[Porphyrias]

MEDICINE GRAND ROUNDS
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PORPHYRINURIA VERSUS PORPHYRIA

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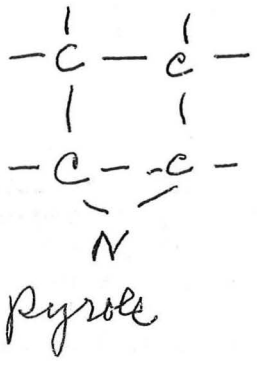
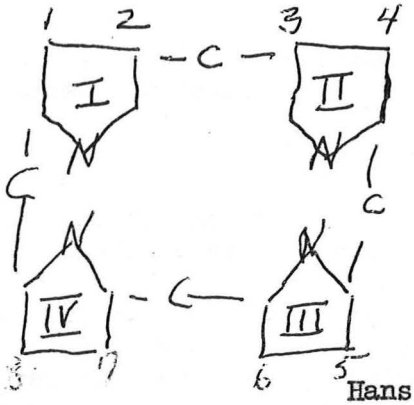
PORPHYRINURIA OR THE NORMAL STATE: The porphyrin molecule is a simple addition product of four pyrole rings with variations on the periphery and in the center. There is good evidence that the basic building blocks are the glycine and acetate units. The first stage of complex formation may be under all conditions (or possibly only abnormal states), the formation of porphobilinogen. By further chemical complex formation this compound may add up to the mature porphyrin. The following formulae are essential in this subject:





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Four pyrole rings become a tetrapyrole or a porphyrin. Dr. Fischer has termed this basic structure an aetioporphyrin. By structural interchanges in the positions at the different corners of the pyrole rings (180° rotations) it is possible to have four possible variations which are the basic isomer patterns (Isomers I, II, III, and IV). Only isomers I and III have been found to exist in biologic life.

The four pyrole rings within the porphyrin ring are indicated by Roman numerals I through IV and have a total of eight terminal points at which there may be the addition of other chemical groups as sidechains. The variations in these eight sidechains (acetic and proprionic acid, vinyl or methyl groups) result in the three clinically important porphyrin compounds:

Uroporphyrin
Coproporphyrin
Protoporphyrin

The isomeric forms of these compounds that are found in the normal human are:

Coproporphyrin I and III
Protoporphyrin III

and are located physiologically as:

	Quantity
Urine	
Coproporphyrin I - - - 70%	Total: 100-300 gamma/day
Coproporphyrin III - - 30%	
Feces	
Coproporphyrin I, III	Total: 400 - 800 gamma/day
Protoporphyrin III	
Red Cells	Total: 35 to 45 gamma/100 ml RBC's
Coproporphyrin I, III	
Protoporphyrin III	

A request to a laboratory for "porphyrinuria check-up" or "check for porphyrins" should really result in a measurement of the amount of coproporphyrin in the urine.

In porphyria one will find the following alterations:

Urine: (a) Uroporphyrin present
and (Usually in great excess)
coproporphyrin present
(b) Porphobilinogen present (This is not diagnostic as cirrhosis or drug poisoning may cause this abnormality).
(c) Porphobilin is present and is the oxidized form of porphobilinogen which turns the urine from port-wine color to black in the classical case when the urine is exposed to heat or sunlight.

Feces: Uroporphyrin now also present in addition to coproporphyrin and protoporphyrin and all are present in increased amounts.

RBC's: Same as fecal alteration.

TECHNOLOGY OF PORPHYRINS: Pyrole rings are not analyzed by clinical laboratory tests. The mono-pyrole, porphobilinogen, is a non-fluorescent compound which is analyzed by a dye-complex/differential solubility test. Urine plus Ehrlichs Reagent plus saturated sodium acetate will give a violet-pink color. This may be due to either urobilinogen or porphobilinogen. Chloroform is then added and any pink color due to urobilinogen will pass down into the chloroform layer leaving the supernatent urine-water layer either colorless or frequently an off-color yellow or brown. This is frequently and erroneously interpreted as a positive test. A positive test for porphobilinogen should only be reported when the supernatent layer remains violet-pink. If there is a large amount of urobilinogen present in the urine one should re-extract the urine/water fraction with chloroform until the choloroform is colorless and then interpret the supernatent pink colored fraction as indicating the presence of porphobilinogen.

The entire group of porphyrins, each type, and each isomer are all similar in that they emit a red-oarnge fluorescent light when excited by a near ultra-violet light. The different porphyrins are separated by their variations in solubilities in acids, alkali, or organic solvents. In white light they are colorless in solution (unless very concentrated) and are deep brick red when crystallized. Careful quantitative analysis depends on prior specific differential solubility extractions (of either urine, RBC's or feces) and then comparing the amount of fluorescence of the sample against a known pure standard in a fluorimeter (a colorimeter modified to use ultra-violet light as a source and to filter all transmitted light except the specific emission spectrum, red).

A simple presumptive test for uroporphyrin which will be positive in active porphyria and negative in the normal or diseased non-porphyric patient is as follows: In a separatory funnel add 100 ml. of urine, add 20 ml. portions of ethyl ether, add glacial acetic acid (5 ml.) and 5 ml. of saturated sodium acetate. The urine should be negative to Congo Red paper. Shake the urine and check for red fluorescence in the two layers. If both are deep red under the ultra-violet light it is suggestive of porphyria. Remove the ether layer and re-extract repeatedly with ether until the ether does not glow pink under ultra-violet light. If the lower layer (water-urine) now shows a pink fluorescence in ultra-violet light this indicates the presence of uroporphyrin and establishes the diagnosis of porphyria.

CLASSIFICATION OF PORPHYRIA:

(a) Porphyria erythropoietica, or infantile type, or congenital porphyria, or light sensitive porphyria.
(b) Porphyria hepatica, or adult porphyria, acute intermittent porphyria, paralytic porphyria.
(c) Porphyria hepatica cutanea tardive, or mixed type, or adult light sensitive porphyria.

In 1950 it was established that there were two congenitally transmitted disease states; inherited as a recessive which could be divided into two types of porphyria dependent on the location of the defect in the anabolic cycle of the porphyrin ring. The one is completely and solely limited to a bone marrow defect and the second to the liver.

CASE HISTORIES:

Case 1: [redacted] was a three year old white female child born of Scandinavian parentage who was admitted to the Pediatric Service because of the following: Pallor, ulcerating lesions on the exposed skin with secondary scar formation, failure to grow normally, discolored teeth, enlarged liver and spleen, the skin and teeth changes had been present since about one year of age. Lab. studies revealed a hemolytic anemia with marked erythropoietic release from the marrow, and impaired liver function. The urine was dark red to black in white or ultra-violet light, the teeth fluoresced in UVL. The blood and feces glowed red in UVL. All of these abnormalities were reversed by a splenectomy. Diagnosis: Porphyria erythropoietica.

Case 2: Mrs. [redacted] This 48 year old white female [redacted] was admitted because of severe abdominal pain, bloating, weakness, nervousness and constipation. There were no positive physical findings and gross inspection of the urine was normal in white light. The urine did not turn dark when allowed to stand in the window for 24 hours. There were mild abnormalities in the liver function tests indicating mild parenchyeal damage. The urine was positive for porphobilinogen and uroporphyrin. Diagnosis: Porphyria hepatica.

Case 3. A 55 year old white [redacted] noticed that he had had epigastric distress for years and he noticed that gradually an exposure to the sun seemed to cause blisters to form on the exposed skin. All the studies and examinations were normal except that large amounts of uroporphyrin were found in the urine. Avoiding exposure to sunlight would decrease the amount of pigment in the urine and prevent the development of the bullae on the skin. Diagnosis: Porphyria hepatica cutanea tardive.

Case 4: A young female was admitted to the hospital with abdominal pain and weakness in both legs. She was given paraldehyde for her pain and seemed to have a marked increase in weakness within 24 hours. She was from Switzerland and one brother had died in a psychiatric hospital following acute psychosis said to be due to porphyria. Physical examination was negative except for a weakness in the lower leg muscle groups. Over a three day period the weakness progressed to flaccid paralysis which progressed craniad and resulted in death despite the use of an artifical respirator. Diagnosis: Porphyria hepatica with CNS involvement.

TREATMENT

1. Avoid all enzyme inhibitors such as alcohol, barbiturates, anesthetics, and narcotics.
2. No specific therapy is available. The most likely to succeed according to recent tests is chlorpromazine. The other drugs that may be tried and are of occasional value are: ACTH, Etamon, and demerol seems to be the least harmful narcotic.
3. Supportive care as the case demands.

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