

Treatment of the Porphyrrias: Mechanisms of Action

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The porphyrias are diseases that result from inherited or acquired abnormalities of porphyrin-heme synthesis in the liver and the bone marrow. Only the hepatic porphyrias are known to be aggravated by exposure to a variety of exogenous drugs and chemicals. Simple avoidance of these agents will reduce the risk of developing hepatic porphyria and may lead to clinical improvement in patients with active disease. Some types of therapy of the hepatic porphyrias are effective because of their ability to modulate the activity of δ -aminolevulinic acid synthetase, the rate-limiting enzyme for heme synthesis. Most of the porphyrias are associated with cutaneous photosensitivity, the treatment of which centers about either reducing the excessive production of porphyrins or of inhibiting the photobiological response to these photosensitizing chemicals in the skin.

Each of the porphyrias represents the clinical expression of diseases that result from abnormalities in the control of heme synthesis due to aberrations in the activities of enzymes in the heme pathway. Both inherited and acquired factors play major roles in the development of these diseases. The clinical manifestations of the porphyrias appear to be due to the toxic properties of porphyrins and porphyrin precursors. In normal individuals these biochemical intermediates are present only in trace amounts and are therefore virtually innocuous. In patients with porphyria, the presence of excessive amounts of these chemicals results in pathologic changes that in turn account for the recognizable clinical features of these diseases.

Rational therapy of the porphyrias requires detailed knowledge of porphyrin-heme biosynthesis and the genetic and environmental factors that influence the activity of this pathway. Ideal therapy of the porphyrias would restore aberrant enzyme activity to normal, thereby reducing the level of the potentially toxic porphyrins and porphyrin precursors to normal. Unfortunately this highly desirable therapeutic endpoint is currently not attainable. While it does appear possible to influence the

activity of certain enzymes in the heme pathway by the administration of certain drugs, no permanent alteration can be achieved with the modalities now available. There are, however, a number of treatments of the various types of porphyria. These range from highly effective modalities such as phlebotomy and chloroquine for porphyria cutanea tarda to marginally effective measures such as photoprotection of the skin. Furthermore, avoidance of exposure to drugs and environmental chemicals that can alter heme pathway enzyme activity may be most helpful in preventing the clinical expression of porphyria.

PORPHYRIAS AS DISORDERS OF THE REGULATION OF HEME SYNTHESIS

The porphyrin-heme pathway is ubiquitous in biological systems. Its activity is carefully regulated such that large amounts of the end-product heme are formed daily whereas pathway intermediates accumulate and are excreted only in trace amounts. It is currently thought that the bone marrow and the liver are the major body compartments in which heme synthesis occurs. Bone marrow heme is needed for daily erythrocyte hemoglobin production and hepatic heme for a variety of heme-proteins with relatively rapid turnover. Since heme cannot be reutilized and is broken down into linear tetrapyrroles that eventuate in bilirubin production, the body must continuously synthesize heme. Heme is required as a prosthetic group by various apoproteins such as globin and apo-cytochrome P-450. As cellular heme binds to these proteins, heme levels diminish. This decrease in cellular heme leads to enhancement of heme synthesis until "normal" levels are restored.

The rate-limiting step for regulating hepatic heme synthesis is the initial enzyme in the pathway, δ -aminolevulinic acid synthetase (ALAS) (Fig 1) [1]. There are several lines of experimental evidence that support the role of mitochondrial ALAS in controlling the rate of heme synthesis. (1) The activity of this enzyme is relatively low compared to that of the other enzymes in the pathway. (2) The half-life of ALAS is relatively short in mammalian liver (60-180 mins). This is considerably less than that of many mitochondrial proteins which have half-lives of 3-5 days. (3) Activity of the enzyme can be induced or enhanced by certain types of drugs and other environmental chemicals as well as selected endogenous substances, particularly steroid hormones and their metabolites. This "enzyme induction" permits the synthesis of larger amounts of heme upon demand particularly for the production of hepatic cytochrome P-450, the heme-protein that is an important component of the microsomal enzyme system that functions in the metabolism of drugs and exogenous chemicals.

The hepatocyte appears to be quite sensitive to heme levels: as heme falls the structural gene coding for ALAS is derepressed. This results in an increased rate of synthesis of this protein. In response to enhanced ALAS activity cellular heme increases. It is utilized for various proteins and also functions as a co-repressor by binding to a putative apo-repressor protein which is capable of repressing the synthesis of ALAS (Fig 2). It is currently thought that only a relatively small fraction of hepatocyte heme (which is not bound to apo-proteins) participates in this regulatory process (the so-called regulatory heme or free heme pool). Certain drugs which are potent inducers of hepatic ALAS may trigger this effect by competing with heme for binding to the aporepressor; furthermore, drugs with pharmacologic effects that result in reduced cellular heme levels will

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Abbreviations:

- AIA: allylisopropylacetamide
- ALA: δ -aminolevulinic acid
- ALAS: δ -aminolevulinic acid synthetase
- COPRO-O: coproporphyrinogen oxidase
- EP: erythropoietic porphyria
- EPP: erythropoietic protoporphyria
- HCP: hereditary coproporphyria
- PBG: porphobilinogen
- PCT: porphyria cutanea tarda
- PROTO: protoporphyrinogen
- PROTO-O: protoporphyrinogen oxidase
- RBC: red blood cell
- TCDD: tetrachlorodibenzo-p-dioxin
- URO: uroporphyrin
- UROD: uroporphyrinogen decarboxylase
- UROS: uroporphyrinogen synthetase
- UROCOS: uroporphyrinogen cosynthetase
- VP: variegate porphyria

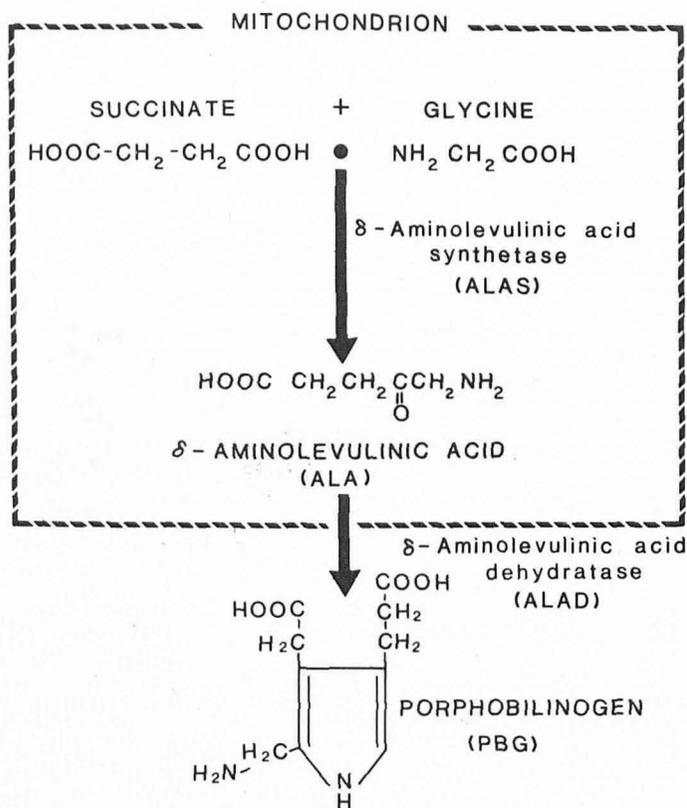


FIG 1. δ -aminolevulinic acid synthetase (ALAS) is the rate-limiting enzyme for heme synthesis.

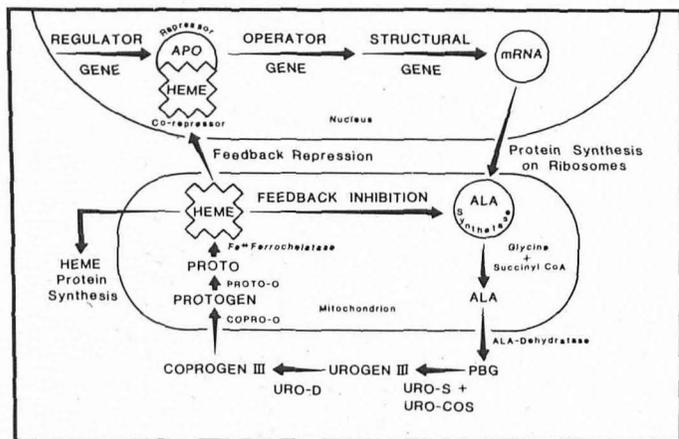


FIG 2. Schematic for hypothetical mechanisms whereby heme synthesis is regulated. Heme may directly inhibit ALAS or may function as a co-repressor to repress the synthesis of ALAS.

also derepress ALAS. This can occur either by enhancing the destruction of existing heme (Fig 3) or by inhibiting the conversion of protoporphyrin to heme (Fig 4) [2,3].

It is important to emphasize that certain of the hepatic porphyrias, the acute hepatic porphyrias (acute intermittent porphyria, variegate porphyria and hereditary coproporphyria), are each characterized by elevated hepatic ALAS activity [4]. It is thought that deficient enzyme activity at one or another of the steps in the porphyrin-heme pathway leads to a decrease in the regulatory or free heme pool. This in turn results in chronic overactivity (derepression) of hepatic ALAS in these patients. Hepatic ALAS may also be slightly increased in porphyria cutanea tarda perhaps due to deficient activity of uroporphyrinogen decarboxylase (UROD) (inherited or acquired), which might also result in diminished heme levels in the liver cell.

Thus in the liver the activity of the heme pathway is largely determined by ALAS which in turn is directly regulated by heme levels within the cell. A variety of inherited or acquired factors may influence heme levels and thus interfere with this normally efficient regulatory scheme. Although most experimental evidence points to a repression-derepression mechanism for controlling hepatic ALAS activity, it is also possible that heme could directly inhibit the enzyme. However, the levels required for direct enzyme inhibition ($\sim 10^{-5}\text{M}$) are unlikely to occur *in vivo*.

The regulation of heme synthesis in the bone marrow is poorly understood but in general ALAS does not appear to be rate-limiting in this tissue. There is experimental evidence to indicate that the activity of several enzymes in the heme pathway increases slightly with accelerated demand for hemoglobin synthesis; furthermore, bone marrow heme pathway enzymes normally function at or near their peak levels and cannot be further stimulated by drugs. Recent studies indicate that in experimental systems, ferrochelatase may become the rate-limiting enzyme for heme synthesis in bone marrow [5].

Since the porphyrias are diseases due either to inherited abnormalities in heme pathway enzymes or to the effects of certain drugs and environmental chemicals on these enzymes, specific treatment should be capable of correcting these aberrations. Furthermore because cutaneous photosensitivity is a major manifestation of the majority of the porphyrias, nonspecific treatment modalities which have no demonstrable effect upon abnormal porphyrin-heme synthesis may nonetheless be beneficial to the patient.

The porphyrias are basically of 2 types: hepatic and erythropoietic. These are listed in Table I. Currently available treatment for each of these will be discussed.

TREATMENT OF THE PORPHYRIAS

Acute Hepatic Porphyrias

The acute hepatic porphyrias include acute intermittent porphyria, variegate porphyria and hereditary coproporphyria. These disorders share 2 fundamental characteristics: (1) elevated hepatic ALAS and (2) deficient activity of specific en-

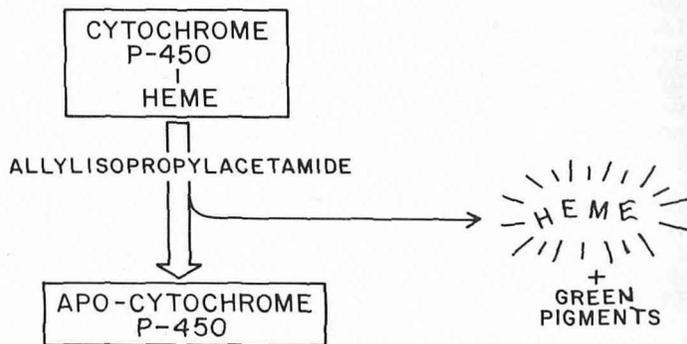


FIG 3. Some drugs may induce hepatic ALAS by destroying heme. This could deplete the regulatory heme pool.

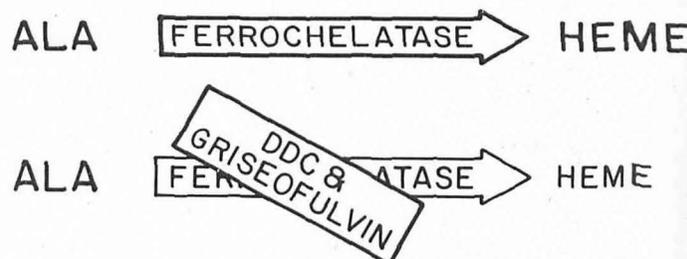


FIG 4. Some drugs may induce hepatic ALAS by blocking heme synthesis. This could deplete the regulatory heme pool.

zyme(s) in the heme pathway. As a result of these individual enzyme defects it has been proposed that regulatory heme levels in the hepatocytes of these patients are low, thereby resulting in elevated ALAS activity [6]. Furthermore it appears that the regulation of heme synthesis in these diseases is abnormal such that there is a particular susceptibility to drugs like the barbiturates which evoke increased heme synthesis by augmenting hepatic cytochrome P-450. Following ingestion of such drugs a cycle of increased demand for heme is coupled with the inability of the liver cell to raise heme levels sufficiently high to restore the regulatory (free) heme pool to normal which would repress ALAS activity.

It is of historical interest that elevated ALAS activity was the first enzyme abnormality identified in patients with acute intermittent porphyria [7,8]. Subsequently, it was shown that there was an inherited deficiency of uroporphyrinogen synthetase (UROS) in patients with this disease and it is thought that this results in diminished heme levels in the liver of these patients coupled with derepression of ALAS [9].

It is currently thought that patients with variegate porphyria have increased hepatic ALAS and decreased ferrochelatase or protoporphyrinogen oxidase (PROTO-O) [10,11]. Patients with hereditary coproporphyrin have increased hepatic ALAS and decreased coproporphyrinogen oxidase (COPRO-O) [12]. In all 3 of the acute hepatic porphyrias, the deficient enzyme activity is inherited in an autosomal dominant pattern. Each of these diseases is characterized by intermittent "attacks" of abdominal pain, autonomic dysfunction, neuropsychiatric symptoms, peripheral neuropathy and paresis. Variegate porphyria and hereditary coproporphyrin are often accompanied by cutaneous photosensitivity. It is important to emphasize that a large number of drugs and steroid hormones and their metabolites appear capable of triggering "attacks" of these diseases (Table II).

The treatment of the acute hepatic porphyrias includes: (1) avoidance of inducer drugs, (2) carbohydrate loading, and (3) hematin infusions.

Avoidance of Inducer Drugs

Drugs which have been incriminated as capable of exacerbating the acute hepatic porphyrias are listed in Table II. The role of these agents has been deduced either from the clinical observation of patients or from studies in experimental systems, primarily the chick embryo liver cell culture system developed by Granick [13]. Avoidance of these drugs will reduce the number of acute attacks of porphyria in many though not all patients. This is simply preventive therapy. Certain patients will suffer repeated attacks of porphyria despite avoiding exposure to these agents. These may be due to hormonal factors, intercurrent infection, starvation, etc. Often a specific etiologic factor for an acute attack cannot be identified in the individual patient.

TABLE I. *The porphyrias*

Erythropoietic	Erythropoietic porphyria Erythropoietic protoporphyria
Hepatic	Acute intermittent porphyria Variegate porphyria Hereditary coproporphyrin Porphyria cutanea tarda

TABLE II. *Drugs that may induce acute attacks of porphyria*

Barbiturates	Sulfonamides
Methyprylone	Dapson
Meprobamate	Griseofulvin
Amidopyrene	Sulfonylureas
Glutethimide	Estrogens
Diphenylhydantoin	Ergot preparations
Mesantoin	

Carbohydrate Loading

It is known that the induction of hepatic ALAS in experimental animals by certain drugs such as allylisopropylacetamide (AIA) is largely abolished by prior carbohydrate feeding of the animal [14]. Furthermore, hepatic ALAS activity decreases in rats fed high doses of carbohydrate. These experimental observations provide a rationale for the use of high doses of carbohydrate in patients suffering from acute attacks of porphyria. Glucose (200–500 grams per day) administered orally or intravenously may be required. A recent study suggested that the use of laevulose (20%) infusions may be helpful [15]. Careful monitoring of urinary ALA and PBG excretion in selected patients has shown a marked decrease after carbohydrate loading suggesting that hepatic ALAS activity has decreased.

The mechanism of the "glucose-effect" is unknown. It was first thought that the elevated carbohydrate generated large amounts of catabolites that could nonspecifically repress protein synthesis in cells. More recently it has been suggested that high carbohydrate levels in the cell may block messenger RNA or may interfere in some way with the induction effects of steroid hormones on hepatic ALAS [16,17].

Hematin Infusions

The rationale for the administration of heme lies in the ability of this substance to both repress the synthesis of ALAS and to directly inhibit the enzyme [18,19]. Hematin is prepared by crystallizing and recrystallizing hemin which is dissolved in 0.25% Na₂CO₃ [20]. Watson et al administered hematin as an intravenous infusion in physiologic saline (3–5 mg/kg) once or twice daily. The compound is given in a bolus over 30–60 min. Prompt and dramatic recovery has been reported following hematin infusions in 2 series of 20 and 11 patients [21,22]. This was accompanied by a rapid decrease in urinary ALA and PBG. Studies have also shown that elevated leukocyte ALAS decreased following hematin infusions [23]. This method of treatment appears to be effective by making heme accessible to liver cells which results in repression and/or inhibition of ALAS activity.

It should be pointed out that hematin infusions are only effective in ameliorating the neuropsychiatric manifestations of the acute hepatic porphyrias. No evaluation of the efficacy of this modality on the photocutaneous syndrome of VP and HCP is currently available.

Porphyria Cutanea Tarda (PCT)

Porphyria cutanea tarda is a different form of hepatic porphyria in which acute attacks do not occur. This disease occurs primarily in middle-aged individuals (male \approx female) and is frequently associated with the ingestion of drugs, such as alcohol and estrogens or exposure to environmental chemicals, particularly selected halogenated hydrocarbons.

There now appear to be two major types of PCT: (1) inherited and (2) acquired or sporadic. In the inherited type, there is deficient activity of UROD [24]. This is transmitted as an autosomal dominant trait and deficient UROD activity has been detected in both the liver and in red blood cells of these patients. A second type of porphyria cutanea tarda, the acquired or sporadic type, is indistinguishable clinically from the inherited type. However, deficient UROD activity may only be detectable in the liver of these patients [25]. Felsher, Norris, and Shih have shown that UROD is deficient in the red blood cells of patients with the sporadic type [26]. The reason for these different findings could relate to differences in the methodology used to measure the enzyme. Further studies are clearly needed to explain these apparent differences in enzymatic activities.

The role of alcohol, estrogens, hexachlorobenzene and other chlorinated hydrocarbons in the clinical expression of PCT is well documented [27]. Furthermore, there is good evidence that PCT is usually accompanied by iron overload in the liver. The mechanism of the iron overload is unclear and the excessive

hepatic iron may result in diminished activity of hepatic uroporphyrinogen cosynthetase (UROCOS) and UROD [28,29]. The former would explain the predominance of I-isomer porphyrin excretion and the latter could explain the elevated URO and 7-carboxyl porphyrins characteristic of the disease.

Treatment of experimental animals with chlorinated hydrocarbons such as hexachlorobenzene and tetrachlorodibenzo-p-dioxin (TCDD) causes inhibition of hepatic UROD after a latent period of several weeks [30]. Iron may also play a permissive role in the inhibitory effect of selected halogenated hydrocarbons on hepatic UROD (Fig 5) [31]. In addition recent studies indicate that iron-depleted mice are resistant to the porphyrinogenic effect of tetrachlorodibenzo-p-dioxin (TCDD) the most potent porphyrinogen yet identified [32]. These data all support a fundamental role for iron in the clinical and biochemical expression of PCT. Treatment measures for PCT include: (1) avoidance of exposure to drugs and chemicals that elicit the disease, (2) phlebotomy, (3) the antimalarial drugs, chloroquine and hydroxychloroquine, (4) metabolic alkalization, and (5) iron chelation.

The simple avoidance of alcohol, estrogens and exposure to chlorinated hydrocarbons will result in clinical and biochemical remission of PCT. However, this usually requires years.

Phlebotomy is the treatment of choice for PCT. This modality was first shown to be effective in PCT by Ippen [33]. Numerous reports from throughout the world have subsequently verified the efficacy of this modality in PCT [34-36]. The rationale, though never proven directly, rests upon certain critical observations: (1) hepatic siderosis frequently improves following phlebotomy therapy, and (2) readministration of iron to phlebotomy-treated patients results in clinical and biochemical exacerbation of the disease [37].

Phlebotomy therapy can be performed in the physician's office. In general, it has been the experience of most investigators that the removal of 2 to 4 liters of blood is required. This can be done at biweekly intervals (~500 ml per phlebotomy). The hemoglobin is monitored until it falls to 10-11 gm%. This is quite variable in the individual patient and recently it has been suggested that monitoring serum ferritin may be the best guide for assessing activity of the disease [38]. This observation requires confirmation.

The response of PCT to phlebotomy is usually highly satisfactory in most patients. Clinical remission does not occur for 6-9 mos and biochemical remission may not be complete for 12-24 mo (Fig 6). The response to therapy varies in individual patients. As shown in Fig 7 and 8, a single course of phlebotomy may bring about a long-term remission of the disease whereas repeated courses of phlebotomy may be required in selected patients. In the latter situation careful evaluation may reveal that the patient has not adhered to avoidance of exposure to porphyrinogenic agents, particularly alcohol. Extensive clinical experience with phlebotomy indicates that this treatment is safe, well-tolerated and effective in the vast majority of patients with PCT.

Treatment with the antimalarial drugs chloroquine and hydroxychloroquine is a satisfactory alternative in selected patients with PCT. Chloroquine is an antimalarial agent that was initially thought to evoke acute attacks of porphyria, since its

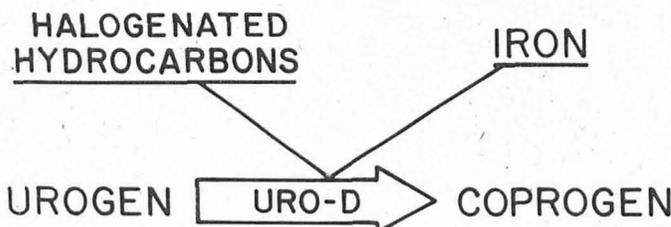


FIG 5. Iron is capable of enhancing the inhibitory effect of chlorinated hydrocarbons on UROD.

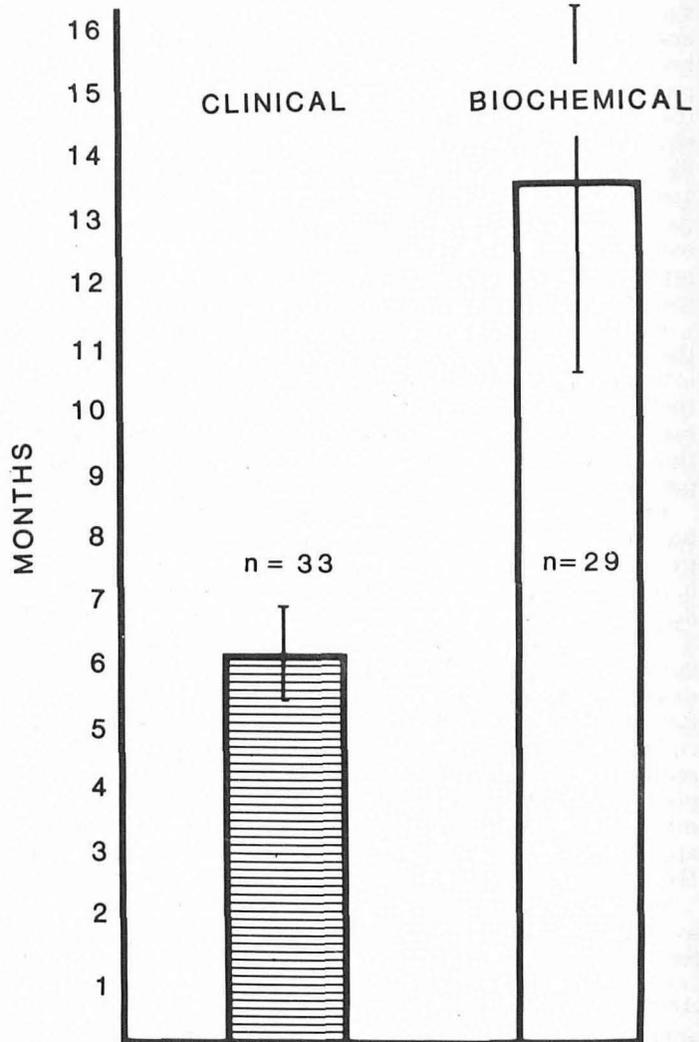


FIG 6. Clinical and biochemical remission of PCT following phlebotomy therapy is usually delayed.

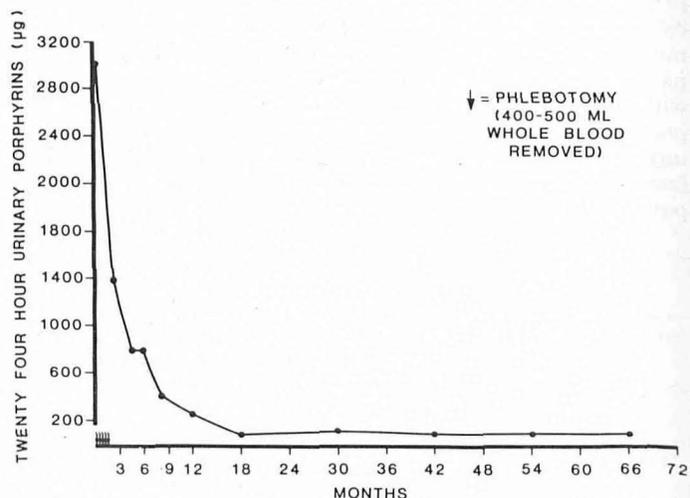


FIG 7. The clinical response of PCT to phlebotomy may be rapid with prolonged remission.

administration was followed by "attacks" of nausea, vomiting, abdominal pain, and biochemical evidence of severe hepatocellular necrosis [39]. It has subsequently been shown that chloroquine does not exacerbate acute hepatic porphyria; rather

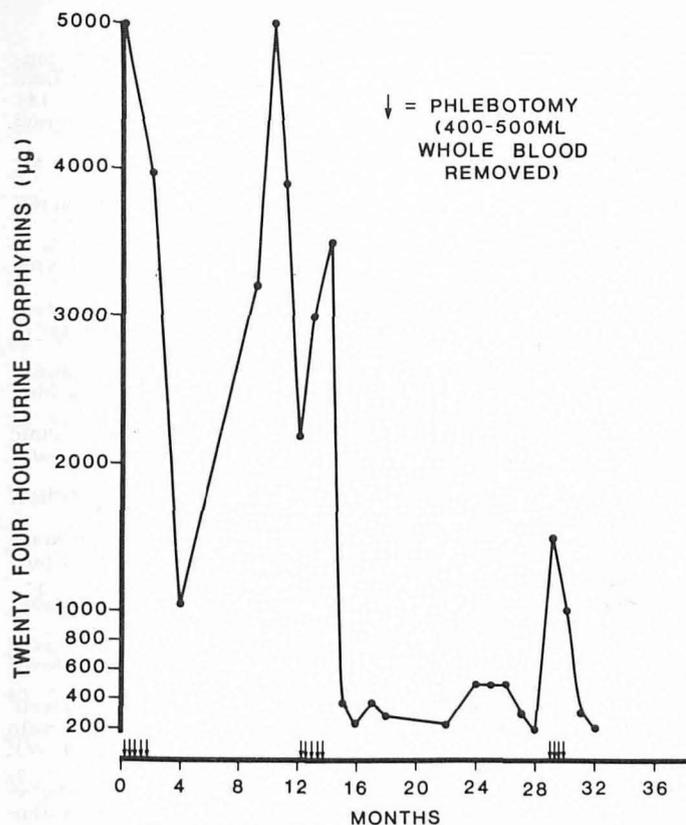


FIG 8. The clinical response of PCT to repeated courses of phlebotomy is shown here.

the drug causes a selective type of hepatotoxicity in PCT [40]. This selective toxic effect is due to binding of the drug to the elevated porphyrins in the hepatocyte forming a porphyrin-chloroquine complex [41]. This complex is highly water soluble and is rapidly "flushed" from the liver resulting in massive increases in urinary porphyrin excretion. It has also been suggested that the mechanism of chloroquine action for PCT is the drug associated removal of iron [42]. Initially it was felt that the hepatotoxic reaction was necessary for the therapeutic effect. It is now clear however that low-doses of the drug (125 mg) administered intermittently (twice weekly) will bring about remission of the disease lasting months to years without hepatotoxicity [43,44].

The onset of remission of PCT induced by the antimalarial drugs is generally similar to that evoked by phlebotomy. However, there is a dose-response relationship in that higher initial doses of these drugs do result in a more rapid onset of clinical and biochemical remission. The length of remission may be shorter than that associated with phlebotomy. Malkinson and Levitt treated 6 patients with PCT using hydroxychloroquine [45]. Initial doses were 100 mg 3 times weekly for 1 mo, then 200 mg 3 times weekly for 1 mo and then 200 mg daily. Thereafter the daily dose was increased to 300 mg or 400 mg depending upon the clinical and biochemical response. Treatment periods ranged from 5 to 13 mo and both clinical and biochemical remission occurred. Four of 6 patients in remission followed for 9 to 24 mo had relapses. Three of the 4 were again retreated with hydroxychloroquine and again improved or went into remission. It was concluded that prolonged remissions may not occur in PCT patients treated with the antimalarial drugs. It is important to emphasize, however, that these patients were not instructed to discontinue alcohol ingestion.

It has also been suggested that the combination of phlebotomy and chloroquine is effective in PCT and that phlebotomy prior to chloroquine administration reduces the risk of hepatotoxicity of the latter [46].

Metabolic Alkalinization

This method of treating PCT is based upon the difference in pK of coproporphyrin and uroporphyrin [46]. It has not been uniformly successful and is not in current use.

Iron Chelation

While theoretically desirable, the use of iron chelators has not been satisfactory [47]. The requirement for repeated painful injections of desferrioxamine has greatly limited its use particularly since other highly effective modalities such as phlebotomy and the antimalarial drugs are available. It is entirely possible that newly developed less toxic iron chelators could offer an effective approach to the treatment of PCT.

Erythropoietic Porphyria (EP)—(Günther's Disease)

This is a rare type of porphyria characterized by mutilating cutaneous photosensitivity and abnormal porphyrin-heme synthesis in the bone marrow. This disease usually is manifest early in life as severe photosensitivity with red-stained fluorescent teeth (erythrodontia) and reddish discoloration of the urine. The photosensitivity is associated with hypertrichosis combined with scarring. Repeated episodes of cutaneous photosensitivity result in sclerotic changes in light-exposed skin that may resemble scleroderma.

In addition to photosensitivity, many patients suffer from hemolytic anemia. Circulating "erythroblasts" are rich in porphyrins and therefore, highly fluorescent RBC's are detectable. The life span of the erythrocyte is frequently shortened and splenomegaly often develops. Whether the hemolytic anemia is due to "photo-hemolysis" of circulating porphyrin-laden erythrocytes remains controversial [48].

The enzymatic abnormality in EP is unclear. Romeo and Levin have shown that UROSC activity is decreased to 1/3 to 1/10 of the normal level in patients with EP [49]. Others have shown that there is a general increase in the activity of several heme pathway enzymes in EP [50]. This has led to the hypothesis that the primary control of heme biosynthesis in EP is at the level of ALAS with a secondary control point at the level of UROSC. Further studies are needed to clarify the specific enzyme defect(s) in EP.

The treatment of EP remains unsatisfactory. Splenectomy in patients with hemolytic anemia and splenomegaly is said to be helpful in diminishing hemolysis and thereby perhaps reducing the circulating porphyrin load [51]. Chloroquine administration (125 mg twice weekly) has been advocated as a method to improve erythrocyte fragility and thereby diminish hemolysis [52]. Shielding in light-opaque celluloid is said to reduce cutaneous photosensitivity [53]. Hematin infusions have been utilized with partial reduction of porphyrin production in a single patient [54]. No long-term studies have been performed to evaluate the usefulness of this modality. Metabolic alkalinization was attempted in 2 patients without success [55].

Erythropoietic Protoporphyrin (EPP)

This is one of the more common types of porphyria and is characterized by a milder form of cutaneous photosensitivity than that seen in EP. The disease usually begins in early childhood and the primary complaint often is that of stinging, burning and swelling of the skin during or shortly after sun exposure [56]. Repeated episodes result in wax-like linear scars on the bridge of the nose and on the bony prominences of the hands. Histopathologic examination of the skin from these areas shows massive amounts of PAS-positive material in and around the vessels of the upper dermis. In most patients cutaneous photosensitivity is the sole clinical manifestation of the disease [56].

Cholelithiasis occurs more frequently than in the normal population and the stones are rich in PROTO [57]. A minority of patients have developed liver disease which may progress

inexorably to terminal hepatic failure [58]. The mechanism of this fatal complication is unclear.

Defective activity of ferrochelatase has been identified in bone marrow, liver, cultured skin fibroblasts, nucleated red cells and mitogen stimulated lymphocytes of patients with EPP [59].

It is important to point out that elevated erythrocyte PROTO is not unique to EPP. In both lead poisoning and in severe iron-deficiency anemia, elevated levels of PROTO also occur and yet no cutaneous photosensitivity develops. This has been explained by chemical differences in the PROTO in EPP as compared to that in lead poisoning and iron-deficiency anemia [60]. In the latter 2 disorders, the excessive RBC PROTO is chelated with zinc and is apparently unable to diffuse out of the red cell. In EPP, the excessive PROTO is unchelated or free and is capable of diffusing from the red cell into the plasma and ultimately into cutaneous tissue where it can absorb solar energy and result in cutaneous photosensitivity.

The treatment of EPP centers about management of the cutaneous photosensitivity and the hepatic failure that may occur in a small number of patients with this disease. The single effective treatment currently available for the cutaneous photosensitivity in EPP is beta-carotene.

Orally administered beta-carotene has improved cutaneous photosensitivity in 84% of 133 patients [61]. This was assessed by determining the ability of patients to tolerate sun exposure before and after treatment with beta-carotene. The drug is available in 30 mg capsules (Solatene) which are usually administered in doses of 60 to 180 mg/day. Toxic reactions have been limited to transient loose stools and to carotenodermia, a yellow-orange discoloration of the skin due to cutaneous deposition of the drug.

The mechanism of action of beta-carotene in EPP is controversial. Photo-excited PROTO is in the triplet state and may destroy cellular components directly or react with oxygen to form singlet oxygen which can oxidize lipid-rich membranes in the cell. This in turn could result in the release of lysosomal hydrolases that would produce tissue damage. Beta-carotene is known to quench free radicals and singlet oxygen [62]. Whether these effects have any relationship to the clinical improvement of photosensitivity seen in most patients with EPP is unknown.

It is of interest that beta-carotene apparently does not reduce the erythrocyte PROTO levels in EPP. In fact it has been shown that RBC PROTO actually increases slightly in patients receiving beta-carotene [63]. The drug is known to protect against erythrocyte lysis by PROTO *in vitro* [64]. It is also possible that leakage of PROTO may be prevented by beta-carotene. This might result in less diffusion of RBC PROTO into the skin, thereby reducing the severity of the cutaneous photosensitivity. It should be pointed out that one clinical study concluded that beta-carotene was ineffective in preventing photosensitivity in EPP [65].

At least 15 cases of terminal hepatic failure in patients with EPP have been reported [59]. The liver disease is characterized by direct hyperbilirubinemia and mild-to-moderate increases in transaminase and alkaline phosphatase. Liver biopsy demonstrates cirrhosis with massive deposits of dark brown pigment which may be precipitated PROTO.

The treatment of hepatic disease in EPP is directed at depleting the excessive PROTO stores in the liver by interrupting the enterohepatic circulation of the porphyrin. Cholestyramine, a nonabsorbed binder of anions, has been used for this purpose. One patient was treated with cholestyramine (12 gm/day in divided doses) and the antioxidant vitamin E (100 units daily) [59]. Over a period of 11 mos plasma PROTO decreased and liver function tests returned to normal. Liver biopsy also showed a reduction in cellular necrosis and inflammation though cirrhosis persisted. Pigment deposition also diminished. This treatment should be attempted in additional patients.

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