured fibroblasts from human subjects with congenital erythropoietic porphyria. The partial cosynthetase deficiency is probably the primary inherited enzyme defect in this disease and explains the observed overproduction of porphyrins of the type I series. Cosynthetase activity in red cell hemolysates from

asymptomatic carriers (heterozygotes) of this condition are intermediate to the activities in normals and homozygotes. Other enzymes in heme biosynthesis have not been determined in this disease.

4. Case #1. [redacted] is a 16-year old boy who was first diagnosed as having a nonspherocytic hemolytic anemia with hepatosplenemogaly at age 7 months. At age 8 1/2 months he had a splenectomy without improvement of the hemolytic anemia. Shortly after splenectomy his diapers were noted to be pink stained. Furthermore, after his first exposure to light he developed vesicular lesions on the exposed parts of his body. In the course of his development, hypertrichosis, in the form of fine downy hair, was noted over his face and extremities; his teeth exhibited a brownish discoloration and fluoresced under UV light . The urine contained very large amounts of uroporphyrin I and much less coproporphyrin I. Marrow red cell nuclei fluoresced under UV light. At the present time he requires a blood transfusion every 3 to 4 weeks, has evidence of siderosis, and has an unexplained thrombocytopenia.

Comment: This patient has had unusually severe hemolytic anemia without benefit from splenectomy. The anemia in this disease is usually normocytic and normochronic with increased circulating nucleated red cells and reticulocytes. The reason for hemolysis is not known but appears to be a corpuscular rather than a humoral defect. There is also ineffective erythropoiesis and the marrow shows erythroid hyperplasia.

B. Protoporphyria

1. Clinical features. This relatively benign form of porphyria comes to clinical attention because of photosensitivity which is quite different from that observed in congenital erythropoietic porphyria. Photosensitivity may be of two types: (a) Urticarial with edema, burning, and pruritis which may persist for days following sun exposure; and, (b) Chronic eczematoid dermatitis with lichenification. Photosensitivity usually becomes apparent during childhood and there are rarely any associated diseases, although some patients have been reported with hemolytic anemia and there may be an increased incidence of gall stones.

Protoporphyria is inherited as an autosomal dominant and is probably one of the most common types of porphyria, since more than 100 cases have been described since 1961 when the disease was first recognized. The reason this disease had gone undiagnosed for so many years is the failure to look in stool, red cells and plasma for porphyrins. There is a marked increase in protoporphyrin in feces, red cells and plasma in protoporphyria, while the urinary porphyrins and precursors

are normal. Treatment consists of avoiding sunlight. Cholestryamine (to bind fecal protoporphyrin) has been tried with unclear results. Beta-carotene has recently been reported to lessen photosensitivity. The mechanism is unknown.

2. Diagnosis. This disease should be considered in all patients with unexplained urticarial or eczematoid photosensitivity. If proper quantitative porphyrin analysis on stool and red cells are performed, diagnosis is no problem. The findings on skin biopsy may be helpful but are not diagnostic.

3. Nature of metabolic defect. Both the liver and bone marrow appear to be responsible for the increase in protoporphyrin production. However, the fundamental defect has not been elucidated. Since ferrochelatase is the enzyme responsible for the further metabolism of protoporphyrin by inserting iron into it, a partial deficiency of this enzyme is consistent with the known clinical and chemical features of protoporphyria. Although overall bone marrow heme synthesis appears to be normal, no good studies of heme biosynthetic enzymes have been reported in this disorder.

4. Case #2. [redacted]) This patient is a 40 year old man who had experienced recurrent episodes of edema and erythema upon exposure to sunlight since the age of 6. He did not have chronic eczematoid skin lesions, attacks of abdominal pain or neurological symptoms. There was no family history of photosensitivity. Red cell, plasma and fecal protoporphyrin were increased with levels which were inversely related to the patient's carbohydrate intake. Protoporphyrin was also elevated in his liver. Hepatic ALA-synthetase activity was normal.

Comment: This patient's cutaneous symptoms are of the recurrent urticarial type rather than the chronic light sensitive dermatitis variety. Although the liver is the site of at least some of the porphyrin formation, these patients never have acute attacks of neurological dysfunction and the urine ALA, PBG and porphyrins are always normal. Drugs are not known to precipitate the skin lesions. The fact that carbohydrate feeding results in decreased protoporphyrin excretion ("glucose effect") is evidence favoring an hepatic source for at least some of the porphyrin.

C. Intermittent Acute Porphyria

This disease was first well described by Waldenstrom in 1937 who established its genetic nature. It is transmitted as an autosomal dominant with a high incidence of about 1:1000 in Lapland and a conservative estimate of 1.5/100,000 in the United States. Although the disease would be expected to occur with equal frequency in males and females, acute attacks are much more common in women. Acute attacks

of gastrointestinal and neurological dysfunction are often precipitated by steroids and therapeutic amounts of a variety of drugs. These attacks usually do not occur until after puberty. Chemically, there is excessive excretion of the porphyrin precursors, ALA and PBG, out of proportion to subsequent intermediates in the pathway.

1. Clinical features. The clinical aspects of this disease are so varied and numerous as to defy complete listing. In general, these symptoms can be considered to be related to the nervous system and have been grouped as follows:

Autonomic Neuropathy
- abdominal pain
- constipation and occasionally diarrhea
- vomiting
- tachycardia
- labile hypertension
- postural hypotension
- retinal artery spasm
- peripheral vascular spasm
- sweating
- vesical symptoms

Peripheral Neuropathy
- muscle and back pain
- asymmetric motor > sensory
- may involve cranial nerves

Cortical Dysfunction
- depression
- confusion
- disorientation
- hallucinations
- seizures
- coma

Hypothalamic Dysfunction
- inappropriate ADH release
- inappropriate growth hormone release
- lactation

Photosensitivity is rarely if ever observed in intermittent acute porphyria. These symptoms may occur in various combinations during acute attacks and in any one patient the symptom complex tends to be similar with recurrences. Between attacks patients are usually completely symptom free, though resolution of the neuropathy may be incomplete and some mental symptoms may persist.

Factors precipitating acute attacks are extremely important in the management of these patients. At least four such precipitating factors are known: drugs, steroids, fasting and infections. Drugs can be placed in four catagories in terms of their effect on the disease:

a. Those which have been implicated in producing acute attacks: barbiturates, sulfonamides, griseofulvin, Librium, meprobamate, dilantin, methsuximide (Celontin), tolbutamide (Orinase), and possibly ergot derivatives and alcohol.

b. Drugs which produce "experimental porphyria" in vitro: glutethamide (Doriden), mephenytoin (Mesantoin), phensuximide (Milantin), methprylon (Noludar), and chloramphenicol (Chloromycetin).

c. Drugs which have been used extensively without precipitating an acute attack: demerol, thorazine, aspirin, pencillin, and probably darvon.

d. Drugs about which no information exists in regard to their effect on porphyrin metabolism or clinical porphyria.

As a general rule, drugs should not be given to patients with intermittent acute porphyria. When they are required, only those which have been shown to be safe should be given. In specific clinical situations it may be necessary to give drugs about which no information exists. This should be done cautiously under close supervision in which caloric intake is not restricted. When surgery is required, nitrous oxide and curare have been shown to be safe. No information exists about halothane or cyclopropane.

The role of steroids in this disease is a complex subject. It can be summarized by the following statements: (a) Attacks can be precipitated by estrogen administration and in some cases by birth control pills; (b) Certain steroids of the pregnane and etiocholane derivatives produce experimental porphyria in cultured liver cells; (c) Certain women with the disease have cyclic attacks which usually occur during the luteal phase of the menstrual cycle. These attacks may be prevented by anovulatory agents; and, (d) The higher incidence of attacks in women and the post-pubertal onset further suggests a role of sex steroids or pituitary hormones in the precipitation of acute attacks.

A variety of bacterial and viral infections appear to have precipitated acute attacks as has starvation.

One or more of the above four groups of precipitating factors can often be recognized as the cause of an acute attack but there are some patients in whom none of these factors have been clearly implicated.

2. Other laboratory findings (not invariably present).

a. Abnormal glucose tolerance test
b. Increased thyroid binding globulin
c. Hypercholesterolemia
d. Hyperbetalipoproteinemia
e. Delayed BSP clearance
f. Hyponatremia and hypomagnesemia
g. Aminoaciduria
h. Decreased red cell volume

3. Diagnosis. From a practical point of view when a patient presents with symptoms suggestive of an acute attack, the Watson-Schwartz test for PBG will almost always be positive if the patient has intermittent acute porphyria. This test is performed by adding 2 ml of Ehrlich reagent (2% diaminobenzaldehyde in 5 N HCl) to 2 ml of urine. If a pink or red color develops, 4 ml of saturated sodium acetate is added to raise the pH. If the color still remains, 4 ml of butanol is added. If PBG is present in 2 to 3 times the normal amount, the red color will remain in the water phase. If the color is extracted into the butanol, it is likely to be urobilinogen. When the test is positive a blank should always be included in which 5 N HCl without Ehrlich reagent is added to the urine. If the test is performed in this way, there are virtually no false positives.

To differentiate intermittent acute porphyria from other genetic hepatic forms, quantitation of urine ALA and PBG plus urine and stool porphyrins is necessary. In intermittent acute porphyria, the urinary ALA and PBG will be elevated with only slight increases in uroporphyrin and coproporphyrin while the fecal porphyrins will be normal. To obtain valid tests the urine and stool must be kept frozen in the dark immediately after collection. Otherwise, PBG in the urine will spontaneously polymerize to porphyrins and confusing data will result.

A common misconception is that the urine in intermittent acute porphyria is red or wine colored at the time of excretion. This is not true. If the urine is allowed to sit in the sunlight or is heated, it will turn a muddy brown color because of the oxidation of PBG to porphobilin.

4. Treatment

a. Avoidance of precipitating factors
b. High CHO intake, 400 grams/day
c. Thorazine of unproved benefit except as a tranquilizer
d. Supportive: Observation for phrenic nerve paralysis and respiratory care; Fluid deprivation if inappropriate ADH release is documented
e. Inosine, AMP, Vitamin E, chelating agents (D-Pencillamine and BAL), and cytochrome c have been used but have not been shown to be effective in controlled studies

5. Nature of metabolic defect. A number of investigators have observed an increase in hepatic ALA-synthetase activity in intermittent acute porphyria, which undoubtedly accounts for the persistent excessive excretion of ALA and PBG. Since ALA-synthetase is rate limiting in the pathway, it remained to be explained why all of the subsequent intermediates in the pathway were also not excreted in excess. Recent data suggest that the enzyme controlling subsequent hepatic metabolism of PBG (uroporphyrinogen I synthetase) is deficient in intermittent acute porphyria. The current concept is that these two enzymatic defects are causally related in the following way. A partial deficiency in uroporphyrinogen I synthetase impairs formation of the end product of the pathway, heme. The negative feedback loop is thus interrupted, resulting in a secondary excessive induction of ALA-synthetase.

6. Case #3. ([redacted]) This 28 year old [redacted] woman developed back and abdominal pain in 1968. Although her urine was sterile, she was thought to have pyelonephritis and was treated with Gantanol. Her condition did not improve and she was referred to the Urology Service at [redacted]. She was noted to be depressed, had labile hypertension, persistent tachycardia, hyperglycemia, hypercholesterolemia, and increased BSP retention. A Watson-Schwartz test was positive and she was diagnosed as having intermittent acute porphyria. There was no family history suggestive of porphyria. She was treated with thorazine and remained well until [redacted] of 1970 when she developed abdominal pain with nausea and vomiting, progressive weakness of her extremities and hoarseness. She was referred to [redacted] where her condition rapidly deteriorated. In spite of glucose therapy, she developed flaccid quadriparesis, severe hyponatremia, and respiratory insufficiency. Following tracheostomy and controlled ventilation she developed pneumonia, tension pneumothorax and died.

Urinary PBG (350 mg/24^{o}) and ALA (110/24^{o}) were markedly elevated with only slight increases in uroporphyrin and coproporphyrin. Serum PBG (362 µg/100 ml) and ALA (76 µg/100 ml) were markedly increased. Fecal porphyrins were normal. Hepatic ALA-synthetase was increased by 10-fold and uroporphyrinogen I synthetase was decreased to less than 50% of normal.

Pathologic examination showed demyelinization of peripheral nerves, chromatolysis of anterior horn cells, pneumonia and tension pneumothorax. There were no abnormalities of the hypothalamus.

Comment: This patient demonstrates a classical history for intermittent acute porphyria but could have had variegate porphyria or hereditary coproporphyria. Although academic in terms of therapy, the diagnosis was made with certainty by quantitation of urinary and fecal porphyrins and precursors.

D. Variegate Porphyria

1. Clinical features. This is the most common type of porphyria in South Africa. In certain parts of South Africa this disease can be found in one out of every 223 hospital admissions. The disease in South Africa has been traced to a Dutch couple who married at the Cape of Good Hope in 1688. Variegate porphyria appears to be much less common than intermittent acute porphyria in the United States. It is transmitted as an autosomal dominant and is clinically similar to intermittent acute porphyria in every respect with the following exceptions: (a) Photosensitive cutaneous lesions associated with hyperpigmentation and hypertrichosis are quite common; and, (b) The pattern of excessive excretion of porphyrins and precursors is uniquely different. During acute attacks these patients excrete all of the intermediates in heme biosynthesis, including ALA and PBG. However, during remissions they excrete excessive amounts of uroporphyrin and coproporphyrin in the urine and increased coproporphyrin and protoporphyrin in the stool. Protoporphyrin excretion is increased out of proportion to the other porphyrins.

2. Nature of the metabolic defect. Like intermittent acute porphyria, hepatic ALA-synthetase activity is increased in this disease, at least during acute attacks. The only other heme biosynthetic enzyme which has been measured is uroporphyrinogen I synthetase, which is normal in variegate porphyria. The possibility that the enzyme responsible for further metabolism of protoporphyrin (ferrochelatase) is deficient in this disease has not yet been investigated. A partial defect in this enzyme could result in impaired heme synthesis and derepression of ALA-synthetase in a manner similar to the mechanism postulated to be operative in intermittent acute porphyria. Alternative explanations exist such as augmented heme catabolism or primary overproduction of ALA-synthetase.

E. Hereditary Coproporphyria

1. Clinical features. This type of hepatic porphyria was described in 1949 by Watson but it was not recognized as genetic. Subsequently, studies in a number of families suggest that hereditary coproporphyria is transmitted as an autosomal dominant. These patients

may have acute attacks of neurological dysfunction just like patients with intermittent acute porphyria. A small percentage have photosensitivity. Between attacks they usually have no symptoms.

The pattern of excessive porphyrin and precursor excretion is distinctive for this disease. During acute attacks there is excessive excretion of ALA, PBG, uroporphyrin, and coproporphyrin but protoporphyrin excretion is normal. During remission there is excessive excretion of coproporphyrin > uroporphyrin, while ALA, PBG and protoporphyrin excretion is normal.

2. Nature of the metabolic defect. Hepatic ALA-synthetase activity is increased in this disease, at least during acute attacks. In this respect this disease is similar to intermittent acute porphyria and variegate porphyria. Hereditary coproporphyria is enzymatically differentiated from intermittent acute porphyria by having normal uroporphyrinogen I synthetase activity. By analogy with the mechanism of excessive ALA-synthetase induction thought to be operative in intermittent acute porphyria, a partial block in heme synthesis at the level of coproporphyrinogen oxidase is postulated. Alternatively, a defect in the transport of coproporphyrinogen into the mitochondrion or auto-oxidation of coproporphyrinogen (and removal from the heme biosynthetic pathway) could explain the biochemical features of this disease.

3. Case #4. [redacted]) A 34 year old man of Cuban extraction was admitted to the hospital in [redacted] of 1967 for elective repair of an inguinal hernia. The past history included an appendectomy in 1948 and 2 episodes of unexplained abdominal pain 6 and 8 months prior to admission. There was no history of alcoholism. He had not taken medications known to provoke porphyria. Except for an inguinal hernia, physical examination was unremarkable. The operative procedure was uneventful; however, on the 7th post-operative day, he began to complain of abdominal and flank pain after having taken secobarbital for five days. The urine darkened after standing overnight and quantitative analysis showed elevated levels of urianry ALA, PBG and porphyrins (predominantly coproporphyrin). Fecal coproporphyrin was markedly elevated without an increase in protoporphyrin. Eventually ALA and PBG excretion returned to normal on a high carbohydrate diet, but coproporphyria excretion remained persistently elevated. Hepatic ALA-synthetase activity was increased 5-fold, ALA-dehydratase was slightly elevated and ferrochelatase was normal. Unfortunately, coproporphyrinogen oxidase was not measured. One of the patient's two sisters was later found to have hereditary coproporphyria.

Comment: This type of porphyria is identical clinically to intermittent acute porphyria in terms of clinical presentation. An accurate diagnosis could be made only by quantitation of stool and urine porphyrins and precursors.

F. Porphyria Cutanea Tarda

1. Clinical features. This type of porphyria is generally considered to be acquired, though there may be predisposing genetic factors which have not yet been elucidated. It is a purely cutaneous syndrome which usually appears after the age of 20. Patients demonstrate marked photosensitivity with blister formation, mechanical fragility, and poor wound healing and scar formation. They also have hyperpigmentation and hypertrichosis which is not confined to sun exposed areas.

The diagnosis is confirmed by excessive excretion of uroporphyrin > coproporphyrin in the urine. The porphyrin is of the type III isomer. In addition, there is excessive excretion of 7-carboxyl porphyrin, which is not observed in any of the other porphyrias. Stool protoporphyrin is normal, thus differentiating porphyria cutanea tarda from variegate porphyria in remission (with cutaneous signs alone).

This is the most common type of porphyria detected clinically and occurs in several groups of patients:

a. Alcoholics with or without cirrhosis. These patients have liver function abnormalities which reflect the stage and severity of their alcoholic liver disease. Almost all have increased iron stores and an elevated serum iron/iron binding capacity. The mechanism of the iron overload is not known. Although this appears to be an important feature of this disease, it cannot be the sole pathogenetic factor since not all patients have iron overload and this disease is not more common in idiopathic hemochromatosis or in transfusional siderosis.

b. Estrogen administration. This has been reported most commonly in men given estrogen for carcinoma of the prostate and also in women taking birth control pills. The mechanism is unknown and has not been investigated. Estrogens do not normally change porphyrin excretion, which suggests that estrogen in some way can activate the disease when it is present in latent form in certain patients.

c. Iron administration. There are a few case reports in which this disease was activated by oral iron treatment.

d. Systemic lupus erythematosis. There is an increased incidence of porphyria cutanea tarda in SLE. The mechanism is unknown. An intriguing, but perhaps not the most likely, possibility is that of formation of autoantibodies which inhibit the enzyme responsible for the decarboxylation of uroporphyrinogen in the liver.

e. Hepatoma. This has been reported in a single case. Resection of a benign adenoma resulted in clinical and chemical remission of the disease. The tumor contained large amounts of uroporphyrin.

2. Treatment:

a. Avoidance of alcohol, estrogen, iron, and sun.

b. Phlebotomy. Reduction in total body iron to an Fe/TIBC of < 20% or drop in hemoglobin by 3.5 gm % by weekly phlebotomy results in permanent remission in more than 90% of cases. This treatment is beneficial even in patients who do not have iron overload. The mechanism is unknown.

c. Chloroquine. This drug is concentrated in the liver and forms a water soluble complex with porphyrins leading to their excretion in the urine. Unfortunately, the complex formation in the liver produces central vein necrosis, at least with large doses of chloroquine. When small doses of chloroquine are given hepatotoxicity is not apparent but only 50% of the patients respond with porphyrinuria. This treatment is not recommended except when other measures fail and then only under careful supervision.

3. Nature of the metabolic defect. This is not known. ALA-synthetase activity has been determined in many patients with variable results. It appears that the activity of this enzyme is normal or minimally elevated. The possibility of a defect in uroporphyrinogen decarboxylase has not been investigated. An alternative mechanism would be that uroporphyrinogen is oxidized to uroporphyrin in the liver, thus removing it from further metabolism. Since iron is involved in lipid peroxidation reactions, this is a possible mechanism whereby porphyrinogens may be oxidized and accumulated.

4. Case #5. ([redacted]) This 55 year old man was referred by Dr. David Shelmire to Dermatology Clinic with a clinical diagnosis of porphyria cutanea tarda. He had a six month history of blistering of his skin in sun exposed areas. The lesions would crust over and become secondarily infected with delayed healing and scar formation. He had never had episodes of abdominal pain or neurological dysfunction. There was no family history of similar symptoms. He had consumed excessive amounts of alcohol for several years but had no overt manifestations of alcoholic liver disease. On exam he had hepatomegaly, healing blisters and scars on sun exposed areas, hypertrichosis, and hyperpgimentation. Liver function tests were normal with the exception of an SGOT of 66 and 7% BSP retention at 45 minutes. Serum iron/TIBC was 84/275. Liver biopsy showed mild periportal fibrosis and small amount of fat. An iron stain showed no increase in hepatic iron. Urinary uroporphyrin was markedly increased with a slight increase in coproporphyrin. Thin layer chromatography of the urine and liver showed increased uroporphyrin and a heptacarboxylic porphyrin band. Hepatic ALA-synthetase activity was normal. Stool porphyrins are pending.

Comment: This patient's clinical manifestations are typical of porphyria cutanea tarda with the exception that he had no evidence of iron overload. The cutaneous lesions are consistent with those seen in variegate porphyria. The urinary porphyria findings are diagnostic of porphyria cutanea tarda. Stool porphyrins should be quantitated to exclude variegate porphyria with certainty.

G. Secondary Porphyrinurias

1. Lead poisoning. Lead inhibits several enzymes in the heme biosynthetic pathway, especially ALA-dehydratase and coproporphyrinogen oxidase. There is, therefore, excessive excretion of ALA and coproporphyrin. With severe lead poisoning other intermediates, PBG and uroporphyrin, may be excreted excessively. Lead poisoning will rarely give a positive Watson-Schwartz reaction for PBG. ALA excretion is much greater than PBG which is the reverse of what is seen in the acute hepatic porphyrias.

2. Coproporphyrinuria

a. Heavy metal poisoning
b. Alcohol, benzene, carbon tetrachloride, methyl chloride, barbiturates
c. Liver disease, cirrhosis, biliary obstruction
d. Dubin-Johnson Syndrome. Increased ratio of type I/ type III. There is very slight elevation in total coproporphyrin excretion. This probably represents a defect in hepatic transport of coproporphyrin isomers.

3. Uroporphyrinuria may occur in certain patients with liver disease associated with coproporphyrinuria.

4. Protoporphyrin excretion in feces is increased with meat ingestion, gastrointestinal bleeding, and in hemolytic anemia. Red cell protoporphyrin levels are increased in iron deficiency anemia, hemolytic anemia, and lead poisoning.

In summary, the clinical porphyrias exist as latent diseases which intermittently become overt with a large variety of clinical presenting symptoms. Unexplained photosensitivity, abdominal pain or neuropathy should raise the question of porphyria. The family history is often quite helpful because of the genetic nature of most of these diseases. The only way to be sure of the diagnosis is to perform quantitative porphyrin and precursor analysis in the urine, stool, and sometimes red cells. Proper diagnosis is critical to the therapeutic approach to these disorders and genetic counselling of involved families.

OUTLINE OF HEME BIOSYNTHESIS

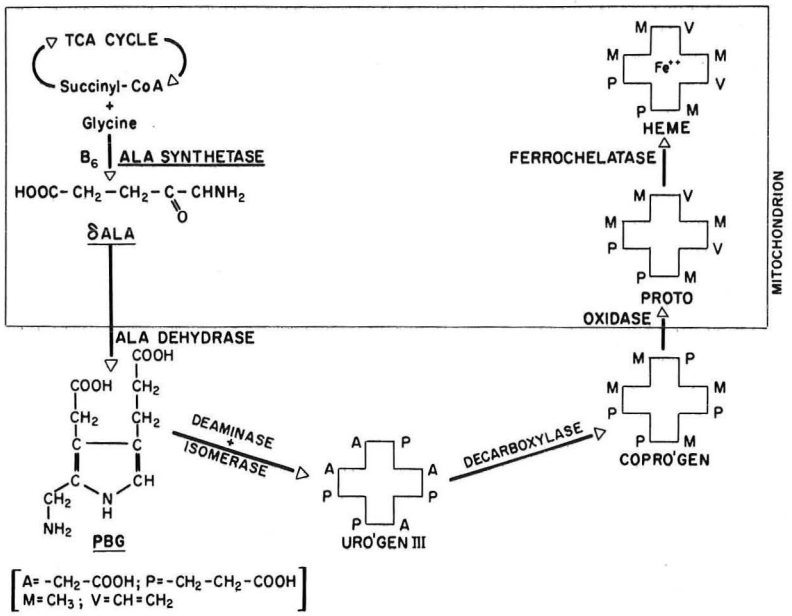

FIGURE I

CLASSIFICATION

I. Erythropoietic Porphyrias

   A. Congenital Erythropoietic Porphyria

II. Hepatic Porphyrias

   A. Intermittent Acute Porphyria (Swedish Porphyria)

   B. Variegate Porphyria (South African Porphyria)

   C. Hereditary Coproporphyria

   D. Porphyria Cutanea Tarda

   E. Toxic Porphyria

   F. Secondary Porphyrinuria

III. Protoporphyria (Erythropoietic Protoporphyria, Erythrohepatic Protoporphyria)

FIGURE 2

SUMMARY OF DIFFERENT TYPES OF PORPHYRIA

TYPE	CLINICAL MANIFESTATIONS	CHEMICAL FINDINGS	INHERITANCE	BIOCHEMICAL DEFECT
Congenital Erythropoietic Porphyria	Photosensitivity Hemolytic anemia Splenomegaly	↑ Uroporphyrin I > coproporphyrin I in bone marrow, RBC's, urine	Autosomal Dominant	↑ Uroporphyrinogen III cosynthetase
Protoporphyria	Photosensitive urticaria or chronic eczematoid dermatitis	↑ Protoporphyrin in bone marrow, liver, RBC's, plasma, feces	Autosomal Dominant	Unknown ? ↓ Ferrochelatase
Intermittent Acute Porphyria	Acute attacks of neurological dysfunction; No photosensitivity	↑ ALA and PBG in liver and urine	Autosomal Dominant	↓ Uroporphyrinogen-I-synthetase ↑ ALA-synthetase
Hereditary Coproporphyria	Acute attacks of neurological dysfunction; Rare photosensitivity	↑ Coproporphyrin > uroporphyrin excretion ↑ ALA and PBG during acute attacks	Autosomal Dominant	Unknown ↑ ALA-synthetase (? acute attacks only) ? ↓ Coproporphyrinogen oxidase ? Defect in coproporphyrinogen transport ? Autooxidation of coproporphyrinogen
Variegate Porphyria	Acute attacks of neurological dysfunction; Photosensitivity common	↑ Protoporphyrin > coproporphyrin > uroporphyrin excretion ↑ ALA and PBG during acute attacks	Autosomal Dominant	Unknown ↑ ALA-synthetase (? acute attacks only) ? ↓ Ferrochelatase ? ↑ Heme catabolism ? Primary overproduction of ALA-synthetase
Porphyria Cutanea Tarda	Photosensitivity No neurological dysfunction	↑ Uroporphyrin > 7-carboxyl porphyrin > coproporphyrin in liver and urine	Unknown, may be acquired	Unknown + ? Normal ALA-synthetase ? ↓ Uroporphyrinogen decarboxylase ? Uroporphyrinogen autooxidation

THE USUAL CHEMICAL FINDINGS IN THE PORPHYRIAS*

Porphyria		URINE				FECES			RBC		
		ALA	PBG	URO	COPRO	URO	COPRO	PROTO	URO	COPRO	PROTO
Congenital erythropoietic porphyria		N	N	+++	++-+++	++	+++	N	+++	++	+
Erythropoietic protoporphyria		N	N	N	N	N-++	N-+	N-+++	N	+	+++
Erythropoietic coproporphyria		N	N	N	N		N		+-++	+++	+
Acute intermittent porphyria	Latent	+-+++	+-+++	N-++**	+	+	±	±	N	N	N
	Manifest	++-+++	++-+++	++-+++	+	+-++	+	+	N	N	N
Variegate Porphyria	Latent	N-++	N-++	N-++	+-++	N	+++	+++	N	N	N
	Manifest	++-+++	+-+++	+++	+++	++	+++	+++	N	N	N
Hereditary coproporphyria	Latent	N-++	N-++	N-+	N-++		+-+++	N-+	N	N	N
	Manifest	+++	+++		++-+++		+++	N-+	N	N	N
Cutanea tarda porphyria		N	N	+++	++-+++		±-++	N-+	N	N	N

ALA: δ-Aminolevulinic acid
PBG: Porphobilinogen
URO: Uroporphyrin
COPRO: Coproporphyrin
PROTO: Protoporphyrin
N: Normal excretion
+-+++: Slight to marked increase

*This table is intended to serve only as a general guide to the usual findings in the porphyrias. In some instances, the data are derived from only a few cases. Exceptions to the above chemical patterns occur.

** Some of the uroporphyrin may be formed nonenzymatically by polymerization of PBG.

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See also I, Reference 3.