The author defines the porphyrias group of diseases, including classic symptoms and necessary anesthetic considerations.

Porphyria, as a clinical entity, was first described by Stokvis in 1889. It was subsequently found to be prevalent in South Africa and the Scandinavian countries. But, it remained an enigma until the genetic theories, enzyme mechanics, and analytic techniques of the past two decades allowed for an understanding of the mechanisms involved in the inheritances and pathogenesis of this disease.

The anesthetist must consider that porphyria presents a situation in a patient where induced drug metabolism may precipitate an acute attack of the disease. It remains as one of the absolute contraindications to the use of barbiturates in any form or manner. And, thus, a knowledge of this disorder is essential to the intelligent selection of anesthetic agents and management of these patients.

Biochemistry and enzymatics

Porphyrins are a relatively forgotten group of compounds that are involved in some of the most vital chemical reactions occurring in biological systems. They present themselves in the whole of the evolutionary tree, having been isolated in subjects ranging from red and brown algae to humans. This implies their fundamental importance in life processes. However, though their distribution is wide, their function has a rather narrow scope. It appears that the porphyrins are important members in the pathways encompassing oxygen utilization, transport, storage, or formation.

In this respect, porphyrins are involved in a number of enzyme systems, that is, catalases, peroxidases, cytochromes b and c, cytochrome oxidase, chlorophylls a and b. Porphyrins have the ability to combine with metals to form metallo-porphyrins which often function as prosthetic groups in larger functional compounds. The following metals have been found to be associated with porphyrins in biological systems:

<table>
<thead>
<tr>
<th>Metal</th>
<th>Associated Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Hemoglobin, myoglobin</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Chlorophyll</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Vitamin B_{12}</td>
</tr>
<tr>
<td>Vanadium</td>
<td>Shale oils—derived from organic sources</td>
</tr>
<tr>
<td>Copper</td>
<td>Turacin—various colors in bird wings</td>
</tr>
</tbody>
</table>

In addition, zinc, manganese, nickel, silver, tin, and cadmium have been combined in vitro with the porphyrins. Thus, their relative scarcity belies their importance; and to understand their pathology, necessitates an understanding of their synthesis. It has been only within the past two decades that the pathways of synthesis have been elucidated; though some of the
intermediate steps are not as yet completely understood.

The synthesis begins with relatively simple compounds obtainable from the body’s stores or metabolic pathways. The first step is the condensation of glycine, the simplest amino acid, and succinyl co-enzyme A and alphaoxoglutarate, both available from the Kreb’s cycle, by 5-amino laevulenic acid synthetase (ALA-S) in the presence of pyridoxal phosphate, a vitamin B₆ derivative, to alpha-amino beta-keto adipic acid. (Figure 1-A.) The alpha-amino beta-keto adipic acid spontaneously loses CO₂ to form 5-amino laevulenic acid. (Figure 1-B.) Two molecules of 5-amino laevulenic acid are then condensed by the enzyme 5-amino laevulenic dehydrase (ALA-D) to form the basic building block of the porphyrins: porphobilinogen (PBG). (Figure 1-C.)

The porphobilinogen molecules (4) are joined via methane bridges by the enzyme uroporphyrinogen I synthetase to form uroporphyrinogen I. But if another enzyme, uroporphyrinogen III co-synthetase, is present, uroporphyrinogen III is formed. (Figure 1-D.) Note the position of the “A” and “P” groups on the No. 4 ring are reversed. This leads to the two isomers. Theoretically, there are two other isomers obtainable, but these have not been found in na-
ture. The “I” series has no known physiological function and proceeds only one step further to that of corroporphyrinogen I.

With regard to the “III” series, the “A” groups on each of the rings undergo successive decarboxylations to form corroporphyrinogen III. (Figure 1-E.) The “P” groups are decarboxylated and dehydrogenated to yield protoporphyrin which contains methyl groups, vinyl groups, and methane.

**Figure 1d**

![Diagram of Uroporphyrinogen I synthesis](image)

**Figure 1e**

![Diagram of Decarboxylation](image)

**LEGEND**

A = -CH₂-COOH
P = -CH₂-CH₂-COOH
M = -CH₃
V = -CH=CH₂

Corroporphyrinogen III
bridges. (Figure 1-F.) The protoporphyrin, in the presence of iron and ferrochelase, is then converted to heme, with the iron coordinately bound to the nitrogen groups. (Figure 1-G.)

The rate limiting step of the whole sequence appears to involve the enzyme 5-aminolaevulenic acid synthetase (ALA-S). In the normal individual the enzyme activity is adjusted so that there are just trace amounts of the heme precursors present in the body. The other enzymes in the system are able to convert all of their precursors to products. Uncoupling of ALA-S from its regulatory mechanisms results in overproduction of precursor substances. The normal regulation of ALA-S is depicted in Figure 2.

The mechanism involves three genes—a regulator, an operator, and a structural gene. The regulator gene exerts its control over the operator gene via an apopressor which the regulator produces. By itself, the apopressor is ineffective in suppressing the operator gene; but, if coupled with a corepressor, it can turn off the operator gene. The operator gene can be thought of as an on and off switch for the structural gene. If sufficient repressor is present, it turns off the structural gene; if not, the structural gene proceeds to produce ALA-S. Heme functions in the
regulatory mechanism as a corepressor, and trace amounts can combine with ALA-S itself to limit production.

Figure 3 illustrates three mechanisms by which this regulator mechanism may go awry yet still be compatible with life. The first involves genetic mutation of either the regulator or operator gene, which would result in the production of ineffective apopresor or an operator gene insensitive to the repressor. The end result would be unchecked ALA-S production and, consequently, increased production of porphyrins.

A second mechanism is that as heme functions as a corepressor in a negative feedback mechanism and if excessive heme catabolism occurs, the result may be an insufficient repressor and an increased ALA-S production. Thus, porphyrins would be in excess of bodily needs and their accumulation. Another means by which repressor mechanisms could fail would be if abnormal amounts of heme were to combine with ALA-S so as to deprive the aporepressor of its corepressor. In the same manner, if intermediate precursors were allowed to combine with the aporepressor, the result would be an ineffective repressor.

A third mechanism occurs when an intermediate enzyme is deficient and results in decreased heme for the negative feedback. Again, excess production is the result. This latter mechanism is by far the easiest understood and may explain the majority of cases. But, one cannot rule out the other mechanisms in less clear cut cases, or that two mechanisms may be operating in the same disease.

Remember, the whole sequence is dependent upon ALA-S for its ultimate output; and heme, the end product, is required in the control of ALA-S production. These two interrelated mechanisms enable one to visualize what is occurring in the porphyrias.

Classification

The porphyrias are a heterogeneous group of disorders that are so classified because of their disordered heme synthesis. As a result, different intermediate products may accumulate in the body. If one uses the site of accumulation of the precursors as a criteria for classification, the following scheme evolves (Elder).

<table>
<thead>
<tr>
<th>Erythropoietic</th>
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<tbody>
<tr>
<td>1. Congenital erythropoietic porphyria</td>
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<tr>
<td>2. Erythropoietic corproporphyria</td>
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<table>
<thead>
<tr>
<th>Erythrohepatic</th>
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<tbody>
<tr>
<td>1. Protoporphyria</td>
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</table>

<table>
<thead>
<tr>
<th>Hepatic</th>
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</thead>
<tbody>
<tr>
<td>1. Hepatic porphyria—inherted as an autosomal dominant</td>
</tr>
<tr>
<td>(a) Acute intermittent porphyria</td>
</tr>
<tr>
<td>(b) Variegate porphyria</td>
</tr>
<tr>
<td>(c) Hereditary corproporphyria</td>
</tr>
<tr>
<td>2. Symptomatic cutaneous hepatic porphyria</td>
</tr>
<tr>
<td>(a) Those with no family history and those</td>
</tr>
<tr>
<td>(1) associated with alcoholism, liver disease, iron overload, and estrogen therapy, and</td>
</tr>
<tr>
<td>(2) associated with hexachlorobenzene poisoning</td>
</tr>
<tr>
<td>(b) Those with family history</td>
</tr>
<tr>
<td>3. Cutaneous porphyria due to hepatic tumor</td>
</tr>
</tbody>
</table>

**Erythropoietic porphyrias**

The erythropoietic porphyrias accumulate the series "I" isomers in the body tissues. And, as the name implies, the site of production of excessive porphyrins is in the hematopoietic tissue of the bone marrow and is confined to the erythropoietic system within that tissue. The individual disorders are summarized as follows.

**Congenital erythropoietic porphyria.** This disease is also known as Gunther's disease and is very rare. Its onset is at or soon after birth. It is characterized by extreme photosensitivity that may lead to disfiguring skin lesions and, quite often, hemolytic anemia. Of the 50 recorded cases, there is equal distribution between males and females. The disease is transmitted as a non-sex linked (autosomal) recessive.
Clinical features include:
1. Early onset—before 6 years of age.
2. Photosensitivity — especially to sunlight. On the exposed areas of the skin, itching, erythema, and bullous eruptions occur that often lead to secondary infections and scarring. The hands become claw-like after repeated attacks. Blindness may occur if the lens is involved.
3. Loss of scalp hair.
4. Hypertrichosis.
5. The biochemical abnormality leads to accumulation of porphyrins in the bones and teeth. The teeth are often brown-pink or darker in color and fluoresce under ultraviolet light.
6. Anemia — often the presenting symptom. This is usually a hemolytic variety and may be due to either the intracorpuscular defect or due to the accompanying hypersplenism.
7. Microscopically, the bone marrow is hyperplastic.

Prognosis is very poor; none of the known cases have survived middle age. Biochemically, porphobilinogen is not excreted in excess, but uroporphyrin I and corproporphyrin I are. If one refers back to the biochemical pathways, this implies that the enzyme defect involves uroporphyrinogen III co-synthesase. Whether it is a relative or absolute deficiency is open to debate. But, the overall production of series "III" porphyrinogens is usually normal.

So, it appears that a relative decrease will increase the series "I" products which the body cannot catabolize or utilize, thus leading to deposition in the skin. The photosensitivity that occurs is probably mediated through histamine release as the result of the combined actions of porphyrins and light.

Erythropoietic corproporphyria. This is a milder form of cutaneous porphyria which was first reported in 1964. The erythrocytes contain large amounts of corproporphyrin I as opposed to uroporphyrin I in the previously described defect. The resulting photosensitivity is milder. Because of lack of cases, little more is known about this entity.

Erythrohepatic protoporphyria
Erythrohepatic protoporphyria is an uncommon form of porphyria in which there is increased erythrocyte porphyrins. But as opposed to the other two cutaneous porphyrias, the enzyme defect is in both the erythropoietic tissue and the liver. The biochemical defect results in the lack of feedback from the heme to the regulatory mechanisms.

The defect is inherited as an autosomal dominant. The onset occurs in early childhood and is usually present with a mild form of photosensitivity. This photosensitivity does have the potential of causing the severe reactions found in congenital erythropoietic porphyria. Protoporphyrin is excreted.

Hepatic porphyrias
Hepatic porphyrias should be of particular concern to the anesthetist in that it has a higher incidence of occurrence and potential severity. In addition, patients so afflicted may react to the drugs administered to them. There are three types of hepatic porphyria, all of which are inherited as autosomal dominants.

Acute intermittent porphyria. This disorder is associated with increased secretion of both 5-aminolaevulenic acid and porphobilinogen. Photosensitivity does not occur. Instead, this disorder has been nicknamed "the little simulator," because many of its symptoms are often mistaken for other diseases, such as, appendicitis, cholelithiasis, or pancreatitis. Between attacks there may be no symptoms, or there may be residuals from previous attacks.

Patients have been known to remain symptomless throughout their lifetimes. Young adults and the middle aged are the most frequently afflicted, and there is a marked familial occurrence. In addition to certain drugs, menstruation, pregnancy, infections, or alcohol, may lead to or precipitate attacks. The sex hormones' role in patho-

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genesis may account for the observation that attacks are common in females, rare before puberty, and may relate to the menstrual cycle of the individual.

*Variegate porphyria.* This type of porphyria is especially prevalent in the white population of South Africa (3/1000); with a much lower incidence elsewhere. In South Africa, it appears the majority of these cases are descendants of a Dutch immigrant that married there in 1688.⁴

The onset of this disorder is usually found in individuals who are from 10 to 30 years of age. There is increased secretion of corproporphyrin and protoporphyrin at all times during the course of the disease. During remission, the patients are asymptomatic. Acute attacks resemble those of acute intermittent porphyria.

*Hereditary corroporphyria.* As with variegate porphyria, this disorder is completely asymptomatic during remission, with the acute attack being the presenting symptom. The lesion leads to increased corroporphyrin III excretion at all times. Photosensitivity does not occur.

From the evidence available, it appears that loss of feedback control is the most likely cause of increased ALA-S activity. The cause is a specific genetic defect involving one of the enzymes of heme synthesis.

**Hepatic porphyrias**

The hepatic porphyrias all have one common characteristic—the acute attack. Severe abdominal pain, vomiting and constipation, neuropathies, and psychiatric disturbances are some of the symptoms involved. Respiratory paralysis is not uncommon; sensory disturbances also occur. Manifestations include: analgesia, hypalgesia, hyperesthesia, paraesthesia, loss of joint and vibration sense, and complete sensory loss. Lower limbs are especially affected. Neurogenic pain is often felt. Epileptic seizures occur in about 20% of the patients.

Mental symptoms include: depression, nervousness, hysteria, confusion, hallucinations, disorientation, and personality changes.

¹. Cardiovascular: characterized by tachycardia (occurs in 60% of the patients). If present, tachycardia may serve as a useful guide to the degree of activity of the disorder. In addition, hypertension is found in 55% of the patients.

². Dermatological: characterized by no photosensitivity.

³. Electrolyte disturbances: characterized by hypotension and hypochloremia; hypokalemia and alkalosis are not uncommon. Origins may be vomiting, renal dysfunction, or inappropriate secretion of ADH. The excretion pattern is such that both 5-amino-laevulenic acid and porphobilinogen are excreted in large amounts, yielding a portwine colored urine.
Recovery from an acute attack is slow. It has been shown that the primary lesion is axonal degeneration. Thus, the rate of axonal regeneration and the amount of degeneration that has occurred governs the recovery time.

Many theories have been put forth to try to explain the peripheral neuropathies. Yet, no one knows for sure the mechanisms involved, though two theories are presently in vogue which are based on the excretion products ALA and PBG. Current research has shown that ALA is capable of inhibiting ATP-ase. If so, this may lead to inhibition of Na+ and K+ balance mechanisms within the cells and result in defective conduction. This may inflict enough insult to the cell to result in a "dying back" process in the axon. PBG has been shown to be capable of producing neuromuscular blockade.

Though extension of these two effects affords a plausible explanation of the neuropathies, they still do not account for central manifestations. The blood-brain barrier does not permit passage of large amounts of heme precursors, and little is known of the results of disordered heme metabolism on the central nervous system. It should be noted, however, that while peripheral neuropathies are of long duration, central disturbances are readily reversed after an acute attack. This suggests that a different mechanism is involved, along with hyponatremia and/or other electrolyte changes.

The individual with an acute attack is not a likely candidate for surgery. In fact, it is more probable that the attack is the result of surgery, since latent or undetected individuals are often misdiagnosed, presented for surgery, given intravenous anesthesia, and develop an acute attack postoperatively.

Symptomatic cutaneous hepatic porphyria. In this disease, there is no family history involved. It is generally accepted as acquired, though genetic predisposition may play a role. It is often found in conjunction with liver pathology, particularly with alcoholism, estrogen therapy, and hexachlorobenzene poisoning.

Usually, the patient is between 40 and 60 years of age. Onset is insidious. Skin lesions occur as the result of photosensitivity. Acute attacks do not occur, and reaction to drugs is normal. The isomer type excreted is variable and large amounts are accumulated in the liver. The exact metabolic disturbance in these cases is unknown.

**Drugs**

Drugs are especially potent stimulators of exacerbations of porphyrias, notably the barbiturates. Many of the drugs known to precipitate attacks are metabolized via heme-containing microsomal enzyme systems which induce ALA-S production. Normally, this production is limited by the feedback mechanism to the amounts required to adequately reduce the inducing agent. However, with the porphyrias, the stimulation results in induction where sufficient heme cannot be produced for the feedback mechanism. The result is overproduction of ALA-S and consequently the precursor product.

Attempts have been made to correlate physical and chemical properties of drugs as to their porphyrinogenicity. Older texts hold that a common structure is involved; newer studies indicate lipid solubility may be more important. For the present, it appears more logical to rely on what experience has taught. And, accordingly, here is a listing of drugs to avoid along with safe/probably safe drugs.

### Drugs to be avoided

**Barbiturates:** All types; any form, any manner

**Antibiotics:** Sulfad drugs

**Anti-convulsants:** Hydantoin (Dilantin®)

**Antifungal agents:** Griseofulvin

**Antihypertensives:** Methyldopa (Aldomet®)

**Ergot preparations:** Methergine®

**Non-barbiturate hypnotics:**

- Chlordiazepoxide (Librium®)
- Glutethimide (Doriden®)
- Meprobamate (Equanil®)
- Methyprylon (Noludar®)

**Pyrazoline compounds:**

- Aminopyrine (Pyramidon®)

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6. If so, this may lead to inhibition of \( \text{Na}^+ \) and \( \text{K}^+ \) balance mechanisms within the cells and result in defective conduction. This may inflict enough insult to the cell to result in a "dying back" process in the axon.

7. PBG has been shown to be capable of producing neuromuscular blockade.

8. Drugs to be avoided

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- Antifungal agents: Griseofulvin
- Antihypertensives: Methyldopa (Aldomet®)
- Ergot preparations: Methergine®
- Non-barbiturate hypnotics:
  - Chlordiazepoxide (Librium®)
  - Glutethimide (Doriden®)
  - Meprobamate (Equanil®)
  - Methyprylon (Noludar®)
- Pyrazoline compounds:
  - Aminopyrine (Pyramidon®)
### Drugs that are safe/probably safe

**Analgesics:** Acetaminophen (Tylenol®), Amitriptyline (Elavil®)

**Antibiotics:**
- Penicillins,
- Streptomycins,
- Tetracyclines,
- Chloramphenicol (Chloromycetin®),
- Nitrofurantoin (Furadantin®),
- Methenamine mandelate (Mandelamine®)

**Antihistamines:**
- Diphenhydramamine (Benadryl®),
- Promethazine (Phenergan®)

**Antihypertensives:**
- Rauwolfia agents, i.e., Reserpine
- Guanethidine (Ismelin®)

**Belladonnas:**
- Hyoscine,
- Scopolamine,
- Atropine

**Corticosteroids**

**Morphine group:**
- Methadone (Dolophine®),
- Codeine,
- Meperidine (Demerol®)

**Phenothiazines:**
- Promazine (Sparine®),
- Chlorpromazine (Thorazine®),
- Trifluromazine (Vasprin®),
- Trifluoperazine (Stelazine®),
- Prochlorperazine (Compazine®)

**Miscellaneous:**
- Vitamin B,
- Vitamin C,
- Adenosine Monophosphate (Adenocrest®),
- Digoxin,
- Prostigmine,
- Neostigmine,
- Chloroquine (Aralen®),
- Diazepam (Valium®)

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### Anesthetic management

When considering anesthetic management of the porphyrias, one concentrates mainly on the hepatic porphyrias. The erythropoietic type individual is very rare, and the cutaneous hepatic porphyrias supposedly have normal reactions to drugs.

Sound management for the hepatic porphyrias would include, preoperatively, a thorough examination, and, if possible, a review of previous anesthetic records. Especially pertinent points to note are (1) neurological changes, (2) electrolyte disturbances, (3) cardiovascular changes, and (4) respiratory changes. Neurological lesions, if present, should be clearly defined on the chart; both for postoperative evaluation and medicolegal reasons. Electrolyte changes may be expected if abdominal symptoms have been prolonged and/or have been accompanied by vomiting. Hypertension associated with attacks tend to be quite likely under anesthesia.

Absolutely no barbiturates should be given preoperatively. There appears to be no contraindication for the other common premedicants when considering porphyria per se. As a premedicant, the phenothiazine drugs are especially good, since they may relieve some of the symptoms and psychic manifestations.

When considering anesthetic agents, again, absolutely no barbiturates should be used. Althesin (Alphaxalone + Alphadolone) has been shown, experimentally in rats, to significantly raise ALA-S activity. Its use would therefore be questionable. Propanidid, ketamine phenoperidine, and droperidol do not increase this activity and would probably be satisfactory. All of the inhalation agents have been reported with safety, and the opiates also appear to be satisfactory.

When considering relaxants, aetocaine still appears to be the agent of choice. This stems from a theoretical objection to the use of reversal agents with the nondepolarizing relaxants. Certain phosphorus containing insecticides that have anticholinesterase activity have been shown to cause demylenization. Extrapolation to the reversal drugs has lead to their avoidance. However, since it has recently been shown that axonal degeneration is the lesion and not demylenization, thoughts on the matter may be changing. The use of neostigmine and curare to control some of the symptoms without consequences lends credence to the view that nondepolarizers and reversal agents are safe for anesthetic use.
In spite of no medical contraindications, conduction anesthesia is not recommended for these patients because of the legal ramification should a neuropathy develop.

Opiates and meperidine may be used for pain control postoperatively. Chloral and paraldehydes may be used for sedation.

Summary

The porphyrias are a result of disordered heme metabolism. The sequelae are related to the accumulation of precursors and/or their metabolism. Induced drug metabolism can lead to acute attacks and may result in fatalities. Careful selection of intravenous agents, absolute avoidance of barbiturates, and use of inhalation agents can enable the anesthetist to administer safe anesthesia to these endangered patients.

REFERENCES


ADDITIONAL READING


AUTHOR

Robert A. Larter, CRNA, holds a BS in Medical Technology and obtained his nurse anesthesia education from St. Mary's Hospital School of Anesthesia in Minneapolis, Minnesota. At the time this paper was written, he was a senior student in anesthesia and submitted the paper at the recommendation of the school's director, Mary A. Crandall, CRNA. Mr. Larter currently practices anesthesia in Minnesota.