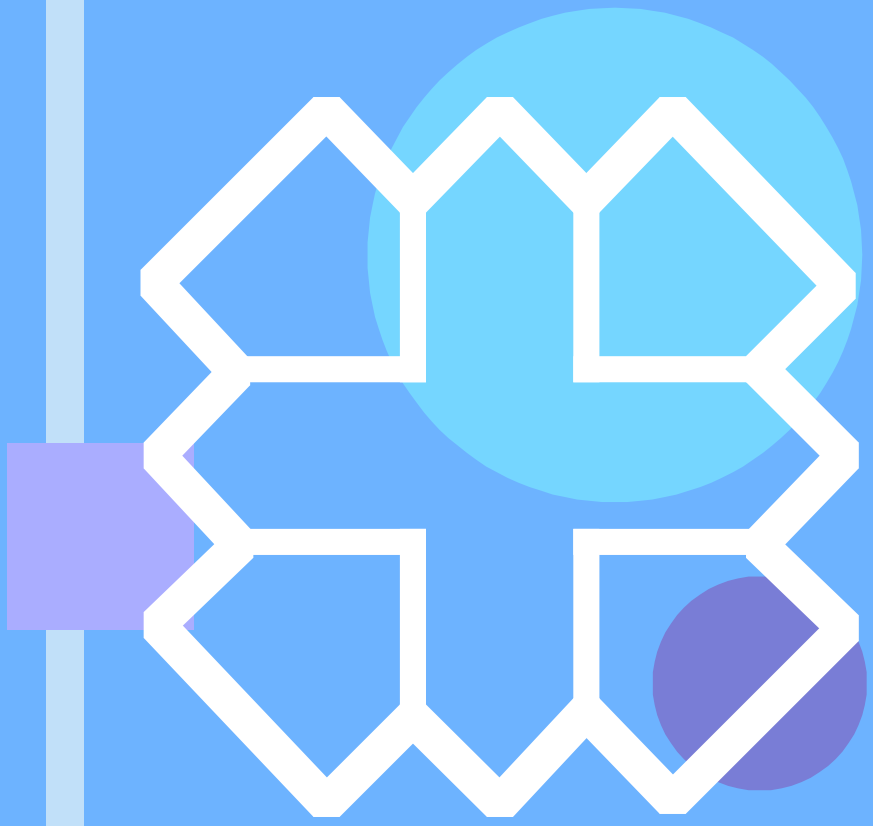
Porphyria Disease Management



American Porphyria Foundation

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Panhematin® (hemin for injection)

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About Porphyria

Porphyria is not a single disease but a group of at least eight disorders that differ considerably from each other. A common feature in all porphyrias is the accumulation in the body of "porphyrins" or "porphyrin precursors." Although these are normal body chemicals, they normally do not accumulate. Precisely which of these chemicals builds up depends upon the type of porphyria.

The clinical manifestations of the different types of porphyria are not the same. Forms of treatment also depend on the type of porphyria. Therefore, it is difficult to make general statements that apply to all these disorders.

The symptoms arise mostly from effects on the nervous system or the skin. Effects on the nervous system occur in the acute porphyrias. Proper diagnosis is often delayed because the symptoms are nonspecific. Skin manifestations can include burning, blistering, and scarring of sun-exposed areas.

The terms "porphyrin" and "porphyria" are derived from the Greek word "porphyrus" meaning purple. Urine from some porphyria patients may be reddish in color due to the presence of excess porphyrins and related substances in the urine, and the urine may darken after exposure to light.

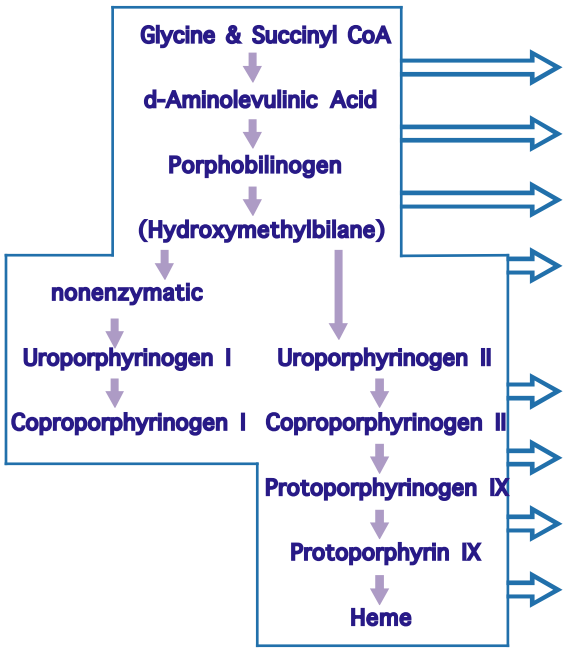
Q: How does one get porphyria?

A: In each type of porphyria, there is a deficiency of a specific "enzyme." These enzymes are involved in the synthesis of "heme," a substance important to many body functions and found in largest amounts in the bone marrow, red blood cells, and the liver. Heme exists as hemoglobin in the bone marrow and red blood cells but has other functions in other tissues such as the liver. The type of porphyria present is determined by which enzyme is deficient. These enzyme deficiencies usually are inherited. Environmental factors, such as drugs, chemicals, diet, and sun exposure can, depending on the type of porphyria, greatly influence the severity of symptoms.

The inherited porphyrias are either autosomal dominant (inherited from one parent) or autosomal recessive (inherited from both parents). "Autosomal" genes always occur in pairs, with one coming from each parent. Individuals with an autosomal dominant form of porphyria have one abnormal gene paired with a normal one, and half of their offspring (on the average) will inherit the gene for the disease, while the other half will inherit the normal gene. Some of those who inherit the abnormal gene will develop symptoms. Individuals with an autosomal recessive type of porphyria have a pair of abnormal genes, and each of their children will inherit one abnormal gene for that disease, which will be paired with a normal gene from the other parent, and there will be no symptoms. If two carriers of the same abnormal recessive gene have children, approximately one fourth of their offspring will inherit two abnormal genes, and these children will develop symptoms of the disease. Because all porphyrias are uncommon, it is very unlikely that more than one type will occur in the same family, or that someone with one type of porphyria will go on to develop another.

Q: How are the porphyrias classified?

A: The best way to classify a case of porphyria is to determine which enzyme is deficient. The enzymes that are deficient in the porphyrias normally act in sequence to make heme from simpler molecules. Heme is a vital substance for all body organs and consists of an iron atom surrounded by a porphyrin molecule. The sequence of enzymes and intermediates in the pathway to produce heme is shown in the diagram.



ENZYME	DISEASE
d-Aminolevulinic Acid Synthase	
a-Aminolevulinic Acid Dehydratase	ALAD Porphyria
Porphobilinogen Deaminase	Acute Intermittent Porphyria
Uroporphyrinogen III Cosynthase	Congenital Erythropoietic Porphyria
Uroporphyrinogen Decarboxylase	Porphyria Cutanea Tarda, Hepatoerythropoietic Porphyri
Coproporphyrinogen Oxidase	Hereditary Coproporphyria
Protoporphyrinogen Oxidase	Variegate Porphyria
Ferrochelatase	Erythropoietic Protoporphyria

As shown, each of the eight types of porphyria is associated with a deficiency of one of these enzymes.

Sometimes, other classifications are useful. For example, the porphyrias often are divided into two groups, the "hepatic" and "erythropoietic" types. Porphyrias with skin manifestations sometimes are called "cutaneous porphyrias." The "acute porphyrias" are those characterized by attacks of pain and other neurological manifestations. These "acute" symptoms can be both rapidly appearing and severe. An individual may be considered "latent" if he or she has the required enzyme deficiency but has never developed symptoms. There can be a wide spectrum of severity between the "latent" and "active" cases of any particular type of porphyria.

Q: What treatment and prevention are available?

A: Treatment depends greatly on the type of porphyria and can be quite successful. Preventive measures, which include avoidance of certain drugs and alcohol, are also important in those who are identified as having inherited porphyria, even if they have never had symptoms.

Asymptomatic carriers as well as patients who have symptoms should be educated about preventive measures.

Q: Is porphyria progressive or lethal?

A: Unlike some genetic diseases in which all individuals who inherit an abnormal gene become ill, the severity of porphyria varies considerably. Such variability is due to certain "additional factors" other than the gene itself. Consequently, risks of severe medical difficulties or even death in the "acute" porphyrias are often diminished when affected individuals are well informed of their diagnoses and adopt suggested precautionary measures. Even with modern treatment and prevention, some patients still have repeated attacks. However, progressive deterioration and death from paralysis in the "acute" porphyrias are very unusual.

Q: Is sunlight always harmful?

A: Sun sensitivity can occur in all but two types of porphyria. The degree of sensitivity to sunlight varies considerably. Patients with sun sensitivity have high levels of porphyrins in the blood plasma which, depending on the type of porphyria, have originated from the liver or the bone marrow. Ultraviolet light interacts with porphyrins in such a way as to damage skin tissue. Some treatments may help patients tolerate sun exposure even without lowering porphyrin levels. In some cases, treatment can lower porphyrin levels, and sunlight can be tolerated.

Q: Should doctors be informed that an individual has porphyria, even if it is latent?

A: Yes! The diagnosis of porphyria is always an important item of medical information, even when there are no symptoms. It may, for example, influence the choice of drugs to treat other conditions, the choice of anesthesia for surgery, or dietary recommendations.

Q: Does surgery or pregnancy pose additional risks?

A: Again, this depends on the type of porphyria. Surgery may increase the risk of an attack of the "acute" porphyrias. This risk can be greatly reduced if certain precautions are taken. Your surgeon and/or anesthesiologist may wish to consult a porphyria expert prior to hospitalization for surgery. Such consultation may also be helpful during pregnancy. Although attacks of "acute" porphyria can occur during pregnancy, the risk appears to be less than was formerly believed. Treatment of acute attacks during pregnancy is quite feasible.

Q: What drugs are safe and unsafe?

A: The following are only partial lists of drugs that are potentially dangerous and probably safe in: Acute Intermittent Porphyria, Variegate Porphyria, Hereditary Coproporphyria and ALAD-Porphyria.

Harmful Drugs
The following is a partial list of drugs that are potentially dangerous.

- Barbiturates
- Sulfonamide antibiotics
- Many other tranquilizers and sedatives (e.g., meprobamate, methyprylon, glutethimide)
- Griseofulvin
- Anti-epilepsy drugs (phenytoin, etc.)
- Birth control pills
- Alcohol
- Ergots
- Metoclopramide
- Rifampin
- Diclofenac
- Danazol

Safe Drugs
The following is a partial list of drugs that are probably safe.

- Narcotic analgesics (morphine, meperidine, codeine, etc.)
- Aspirin & acetaminophen
- Phenothiazines (e.g., chlorpromazine)
- Penicillin and derivatives
- Chloral hydrate
- Streptomycin
- Glucocorticoids
- Bromides
- Insulin
- Atropine
- Cimetidine
- Serotonin reuptake inhibitor (antidepressants)

Recommendations about drugs for these porphyrias are based on experience with the porphyria patients in whom attacks have been caused by drugs and by tests in animals that have experimental porphyria. Since most commonly used drugs have not been tested, they should be avoided if at all possible. If a question of drug safety arises, a physician or medical center specializing in porphyria should be contacted. A list of these institutions may be procured from this foundation.

Q: What diagnostic tests are available?

A: There are many laboratory tests available for porphyrias, and it is often difficult to decide which should be chosen. Many of these tests are expensive. The results are often difficult to interpret. The tests vary in sensitivity and specificity. If a test is sensitive, it is unlikely to be falsely negative (i.e., fail to diagnose porphyria in a patient who has the disease). If a test is specific, it is unlikely to be falsely positive (i.e., diagnose porphyria in a patient who does not have porphyria). Certain tests are both sensitive and specific in patients who have symptoms that are suggestive of porphyria. When abdominal and neurological symptoms suggest an acute porphyria, the best screening tests are urinary ALA and PBG. When there are cutaneous symptoms that suggest porphyria, the best screening test is a plasma porphyrin determination. If one of these screening tests is abnormal, more extensive testing, including urinary, fecal and red blood cell porphyrins, are then indicated. Urinary, fecal, and red blood cell porphyrin

measurements are not very useful for initial screening, because they lack either sensitivity or specificity and, therefore, are often difficult to interpret. Measurement of heme biosynthetic enzymes in red blood cells or lymphocytes is not appropriate for screening, unless it is part of a family study that is done after someone in the family is already known to have a particular enzyme deficiency. It is advisable to have testing performed by a laboratory that has expertise in the clinical aspects of porphyria and can provide a valid interpretation of the test results.

If testing has been performed in laboratories other than porphyria laboratories, consultation with a porphyria expert is advised before a final diagnosis of acute porphyrias is accepted.

Types of Porphyria

ALAD Porphyria (ADP)

This form of porphyria is inherited as an autosomal recessive trait and seems to be extremely rare. The symptoms are very similar to acute intermittent porphyria. There is a deficiency of the enzyme delta-aminolevulinic acid dehydratase (ALAD) and increased excretion of delta-aminolevulinic acid (ALA) in the urine.

Acute Intermittent Porphyria (AIP)

This is one of the hereditary hepatic porphyrias. Its inheritance is autosomal dominant. The deficient enzyme is porphobilinogen deaminase (PBGD), also known as hydroxymethylbilane synthase. This enzyme was formerly known as uroporphyrinogen I-synthase, and this term is still used by some clinical laboratories. A deficiency of PBGD is not sufficient by itself to produce AIP, and other activating factors must also be present. These include hormones, drugs and dietary changes. Sometimes, activating factors cannot be identified.

Symptoms
Most people who inherit the gene for AIP never develop symptoms. AIP manifests after puberty, especially in women (due to hormonal influences). Symptoms usually occur as attacks that develop over several hours or days. Abdominal pain, which can be severe, is the most common symptom. Others may include:

- nausea
- vomiting
- constipation
- pain in the back, arms and legs
- muscle weakness (due to effects on nerves supplying the muscles)
- urinary retention
- palpitation (due to a rapid heart rate and often accompanied by increased blood pressure)
- confusion, hallucinations and seizures

Sometimes the level of salt (sodium and chloride) in the blood decreases markedly and contributes to some of these symptoms. The skin is not affected.

Diagnosis
Because this disease is rare and can mimic a host of other more common conditions, its presence is often not suspected. On the other hand, the diagnosis of AIP and other types of porphyria is sometimes made incorrectly in patients who do not have porphyria at all, particularly if laboratory tests are improperly done or misinterpreted. The finding of increased levels of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) in urine establishes that one of the acute porphyrias is present. If PBGD is deficient in normal red blood cells then the diagnosis of AIP is established. However, measuring PBGD in red blood cells should not be relied upon by itself to exclude AIP in a sick patient, because the enzyme is not deficient in red blood cells of all AIP patients.

If it is known that someone in a family has AIP and their enzyme value is low in red blood cells, other family members who have inherited a deficiency of PBGD can be identified by measuring the enzyme in their red blood cells. Latent cases so identified can avoid agents known to cause attacks. However, in some AIP families, PBGD is normal in red blood cells and is deficient only in the liver and other tissues. Falsely low values sometimes occur due to problems with collecting and transporting the sample.

DNA is the material in cells that encodes all the genetic information of an individual. Many different mutations have been identified in the portion of DNA that comprises the gene for PBGD. Almost every family with AIP has a different mutation in this gene. Within one family, however, everyone who inherits a deficiency of PBGD has the same mutation. It is advantageous to know the precise mutation in a family, because that knowledge enables the identification of AIP gene carriers by DNA testing. This approach is much more precise than measuring PBGD enzyme activity in red blood cells. At present, DNA testing for AIP and other porphyrias is available only through a few research laboratories.

Treatment and Prognosis

Hospitalization is often necessary for acute attacks. Medications for pain, nausea and vomiting, and close observation are generally required.

A high intake of glucose or other carbohydrates can help suppress disease activity and can be given by vein or by mouth. Intravenous heme therapy is more potent in suppressing disease activity. It can be started after a trial of glucose therapy. However, the response to heme therapy is best if started early in an attack. Therefore, delaying heme therapy until glucose alone has not been effective may not be warranted unless an attack is mild.

Heme must be administered by vein. Panhematin®, from Ovation Pharmaceuticals, Inc., is the only commercially available heme therapy for treatment and prevention of acute porphyric attacks in the United States. Please refer to **Section 4: Panhematin** for more information.

During treatment of an attack, attention should be given to salt and water balance. Harmful drugs should be stopped. These include barbiturates, sulfonamides, and many others. Attacks are often precipitated by low intake of carbohydrates and calories in an attempt to lose weight. Thus dietary counseling is very important (see below). Premenstrual attacks often resolve quickly with the onset of menses; hormone manipulations may prevent such attacks.

AIP is particularly dangerous if the diagnosis has not been made and if harmful drugs are administered. The prognosis is usually good if the disease is recognized and if treatment and preventive measures are begun before severe nerve damage has occurred. Although symptoms usually resolve after an attack, some patients develop chronic pain. Nerve damage and associated muscle weakness can improve over a period of months or longer after a severe attack. Mental symptoms may occur during attacks, but are usually not chronic.

Wearing a Medic Alert bracelet is advisable for patients who have had attacks but is probably not warranted in most latent cases. It should be remembered that AIP patients can develop other diseases, and symptoms may not always be due to porphyria.

Diet
AIP patients prone to attacks should eat a normal or high carbohydrate diet and should not greatly restrict their intakes of carbohydrate and calories, even for short periods of time. If weight loss is desired, it is advisable to consult a physician who may then request that a dietitian estimate an individual's normal caloric intake, which varies greatly from one person to another. Then it may be appropriate to prescribe a diet that is approximately 10% below the normal level of calories for the patient. This should result in a gradual weight loss and usually will not cause an attack of porphyria.

Having Children
Pregnancy is tolerated much better than was formerly believed. Offspring have a 50% chance of inheriting the gene for AIP, but the great majority of them remain "latent" for all or most of their lifetimes. The minority that eventually have symptoms usually benefit from treatment. Given these considerations, most patients or individuals with "latent" porphyria elect to have children for the same reasons as anyone else.

Congenital Erythropoietic Porphyria (CEP)

This disease is extremely rare and is autosomal recessive. It is also known as Gunther's disease. The deficient enzyme is uroporphyrinogen III cosynthase (or uroporphyrinogen III synthase). Various mutations in the gene for this enzyme have been identified in different families. As is characteristic of the erythropoietic porphyrias, symptoms begin during infancy. Sometimes CEP is recognized as a cause of anemia in a fetus before birth. In less severe cases symptoms may begin during adult life. Porphyrins are markedly increased in bone marrow, red blood cells, plasma, urine and feces. Porphyrins are also deposited in the teeth and bones.

Symptoms
Skin photosensitivity may be extreme and lead to blistering, severe scarring and increased hair growth. Bacteria may infect the damaged skin. Facial features and fingers may be lost through phototoxic damage as well as infection. Red blood cells have a shortened life span, and anemia often results. Synthesis of heme and hemoglobin is actually increased to compensate for the shortened red blood cell survival.

Treatment and Prognosis
Blood transfusions and perhaps removing the spleen may reduce porphyrin production by the bone marrow. Activated charcoal given by mouth is sometimes effective. Bone Marrow Transplantation has been very effective in some patients. Stem cell transplantation and gene therapy may also be an option in the future.

Porphyria Cutanea Tarda (PCT)

This disease is the most common of the porphyrias and results from a deficiency of the enzyme, uroporphyrinogen decarboxylase (UROD). PCT is essentially an acquired disease, but some individuals have a genetic (autosomal dominant) deficiency of UROD that contributes to its development. These individuals are referred to as having "familial PCT". Most individuals with

the inherited enzyme deficiency remain latent and never have symptoms.

PCT is one of the hepatic porphyrias. Large amounts of porphyrins build up in the liver when the disease is becoming active. The disease becomes active when acquired factors, such as iron, alcohol, hepatitis C virus (HCV), HIV,estrogens (used, for example, in oral contraceptives and prostate cancer treatment) and possibly smoking, combine to cause a deficiency of UROD in the liver. Hemochromatosis, an iron overload disorder, also can predispose individuals to PCT.

Symptoms
The symptoms in PCT are confined mostly to the skin. Blisters develop on sun-exposed areas of the skin, such as the hands and face. The skin in these areas may blister or peel after minor trauma. Increased hair growth, as well as darkening and thickening of the skin may also occur. Neurological and abdominal symptoms are not characteristic of PCT.

Liver function abnormalities are common but are usually mild. These sometimes progress to cirrhosis and even liver cancer. PCT is often associated with hepatitis C infection, which also can cause these liver complications. However, liver tests are generally abnormal even in PCT patients without hepatitis C infection.

Diagnosis
The preferred screening test for PCT is a measurement of porphyrins in plasma. This can differentiate PCT from variegate porphyria. The patterns of porphyrins in urine (predominately uroporphyrin and 7-carboxylate porphyrin) and feces (predominately isocoproporphyrin) help to confirm the diagnosis. The presence of an inherited deficiency of UROD can be demonstrated by measuring the enzyme in red blood cells and is present in about 20% of patients with PCT

Treatment and Prognosis
PCT is the most treatable of the porphyrias. Treatment seems to be equally effective in familial and non-familial PCT. Factors that tend to activate the disease should be removed. The most widely recommended treatment is a schedule of repeated phlebotomies (removal of blood), with the aim of reducing iron in the liver. This actually reduces iron stores throughout the body. Usually, removal of only 5 to 6 pints of blood (one pint every one to two weeks) is sufficient, which indicates that iron stores are not excessively increased in most PCT patients. The best guides to response are measurements of serum ferritin and plasma porphyrins. Phlebotomies are stopped when the ferritin falls to -~20ng/ml. Another treatment approach is a regimen of low doses of either chloroquine (125mg twice weekly) or hydroxychloroquine (100mg twice weekly). Usual dosages of these drugs should not be used because they can cause transient but sometimes severe liver damage and worsening of photosensitivity in PCT patients. Recurrences can be treated in the same manner. But PCT usually does not recur after treatment. It is not necessary to continue phlebotomies after a remission has been achieved.

Hepatoerythropoietic Porphyria (HEP)

This very rare type of porphyria is also due to a deficiency of uroporphyrinogen decarboxylase. The enzyme deficiency is inherited as an autosomal recessive trait. The manifestations of HEP resemble CEP, with symptoms of skin blistering usually beginning in infancy. Porphyrins are

increased in bone marrow and red blood cells, in contrast to PCT, as well as liver, plasma, urine and feces.

Hereditary Coproporphyria (HCP)

This is an autosomal dominant form of hepatic porphyria that is similar to AIP, except that some patients develop skin photosensitivity. The deficient enzyme is coproporphyrinogen oxidase. The diagnosis is established by finding excess coproporphyrin (especially coproporphyrin type III) in urine and stool. Other types of porphyrins show little or no increase. Urinary ALA and PBG are increased during acute attacks but may become normal on recovery. Reliable assays for the deficient enzyme are not generally available. If the enzyme is measured, red blood cells should not be used. The enzyme is found in mitochondria which are not present in red blood cells. Precautions and treatment for acute attacks are as described for AIP.

Variegate Porphyria (VP)

This form of hepatic porphyria is most common in the South African white population. It is less frequent elsewhere. It is an autosomal dominant disorder and may produce acute attacks (as in AIP) as well as skin photosensitivity. The deficient enzyme is protoporphyrinogen oxidase. The diagnosis is made by finding excess coproporphyrin in urine and both coproporphyrin and protoporphyrin in feces. The most sensitive screening test for VP is probably a plasma porphyrin assay. In patients with skin manifestations, it is important to distinguish VP or HCP from PCT, because treatment by phlebotomy or low-dose chloroquine is not successful in VP and HCP. Acute attacks are managed and may be prevented as in AIP.

Erythropoietic Protoporphyria (EPP) or Protoporphyria

This porphyria is due to a deficiency of ferrochelatase. It is inherited as an autosomal dominant trait. Many different mutations of the ferrochelatas gene have been found in various EPP families. Protoporphyrin accumulates in the bone marrow, red blood cells and sometimes the liver. Excess protoporphyrin is excreted by the liver into the bile, after which it enters the intestine and is excreted in the feces. Urinary porphyrins are normal. The diagnosis is established by finding increased protoporphyrin in plasma, feces and red blood cells.

Symptoms
Swelling, burning, itching, and redness of the skin may appear during or immediately after exposure to sunlight, including sunlight that passes through window glass. Usually, these subside in 12 to 24 hours and heal without significant scarring or discoloration of the skin. Occasionally, the skin problems occur only after extended sunlight exposure. The skin lesions may progress to a chronic stage persisting for weeks and healing with superficial scars. However, blistering and scarring is less common than in other types of "cutaneous" porphyria. Skin manifestations generally begin during childhood. They are more severe in the summer and can recur throughout life. Other manifestations may include gallstones containing protoporphyrin, and occasionally, severe liver complications. Some carriers of the gene for EPP

have no symptoms and may even have normal porphyrin levels.

Treatment and Prognosis
Treatment with beta-carotene improves sunlight tolerance but does not lower porphyrin levels. Lumitene (Tishcon, Inc.) is the only pharmaceutical grade beta-carotene preparation recommended for treatment of EPP. Cholestyramine ingestion may lower porphyrin levels in some patients.

Patients with EPP may develop excess deposition of protoporphyrin in the liver which can progress to scarring and liver failure. Fortunately, this seldom occurs.

EPP is generally not associated with neurological problems. However, a few patients with EPP and advanced liver damage have developed neurological symptoms similar to those in the "acute" porphyrias. To avoid liver complications, it is a good idea to avoid drugs that impair bile flow (cholestasis), including estrogens and alcohol. Some patients with EPP report that drinking alcoholic beverages increases their photosensitivity.

Testing

Why laboratory tests are important for diagnosis of porphyrias

The porphyrias are readily diagnosed by laboratory testing, especially at or near the time of symptoms. However, the number of tests available is very large, and the results among laboratories are not always reliable. It may be difficult to choose the most appropriate test and properly interpret the results. Many of these tests are overused, resulting in unnecessary expense, delay in diagnosis, and even misdiagnosis of porphyria. For these reasons, it is important to locate a laboratory skilled in performing tests for porphyria and a physician skilled in interpreting the test results. The American Porphyria Foundation can help you locate laboratories and physicians with expertise in porphyria.

Many of the symptoms of porphyria are very similar to those experienced with other more common diseases. In other words, the symptoms of porphyria are nonspecific. This is why the diagnosis of porphyria is often delayed or even missed altogether. To avoid this problem, porphyria should be considered and ruled out in the many patients who have compatible symptoms but may turn out not to have porphyria. Laboratory testing is much more effective for confirming or excluding a diagnosis of porphyria than is the case for many other types of illnesses. Therefore, laboratory tests are extremely important when a diagnosis of porphyria is suspected.

As will be explained in this pamphlet, the most common tests used for porphyrias are measurements of substances that accumulate in large amounts in the body, especially when someone has active porphyria. These substances, porphyrin precursors and porphyrins, can be measured in red blood cells (erythrocytes), blood plasma, urine and feces. Measuring enzymes in cells and looking for changes (mutations) in DNA is useful for confirmation and for family studies.

Substances that accumulate in porphyrias and are important for diagnosis

The porphyrias are caused by deficiencies of enzymes of the heme biosynthetic pathway. This pathway, like other chemical pathways in the body, is a sequence of steps leading to a final product, in this case heme. Heme is essential for life, and each enzyme is also essential, because it is responsible for one of the eight steps in making heme. Each porphyria is due to a deficiency but not a complete absence of one of the enzymes. (Table 1 shows the enzymes that are deficient in each of the porphyrias.)

As in other pathways in the body, each enzyme acts by making a specific change in a chemical called it's substrate, to form a product. The product of one enzyme is the substrate for the next. The substrates and products are also known as intermediates in the pathway. When an enzyme is deficient the substrate for that enzyme may accumulate. (Table 1 also shows the substrates and products of the pathway with the sequence indicated by arrows.)

In the porphyrias, large amounts of intermediates can accumulate in the body, especially when the conditions are active. These intermediates include porphyrin precursors (delta-aminolevulinic acid and porphobilinogen) and porphyrins. Depending on the type of porphyria, the excess intermediates are produced and accumulate first in the liver or the bone marrow and then appear in blood. They are excreted from the body in urine and feces. Some of the intermediates undergo changes after they leave cells in the liver and bone marrow and before they are excreted from the body (see Table 1).

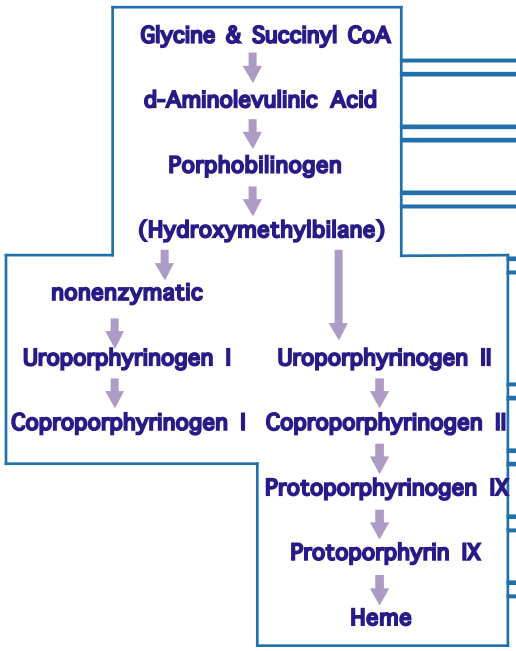
The most common and useful tests measure porphyrin precursors and porphyrins in blood (plasma and red blood cells), urine or feces. Which intermediates accumulate depends on the type of porphyria. When porphyria is active, the amounts that accumulate are very large. This enables a diagnosis of active porphyria to be made quite readily.

Sensitivity and specificity of tests for porphyria

Sensitivity is a feature of many of the diagnostic tests for porphyrias, especially when they are done at or near the time of symptoms. Tests that are sensitive for diagnosis of active porphyrias are almost always abnormal when symptoms of porphyria are present. But the tests vary in specificity, meaning that some of the tests (those with lower specificity) are abnormal in other diseases.

In choosing a test to screen for a disease that is not only uncommon but also causes symptoms that mimic more common diseases, it is obviously important to choose a test that is both sensitive and specific. Fortunately, some tests for porphyria have both of these features. With such tests, it should always be possible to determine if symptoms might be due to one of the porphyrias.

Table 1. Diseases due to deficiencies of specific enzymes of the heme biosynthetic pathway
The enzymes and their intermediates (substrates and products) are shown in sequence. Some intermediates are porphyrinogens (reduced porphyrins); these are excreted and measured mostly as oxidized porphyrins (shown in the right column). A deficiency of the first enzyme, ALAS, causes a type of anemia rather than a porphyria. Abbreviations and alternate names are shown in parentheses. (Uroporphyrinogen I synthase is an obsolete term for PBGD and is not shown in the Table.)



ENZYME	DISEASE
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a-Aminolevulinic Acid Dehydratase	ALAD Porphyria
Porphobilinogen Deaminase	Acute Intermittent Porphyria
Uroporphyrinogen III Cosynthase	Congenital Erythropoietic Porphyria
Uroporphyrinogen Decarboxylase	Porphyria Cutanea Tarda, Hepatoerythropoietic Porphyri
Coproporphyrinogen Oxidase	Hereditary Coproporphyria
Protoporphyrinogen Oxidase	Variegate Porphyria
Ferrochelatase	Erythropoietic Protoporphyria

Porphyria should be suspected quite frequently, because the symptoms that suggest the diagnosis are common. If a diagnosis of porphyria is not made promptly, serious consequences to the patient may follow. But more often than not, laboratory testing will show that the patient does not have porphyria, because other diseases with symptoms that mimic porphyria are much more common. An effective approach to laboratory testing must be one that does not often miss the diagnosis and also does not often incorrectly suggest that porphyria is present

Approach to laboratory testing—Screening followed by confirmation

Many tests are offered for the diagnosis of one of the porphyrias. One might think that this is an advantage in diagnosing porphyrias. However, it may be difficult to choose the proper tests and interpret the results, resulting in delay in diagnosis and even misdiagnosis of porphyrias. Tests may be overused, leading to unnecessary expense.

In the past, it was customary to obtain many or all available tests when porphyria was suspected and then examine patterns of any abnormal results. Abnormal results might be compared with tables showing patterns of abnormalities to be expected in the various porphyrias. This approach did not adequately consider the sensitivity and specificity of the various tests or how abnormal the results should be for making a diagnosis of porphyria.

A better and less costly approach is to rely on a few screening tests that are both sensitive and specific. If a well-chosen screening test is normal, the possibility of porphyria as a cause of symptoms is effectively ruled out. If the test is positive, further testing is needed to establish which type of porphyria the patient has. The screening tests may be regarded as "first-line" tests, and the tests that follow (when a screening test is positive) as "second-line tests."

Consultation with a porphyria expert may be needed to choose and interpret the tests that should follow a positive screening test.

An approach that prioritizes laboratory testing in this manner has many advantages. It is cost effective, because porphyria can be ruled in or out in many patients with nonspecific symptoms with only one or a few tests. As already noted, porphyria is ruled out much more commonly than it is ruled in, and therefore one or a few negative screening tests can be effective and also keep medical costs down. Relying on a few screening tests that have a high degree of specificity also avoids misdiagnosis of porphyrias.

Suitable screening tests for porphyrias

No single test is effective for screening for all porphyrias. However, one of two tests can be relied upon in almost all situations, depending on the symptoms. Information about screening tests is summarized in Table 2.

The symptoms of porphyrias are either due to effects on the nervous system or the skin. Acute porphyrias lead to a variety of effects on the nervous systems such as abdominal pain, nausea, vomiting, pain in the extremities and elsewhere, muscle weakness and altered mental functioning. Cutaneous porphyrias lead to skin manifestations in sun-exposed areas (photosensitivity). These may include chronic blistering or more acute pain and swelling. Some porphyrias have both cutaneous and neurological manifestations.

Acute porphyrias. Measurement of porphobilinogen (PBG) in urine can be relied upon for screening for the acute porphyrias when there are neurological symptoms such as abdominal pain. PBG is markedly increased in almost all patients with symptoms of acute porphyrias and is never markedly increased in diseases other than acute porphyrias. Therefore this test is both sensitive and specific.

Measurement of PBG is often combined with delta-aminolevulinic acid (ALA) and total urine porphyrins. ALA is increased, but PBG is not, in ALAD porphyria (ADP), the most rare form of acute porphyria. In some patients with acute porphyrias, urinary porphyrins may remain increased longer than ALA and PBG. But it must be remembered that increases in urinary porphyrins occur in other medical conditions, and are therefore much less specific than increases in ALA and PBG. In urgent situations, PBG can be measured immediately (as a STAT test) and the urine sample saved for later measurement of ALA and total porphyrins.

If urine ALA, PBG and total porphyrins are normal, it is quite certain that any recent symptoms are not due to an acute porphyria. If these are markedly increased, further testing is needed. An isolated increase in urine porphyrins (especially coproporphyrin) is nonspecific and therefore does not always require further testing.

Cutaneous porphyrias. Measuring total plasma porphyrins is effective for screening patients with skin photosensitivity, because the value can be expected to be very much increased in any patient with skin manifestations due to porphyria. Plasma porphyrins are seldom increased in other medical conditions.

If this test is normal, cutaneous porphyrias that cause blistering skin lesions are effectively excluded. Further testing is needed if total plasma porphyrins are increased. But although this is a highly effective screening test, in that it is both sensitive and specific, it is less sensitive than an erythrocyte protoporphyrin determination in detecting EPP.

Table 2. First-line testing for patients in whom porphyria is suspected as a cause of either neurological symptoms or photosensitivity.

Symptoms	Most sensitive and specific test for screening when symptoms are present
Neurological (acute abdominal pain, etc.)	Urinary delta-aminolevulinic acid and porphobilinogen (a total urinary porphyrin determination is also recommended.)
Skin photosensitivity	Total plasma porphyrins

Summary of tests available for the diagnosis of porphyria

The porphyrin precursors ALA and PBG and porphyrins are readily measured in urine. Normal urine contains appreciable amounts of these substances, and different individuals may have widely different levels. It must also be remembered that "normal ranges" do not necessarily include all normal people. Therefore, small "increases", especially in porphyrins are not always significant.

ALA is an amino acid, and PBG is a pyrrole. Both are colorless, but when present in large amounts in a solution such as urine, PBG can spontaneously form uroporphyrin, which is reddish, and other products that are brownish.

The Mauzerall-Granick method and variations of that method are preferred for measuring ALA and PBG and have been available for many years. The test involves first separating ALA and PBG from each other and from interfering substances in urine, and converting ALA to a pyrrole. Ehrlich's reagent, which reacts with pyrroles (and some other chemicals) to make a colored substance that is readily seen, is added, and the color is measured separately for both ALA and PBG with an instrument called a spectrophotometer. The Watson-Schwartz test and the Hoesch test are qualitative tests (result either positive or negative) for PBG that also use Ehrlich's reagent; they may lead to false-positive results if the person doing the test lacks experience in interpretation. A more reliable qualitative test is available for screening (TraceÆ PBG Test Kit) and is based on the Mauzerall-Granick method. If a qualitative test is positive, a quantitative assay should be done later on the same sample.

Because PBG is generally so strikingly increased during an attack of acute porphyria, quantitation even on a spot sample (rather than a 24 hour collection) is highly informative. Requiring a 24-hour urine collection for quantitative measurements during an attack may result in considerable delay in confirming the diagnosis. Furthermore, ALA and PBG may drop

considerably (especially in HCP and VP) if there is a delay of several days in collecting a 24 hour urine.

In HCP and VP, urinary porphyrins generally remain increased longer after an acute attack than ALA and PBG. Therefore, screening for acute porphyrias should probably include measurement of total urinary porphyrins. However, it needs to be kept in mind that nonspecific increases in urinary porphyrins are common.

Measurement of PBG in serum is useful when acute porphyria is suspected and urine cannot be collected—for example in patients with kidney failure. Serum PBG is increased in serum in the acute porphyrias, although when kidney function is normal the concentrations are lower than in urine.

Porphyrins are tetrapyrroles (composed of four pyrroles). Porphyrins in their oxidized forms are reddish in color and are also fluorescent. Fluorescent substances, when exposed to light at certain wavelengths, emit light with a different wavelength. Porphyrins appear intensely red when exposed to long-wave ultraviolet light (UV-A). This makes them visible with a Wood's lamp, and enables them to be measured accurately with a spectrofluorometer. Within cells, all porphyrins that are intermediates in the heme biosynthetic pathway, with one exception, are in the reduced form, and are colorless and nonfluorescent. The last intermediate, protoporphyrin, is an oxidized porphyrin. Porphyrins that leave the cells and appear in blood, urine and feces are mostly oxidized and appear reddish to the naked eye and are fluorescent.

The total amount of porphyrins in a urine sample is easily measured. This is a useful test for screening especially when combined with ALA and PBG. But an increase in urine porphyrins is nonspecific, and may not be an indication of an acute porphyria if ALA and PBG are normal.

A variety of porphyrins are present in urine. When there is an increase, particularly a large increase, in total urine porphyrins, it is often useful to determine the individual porphyrins found in urine. It is seldom important to do this if the total in normal.

The most common method for separating the individual porphyrins is "high performance liquid chromatography" (HPLC). This method will measure amounts of porphyrins with 4 or more carboxyl groups found in urine (see Table 3). In interpreting HPLC results, it is most useful to see which porphyrins predominate rather than focus on the amounts of each porphyrin.

Table 3. Porphyrin names and the corresponding number of carboxyl groups
Carboxyl groups make the porphyrin more soluble in water. Porphyrins with less than 4 carboxyl groups are not found in appreciable amounts in urine. The less soluble porphyrins with 2-3 carboxyl groups are excreted mostly in bile and feces. Coproporphyrin is excreted by both routes.

Porphyrin names	Number of carboxyl groups
Uroporphyrin (octacarboxyl porphyrin)	8
Heptacarboxyl porphyrin	7
Hexacarboxyl porphyrin	6
Pentacarboxyl porphyrin	5
Coproporphyrin (tetracarboxyl porphyrin)	4
Harderoporphyrin (tricarboxyl porphyrin)	3
Protoporphyrin (dicarboxyl porphyrin)	2

Coproporphyrin predominates in normal urine. An increase in total urine porphyrins with a predominance of coproporphyrin is seen especially in HCP and VP. But this finding alone is very nonspecific, because increases in urine porphyrins and especially coproporphyrin are common in many medical conditions such as liver diseases, bone marrow disorders and lead poisoning. Therefore, increases in urine coproporphyrin are often not due to porphyria.

When total urine porphyrins are increased due to PCT or HEP, the increase is predominantly accounted for by uroporphyrin and heptacarboxyl porphyrin. Hexa- and pentacarboxyl porphyrin are increased to a lesser degree. These increases are understandable, because the corresponding reduced porphyrins are, in sequence, substrates for UROD, the enzyme that is deficient in PCT and HEP (Table 1). The enzyme removes 4 carboxyl groups from uroporphyrinogen one at a time to form coproporphyrinogen. Therefore, uroporphyrinogen and the intermediates with 7, 6, and 5 carboxyl groups also accumulate when the enzyme is markedly deficient. Adding to the complexity of the porphyrins in PCT is a series of porphyrins called isocoproporphyrins, which result from the next enzyme in the pathway acting on pentacarboxyl porphyrin.

The body makes primarily the isomer III type of porphyrinogens, because only these are precursors of heme. But some isomer I porphyrinogens are made in small amounts and are excreted. HPLC detects the different isomers, which adds even greater complexity. The isomer I porphyrins predominate in urine (as well as erythrocytes, plasma and feces) in CEP, because of the marked deficiency of the enzyme UROS.

Sodium carbonate (5 grams, added to a 24 hour urine bottle prior to collection) is widely recommended for urine specimens intended for measurement of PBG and porphyrins. It is widely recommended that acid be added to containers for collection of urine in which ALA is to be measured, because ALA is more stable in acid. This may be suitable if only ALA is to be measured as, for example, in screening for lead poisoning. Unfortunately, acid conditions enhance degradation of PBG, and it is seldom important to measure only ALA. Therefore, if porphyria is suspected sodium carbonate rather than an acid should be used, because it will be important to measure PBG and possibly porphyrins, as well as ALA in the sample.

Fecal Porphyrins

Total fecal porphyrins are markedly increased especially in active HCP and VP and to a lesser extent in PCT and EPP. Fecal porphyrins can be separated and measured individually by HPLC. Porphyrins with 2-4 carboxyl groups generally predominate in feces. These are excreted by the liver into the bile and then flow into the intestine.

As with urine, it is most useful to measure the total amount of porphyrins in a fecal sample. If this is increased, then the laboratory should determine by HPLC which porphyrins predominate rather than focus on the amount of each porphyrin. Fecal porphyrin determinations may be confounded by variations in fecal flow; most people have one or a few bowel movements daily and a "24 hour stool collection" is really not uniform from day to day. Substances in the diet and any internal bleeding into the stomach or intestines may also interfere.

Blood tests—plasma or serum

Plasma (or serum) total porphyrins. Normally there are only trace amounts of porphyrins in plasma, and the amounts increase markedly in patients with cutaneous porphyrias. This is a very useful and underutilized test when a porphyria is suspected as a cause of photosensitivity. Being both sensitive and specific, it is increased in any patient with skin problems related to any type of porphyria and is seldom increased in other conditions.

The preferred method at least for screening involves diluting plasma with a nonacid, neutral buffer and measuring the porphyrins directly by fluorescence scanning. This can serve not only as a rapid screening method for all cutaneous porphyrias but can determine whether a patient has VP rather then PCT and other porphyrias that can cause blistering skin lesions. This method also detects some cases of latent VP.

The excess porphyrins in plasma in VP are mostly covalently linked to plasma proteins and are readily detected by this method but may not be detected by the HPLC methods. It needs to be kept in mind that the normal range for plasma porphyrins is higher in patients with end stage renal disease. Moreover, hemolysis of a blood sample invalidates a plasma porphyrin determination, because normal erythrocytes contain much larger amounts of porphyrin (in the form of Zn protoporphyrin) than does normal plasma. When the total plasma porphyrin is increased, HPLC can be used to determine which porphyrins predominate. This is done less commonly than for urine.

Plasma porphyrin measurements may be less useful for detecting EPP than other cutaneous porphyrias. One reason for this may be that protoporphyrin is very light sensitive, and the concentration in the sample can decrease rapidly if it is exposed to light during processing. Therefore, erythrocyte porphyrins should be measured if EPP is strongly suspected.

Blood tests—erythrocytes

Erythrocyte porphyrins. Normal erythrocytes, in contrast to plasma, contain appreciable amounts of porphyrins. This is almost all protoporphyrin. Therefore, erythrocyte porphyrin measurements are customarily reported as erythrocyte protoporphyrin. However, the methods can detect other porphyrins and would more accurately described as measuring total erythrocyte porphyrins.

Because increases in erythrocyte porphyrins almost always are due to increased protoporphyrin, it is seldom necessary to separate the porphyrins in erythrocytes by HPLC. In CEP, however, isomer I uroporphyrin and coproporphyrin are usually the predominant porphyrins, as can be demonstrated by HPLC.

The protoporphyrin normally found in erythrocytes is complexed with zinc (Zn) as Zn protoporphyrin. Zn protoporphyrin increases in many conditions other than porphyrias, including iron deficiency, lead poisoning and almost any type of disorder that affects erythrocytes. Therefore, increases in erythrocyte porphyrins are not specific for porphyrias. The only condition in which free protoporphyrin (not complexed with Zn) is increased is EPP. An increased erythrocyte protoporphyrin can be shown to be due to free protoporphyrin by a simple procedure called ethanol extraction. This is useful for confirming a diagnosis of EPP.

Erythrocyte enzymes

Assays for heme biosynthetic pathway enzymes in erythrocytes, especially ALAD, PBGD and UROD, have become widely available. These assays should not be used as first-line tests for porphyrias when screening patients with symptoms. They are useful for family studies, when it is established that an index case has a particular enzyme deficiency. Difficulties with these assays in clinical practice include the following. (i) Ranges for a particular porphyria and normals may overlap. (ii) Some mutations may cause a particular enzyme to be deficient only in nonerythroid tissues. (iii) Falsely low values are common due to problems with collecting or transporting the sample. Some laboratories employ coupled enzyme assays that may lack specificity. If a patient is found to have a deficiency of more than one enzyme in erythrocytes, it is likely that the results are not reliable.

DNA tests

Specific mutations can be identified by DNA testing. This may be the ultimate means of confirming a diagnosis of porphyria. Once a mutation is identified in a family, this is the most reliable means of detecting other carriers of the same porphyria associated mutation.

Not every family with a given type of porphyria has the same mutation. For example, more than 200 different mutations have been identified in the PBGD gene in different AIP families. No single test for all of these DNA variations is available. Therefore, DNA testing is not suitable for screening for porphyrias, except within families.

Furthermore, not all DNA variations cause the enzyme product to be impaired and lead to a disease. Therefore, a new mutation requires further research work in the laboratory to show that it impairs the enzyme product. For these reasons, DNA testing is most meaningful only after standard testing for porphyria has confirmed a diagnosis.

Laboratory testing of relatives and patients with subclinical porphyria

In all types of porphyrias there are striking increases in porphyrins and/or porphyrin precursors when these conditions are symptomatic. However, even in porphyrias that are inherited in an autosomal dominant pattern, there may be no such increases in many family members who carry the abnormal gene. Therefore, tests in addition to those useful in the presence of symptoms must be considered in patients with latent or subclinical disease.

Before deciding which tests are appropriate for asymptomatic family members, the diagnosis of porphyria should be firmly established in the propositus (index case) or another individual in the family with a history of porphyria. Results of previous testing in the propositus should be reviewed. It may be necessary to retest either the propositus or another family member with confirmed porphyria before undertaking screening of family members. DNA testing is ideal for detecting carriers of a known mutation in a particular enzyme, but requires that the mutation first be fully characterized in the propositus.

Porphyrias seldom become completely latent (such that all levels of porphyrins and porphyrin precursors become normal) within a short period of time. However, it does become more difficult to "rule out porphyria" if testing is delayed until after there is resolution of symptoms. If it is clinically important to exclude subclinical porphyria in a patient with past suggestive symptoms, and if definitive testing was not conducted near the time of symptoms, a specialist physician and laboratory should be consulted to advise on the choice and interpretation of laboratory tests.

Misinterpretation of porphyria test results

Diagnosis of porphyria is often delayed, and it has become widely recognized that physicians should maintain a high index of suspicion for these conditions. It is less widely appreciated that incorrect diagnoses of porphyria are common in patients with symptoms due to other diseases. Therefore, in patients with a past history of porphyria, it is important to review the laboratory data that were the basis for the original diagnosis. Further testing may be necessary if the diagnosis was not adequately documented.

Incorrect diagnoses of porphyria can occur in patients having minimal abnormalities in laboratory tests, such as small elevations in urinary porphyrins or porphyrin precursors that in fact have little or no diagnostic significance. Incorrect diagnoses are less likely if reliance is placed on a few first-line tests in most clinical situations, as described above. Overuse and over interpretation of minor abnormalities in results of second-line tests including erythrocyte PBGD, other enzyme assays, and fractionation of urinary and fecal porphyrins, account for many incorrect diagnoses of porphyria.

Directions For Collecting A 24-Hour Urine Sample

Many members have asked about the proper way to collect a 24-hour urine. Here are the directions from one porphyria laboratory. You might want to compare these directions with those from your own laboratory.

1. Please use a dark plastic jug for collecting the urine. The urine should be protected from light during collection and during shipping. Add 5 grams of sodium carbonate to the jug, which is a powder that will readily dissolve in the urine. This adjusts the acidity of the urine and helps preserve the things the lab will be measuring. It is not toxic or irritating.

2. A 24-hour urine collection must be started at a specific time and then ended at the same time the next day. You can choose any time that is convenient for you to start the collection. But you must also be sure that you can end the urine collection at the same time the next day.

3. Record the time that you have chosen to start the collection. You need to start the urine collection with an empty bladder. Therefore, at exactly this time, empty your bladder and discard the urine. In other words, *when you start the urine collection, you should empty your bladder and not add that urine to the jug.*

4. From that time on, add any urine that you pass to the bottle. You do not need to record the time each time you urinate.

5. During the collection, store the urine jug tightly capped in a refrigerator or place it in an ice chest.

6. At exactly 24 hours after you start the urine collection, you should *end the urine collection by emptying your bladder into the bottle for the last time.*

US labs and specialists

There are only a few laboratories in the United States that can perform the complex analysis to diagnose porphyria. The laboratories listed below also have porphyria experts connected to them to provide consultation about the test results.

University of Texas Medical Branch
Porphyria Center
Dr. Karl Anderson
Rt-J 09 Ewing Hall
Galveston, TX 77550
(409) 772-4661

ARUP Laboratory
University of Utah
500 ChipetaWay
Salt Lake City, UT 84108
(801) 583-2787

Fairview University Diagnostic Laboratories
Watson Laboratory
Dr. Claus Pierach
University Campus, Mayo Bldg. Rm D293
420 Delaware St. S.E. (UH198)
Minneapolis, MN 55455
(800) 888-8642
(612) 626-3231

Mt Sinai Hospital
Department of Human Genetic Laboratory
Dr. Kenneth H. Astrin
One Gustv Levy Place
New York, NY 10029
(212) 241-9192
DNA Testing for individuals in families with already identified porphyrias

Quest Diagnostics
33608 Ortega Highway
San Juan Capistrano, CA 92690
(800) 286-4643

Mayo Clinic
Biochemical Genetics Laboratory
200 First St. S.W.Rochester, MN 55905
(507) 255-3681
(507) 266-2888

US Specialists

Locating laboratories and physicians specializing in porphyria is of extremely important. The following list is provided for your use if you would like to schedule an appointment with a specialist in your area. Also, you might give a copy of the list to your physicians if they need to consult with a specialist about your diagnosis or treatment.

If the following specialists do not perform diagnostic tests, they use the testing centers above.

Dr. Karl Anderson
Testing and treatment
(409) 772-4661 - Texas

Dr. Montgomery Bissell
Testing and treatment
(415) 476-5072 - California

Dr. Joseph R. Bloomer
Testing and treatment—all porphyrias
(205) 975-5676 - Alabama

Dr. Herbert Bonkovsky
Testing and treatment
(860) 679-8457 - Connecticut

Dr. Sylvia Bottemley
Testing and treatment-all porphyrias
(405) 270-1565 - Oklahoma

Dr. John Epstein
Testing and treatment—PCT, EPP
(415) 781-4083 - California

Dr. Richard A. Galbraith
Testing and treatment
(802) 847-2777 - Vermont

Dr. James Kushner
Testing and treatment
(801) 581-6736 - Utah

Dr. Claus Pierach
Testing and treatment
(612) 863-4342 - Minnesota

Dr. Neville Pimstone
Testing and treatment
(530) 734-2890 - California

Dr. Maureen Poh-Fitzpatrick
Testing and treatment
(901) 448-5795 - Tennessee

Dr. Michelene Mathews-Roth
Testing and treatment - EPP
(617) 525-2249 - Massachussetts

Dr. Steven Shedlofsky
Testing and treatment
(859) 323-5575 - Kentucky

Dr. Peter Tishler
Testing and Treatment
(617) 525-2123 - Massachussetts

Telemedicine Consultations

If you need to consult with a porphyrla specialist and are unable to do so because of distance to a porphyria center, you now have the opportunity to consult electronically.

A porphyria specialist and member of the APF scientific advisory board, Dr. Karl Anderson, will be consulting with porphyria patients via a telemedicine service from the General Clinical Research Center of the University of Texas Medical Branch at Galveston.

To access this service, you need to first locate a video teleconferencing facility in your community. These facilities are often found in libraries, businesses, universities, research centers. etc. Unfortunately, neither the APF nor Dr. Anderson can provide you with a list of facilities with teleconferencing capabilities. Next, call Dr. Karl Anderson (409) 772-4661 to arrange for an appointment and to advise you as to the information you might need prior to the telemedicine visit.

During the teleconference Dr. Anderson will discuss your case with you in the same fashion as a regular office visit. This project was funded, in part, by the American Porphyria Foundation.

Panhematin® (hemin for injection) Therapy for The Acute Porphyrias

What are *Acute* Porphyrias?

Four types of porphyria share the common manifestation of an acute attack: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and ALAD porphyria (ADP). These four types are sometimes referred to as acute porphyrias.

Some attacks are triggered by certain drugs, hormones, infections, restrictions in diet, or the luteal phase of the menstrual cycle, while others have no discernible precipitating cause. Clinical manifestations and diagnostic tests to determine disease type can vary between these types. However, treatment is much the same for all of the acute porphyrias. Panhematin® (hemin for injection) is an effective treatment for AIP and other acute porphyrias.

Panhematin® Treatment

Panhematin® from Ovation Pharmaceuticals, Inc. in Deerfield, IL, is a lyophilized form of alkaline heme that has to be reconstituted immediately prior to administration. Panhematin® should be infused into a large peripheral vein. A large central line or port may be used, if available.

Doctors administer Panhematin® to correct heme deficiency in the liver and repress production of porphyrin precursors. Panhematin® almost always normalizes porphyrin and porphyrin precursor values. Three to four mg/kg of Panhematin® given once daily for four days early in an attack produces a highly beneficial effect in most patients. Commonly noted are decreases in pulse rate, blood pressure, abdominal pain, as well as decreased levels of urinary porphobilinogen (PBG). These effects can occur within a day.

Panhematin® is the only commercially available heme therapy in the United States. (Heme arginate is another preparation, but is only available outside of the U.S.) While a high carbohydrate diet is recommended for patients with porphyria, it is not regarded as highly effective by itself. Intravenous glucose therapy is a treatment option for mild attacks. When heme therapy was introduced as a treatment, it was recommended that it be initiated only after several days of glucose therapy was unsuccessful.

Today, porphyria specialists advocate the immediate use of Panhematin® because it is more effective than glucose in reducing excretion of porphyrin precursors. Delaying Panhematin® therapy until establishing that glucose alone is ineffective is not warranted unless an attack is mild. Periodic infusions of Panhematin® can even prevent attacks.

Many experts recommend reconstituting Panhematin® with albumin as this makes it more stable.

This helps prevent phlebitis and an anticoagulant effect. Like Panhematin,® albumin is a biologic product, which is approved and regulated by the FDA.

In addition to Panhematin® therapy, supportive measures such as nursing care, attention to electrolyte imbalance, and sufficient pain medication help in treating acute attacks.

During treatment, attention should be given to salt and water balance. Harmful drugs should be stopped. These include barbiturates, sulfonamide antibiotics, and many others.

For questions from healthcare professionals regarding general use and administration, please call 1-800-455-1141. If your physician would like to speak to a porphyria expert who has expertise in using Panhematin,® the American Porphyria Foundation (APF) will gladly provide that information. Call us at 713-266-9617.

The Earlier The Better

Although there have been no controlled studies, the results since the first report in 1971 are impressive enough to advocate the early use of Panhematin® for porphyric attacks. When Panhematin® is given late in an attack, less benefit may occur.

Although it is generally agreed that the outlook for patients with porphyria has improved, an attack can still be life threatening. Respiratory insufficiency may require use of an artificial respirator. Therefore, porphyria attacks should be treated as early and effectively as possible. Fortunately, in patients with known porphyria, many attacks can be prevented. However, some patients may have an occasional attack even if they are careful in their lifestyles. And although prophylactic use of Panhematin® to prevent attacks has not been formally studied, Panhematin® is widely used in this manner for patients known to have acute porphyria and attacks that recur frequently.

Safety Considerations

Although Panhematin® has few side effects, it does act as a mild anticoagulant. Thus, concurrent use of other anticoagulants such as heparin or Coumadin® (warfarin) should be avoided. Panhematin® may also produce superficial thrombophlebitis, especially if infused into a small vein. Panhematin® is less likely to produce phlebitis if it is mixed with human albumin before it is given. Before Panhematin® is used, it should be clear that the patient indeed suffers from one of the acute porphyrias (AIP, HCP, VP, ADP) and that the patient's symptoms are due to an acute attack. Panhematin® therapy may not be indicated unless the diagnosis of acute porphyria is proven by a marked increase in urine PBG.

Although there are chemicals in Panhematin® that are derived from human blood, the risk of viral contamination is extremely low. The organization at the FDA that regulates biologic agents (CBER) is very demanding. And Ovation’s manufacturing process for Panhematin® meets all federal requirements. Since Panhematin® was approved by the FDA in 1983, there have been no

reports of viral or bacterial contamination associated with the product. Panhematin® is a high-quality product and meets all pharmaceutical industry rules and regulations related to good manufacturing practice requirements.

Quick Delivery

Your physician or hospital pharmacy can order Panhematin® through a wholesaler of choice. Healthcare professionals can call 1-888-514-5204 to receive help with regular and emergency shipments. In an emergency event, when the hospital/ physician/wholesaler does not have Panhematin® in stock, Ovation will ship directly from Chicago's O'Hare airport to anywhere in the U.S.—usually within 12-14 hours.

Other Important Treatment Considerations for the Acute Porphyrias

- Hospitalization is often necessary for acute attacks. Medications for pain, nausea, and vomiting, as well as close observation are generally required.
- A high intake of glucose or other carbohydrates can help to suppress disease activity and can be given by vein or by mouth.
- Attacks are often precipitated by low intake of carbohydrates and calories in an attempt to lose weight. Thus dietary counseling is very important.
- Premenstrual attacks often resolve quickly with the onset of menses. Hormone manipulations may prevent such attacks.
- Acute porphyria is particularly dangerous if the diagnosis has not been made and if harmful drugs are administered. The prognosis is usually good if the disease is recognized and if treatment and preventive measures are begun before severe nerve damage has occurred. Although symptoms usually resolve after an attack, some patients develop chronic pain. Nerve damage and associated muscle weakness can improve over a period of months or longer after a severe attack. Mental symptoms may occur during attacks but are usually not chronic.
- Wearing a MedicAlert® bracelet is advisable for patients who have been diagnosed with porphyria.

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