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PORPHYRIA — AN "ENZYME LESION" REVIEW OF BASIC AND CLINICAL ASPECTS

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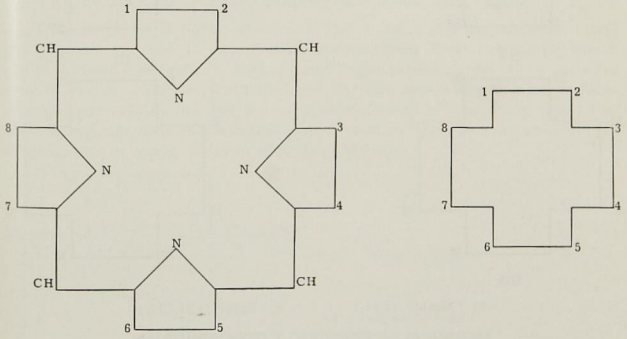
As knowledge of cellular bio-chemistry increases, physicians have more and more begun to think of disease processes in terms of defects or alterations in the myriad of chemical reactions within the cell. We hear now in discussions of diseases such as Cushing's disease, pernicious anemia, gout and adrenogenital syndrome, the term "enzyme lesion" or enzymatic defects. The term "enzyme lesion" was coined by Gerti Cori who described the first one completely understood — glycogen storage disease. An intimate knowledge of bio-chemistry is becoming as valuable a tool in clinical medicine as the stethoscope or palpating hand. The disease here presented, acute intermittent porphyria, affords an opportunity to review the important metabolism of a group of chemical compounds known as the porphyrins. The porphyrins are much more important than porphyria. Porphyria is very uncommon, whereas the porphyrins are important in the cellular activity of all the cells of the body.

The porphyrins comprise a large class of pigments, and the exact chemical constitution of the majority of them is unknown. Porphyrins are found throughout the animal and vegetable kingdom. Chlorophyll, for example, intimately involved in photo-synthesis, is a porphyrin containing magnesium. All the porphyrins contain the porphin nucleus as their basic structure. Porphin may be synthesized, but it is purely a laboratory creation and does not exist in nature. It is composed of four pyrrole rings connected by four methene bridges. By the addition of side chains on carbon atoms 1 through 8, all the porphyrins may be represented.



PORPHIN

PORPHIN (SHORTHAND REPRESENTATION)

FIGURE I — BASIC COMPOUND PORPHIN

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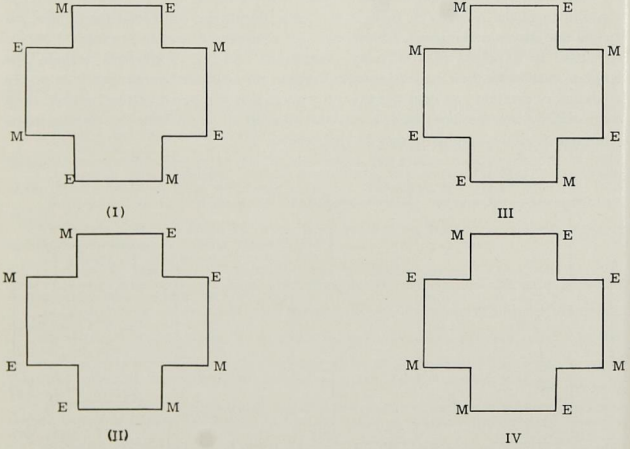
In figureI I the basic compound porphin is represented. To simplify its representation the shorthand method of Fischer is usually used as shown. The porphyrins which demand our interest in clinical medicine, and whose structure will be shown, are protoporphyrin, coproporphyrin and uroporphyrin.[1] These compounds are important only because they are intermediates in the production of the metalloporphyrins — hemoglobin, oxidases, catalases, peroxidases and cytochromes, all of which are respiratory enzymes. It should be emphasized that uroporphyrin, coproporphyrin and protoporphyrin are steps in the synthesis of the metalloporphyrins and are not breakdown products.

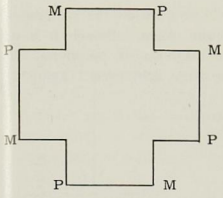
The question arises regarding the numbering of the porphyrins. For example, we read of uroporphyrin I and uroporphyrin III. The numbering has its origin in the classic work of Hans Fischer, who in 1937 synthesized a basic porphyrin compound which he called etioporphyrin, a tetramethyltetraethyl porphyrin, (again only a synthetic compound). This is represented in figure II using the shorthand symbol of Fischer for the porphyrin nucleus and showing the four possible isomers. Any porphyrin having just 2 different side chains and 4 of each has only 4 possible isomers.



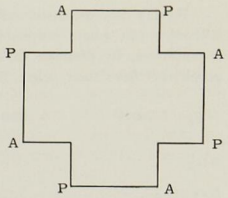
M Methyl (CH_3) E Ethyl (CH_3CH_2)

FIGURE II — ISOMERIC ETIOPORPHYRINS

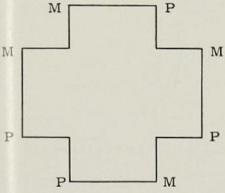
Regarding the structure of the clinically important porphyrins, coproporphyrin has side chains of methyl and propionic acid, and uroporphyrin has acetic acid and propionic acid for side chains. Again 4 isomers of each are possible, but only numbers I and III exist naturally, and these are shown in figure III.



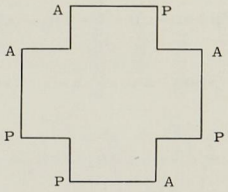
Coproporphyrin I



Uroporphyrin I



Coproporphyrin III

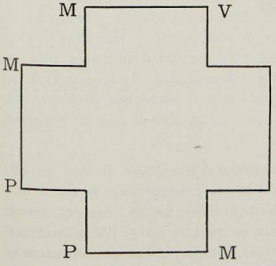


Uroporphyrin III

M Methyl (CH_3) P Propionic Acid (CH_2CH_2COOH) A Acetic acid (CH_2COOH)

FIGURE III — PROTOPORPHYRIN WITH SIDE CHAINS

Proto porphyrin is slightly different in that it has 3 side chains, methyl, vinyl and propionic acid and 15 isomers. The protoporphyrin found naturally is type 9 and is represented in figure IV. It is so called simply because it was 9th in the series listed by Fischer. Here the parenthetical type III might lead to some confusion. However, this refers only to the fact that protoporphyrin type 9 is related to type III of the etioporphyrins since all the methyl groups are in the same position, and this type III designation is usually added to show this relationship.



M Methyl (CH_3)

V Vinyl ($CH\ CH_2$)

P Propionic Acid (CH_2CH_2COOH)

FIGURE IV — PROTOPORPHYRIN NO. 9 (Type III)

Having now discussed individual porphyrins, we will now review the synthesis to determine just where porphobilinogen fits into the picture, since, although it is not a porphyrin, its presence in the urine establishes the diagnosis of porphyria. The porphyrins have their origin from succinic acid of the citric acid cycle. (figure 5).

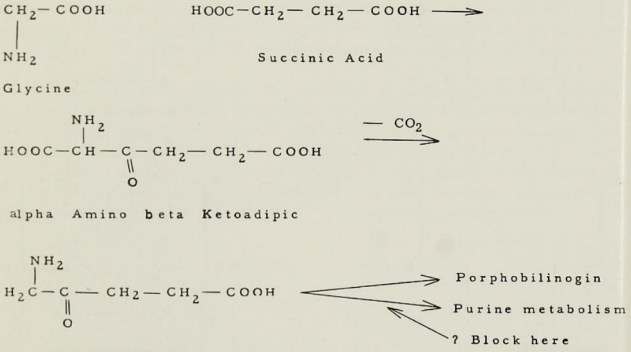


FIGURE V — SYNTHESIS OF DELTA-AMINOLEVULINIC ACID

To succinic acid is added glycine from the glycine pool and alpha-amino-beta-ketoadipic acid is formed. This is decaraboxylated to delta-aminolevulinic acid and two molecules of delta-aminolevulinic acid fuse to form porphobilinogen. (figure 6).

Delta-aminolevulinic acid is not simply a stage in the path from the citric acid cycle to the porphyrins, but is rather a fork in the metabolic road since it is also deaminated to form ketogluteraldehyde and progresses into the purine metabolism. It is here that an enzymatic block might occur in the conversion of delta-aminolevulinic acid into the purines with the result that more delta-aminolevulinic acid could be forced into porphyrin synthesis at the expense of the purines.[3] Manifestations of porphyria might, therefore, be due to diminished purine metabolism rather than an overabundance of presumably "toxic" porphyrin intermediates. To come back to porphobilinogen, the metabolic pathway to this point is well established. However, the exact pathway beyond is speculative; presumably on a gross scale it may be presented as shown in figure VI and VII.

In this process the uroporphyrin I and coproporphyrin I are formed as side products and excreted. As far as the excretion of these compounds is concerned, corproporphyrins are excreted in detectable amounts in the urine and stool of normal individuals. The normal values of corproporphyrin in urine is 100 - 300 micrograms; 60 to 90% of this is in the form of isomer type I. Uroporphyrins are not excreted in detectable amounts in normal persons, although uroporphyrin may be shown in

FIGURE VI
SYNTHESIS
OF
PORPHOBILINOGEN

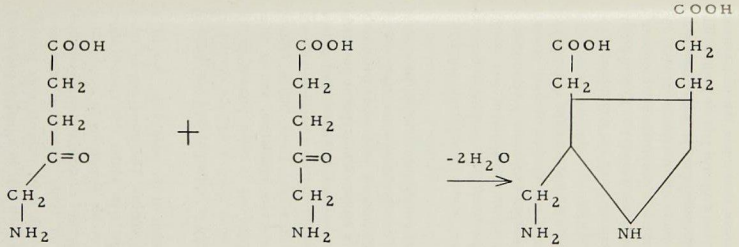
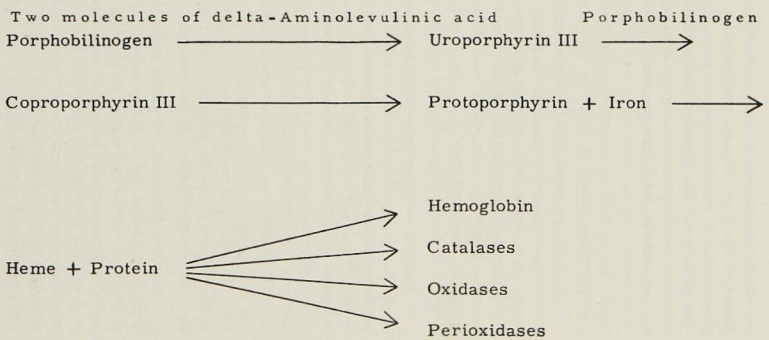


FIGURE VII
METABOLIC
PATHWAYS
BEYOND
PORPHOBILINOGIN
(Schematic)



the urine by more precise methods not readily available. Porphobilinogen is not normally present in the urine. This has great practical significance then since the diagnosis of porphyria for all practical purposes is made by finding the uroporphyrin or porphobilinogen in the urine. The Schwartz-Watson Test for porphobilinogen[4] is readily available, and this is usually positive during the acute stages of acute intermittent porphyria, and in some of the cases of mixed porphyria. It is not positive in porphyria erythropoietica or porphyria cutanea tarda, but it may be positive in latent porphyria. Coproporphyrinuria has in itself no diagnostic value since its presence may be symptomatic and indicate another disease process. This will be discussed later.

Clinically, porphyria may be defined simply as an INBORN ERROR in porphyrin metabolism. Various classifications have been presented but that of Watson is most widely used. Porphyria is divided into two main groups: Porphyria erythropoietica and porphyria hepatica. This classification is based upon the apparent site of the abnormal porphyrins in the bone marrow and in the liver. The porphyria hepatica is further subdivided into 4 groups, late porphyria, acute intermittent porphyria, porphyria cutanea tarda and mixed porphyria.

Porphyria erythropoietica (also called congenital porphyria, although in a sense all the porphyrias are congenital or inborn errors of metabolism) is the rarest of all the forms of porphyria and is characterized by splenomegaly and appearance early in life of sensitivity to light with the formation of skin lesions. This type of porphyria is apparently not familial, and there is no difference in the sex incidence. Red stained diapers may be the first clue to its presence, but usually vesicles or bullae with sun sensitivity are the trade mark of porphyria erythropoietica. These bullae become infected, necrotic and show deep scarring, producing severe mutilation, and at times loss of fingers, toes or ears has been noted. Hypertrichosis is often present in this form. The abnormal prophyrins are produced in the bone marrow and the developing erythrocytes may show fluorescence. Uroporphyrin I and coproporphyrin I are found in the urine; porphobilinogen is not excreted.

Porphyria hepatica is the second major classification of the porphyrias. Porphyria hepatica is familial and is slightly more common in women. The usual age of onset is 20 to 40. *Acute intermittent porphyria* is the first type under this classification, and it may present with abdominal, neurologic or psychic symptoms in combination or alone. The abdominal complaints may mimic any sort of acute abdominal condition. The ability of the porphyrin to masquerade as an acute abdominal emergency is attested to by the number of abdominal scars which these patients may present. Index of suspicion of porphyria is to be multiplied for each scar in a patient presenting with acute abdominal pain. (The pain is usually cramping in nature and, by way of help in differentiation, although leucocytosis is usual, the abdomen is usually soft and tenderness is minimal). Involvement of the nervous system may occur in any of its parts — central, peripheral or autonomic and consequently may take many forms. The paralysis is of the flaccid variety and may vary from foot or wrist drop to a flaccid quadriplegia. Paralysis may progress in a manner suggesting Landry's paralysis. The Guillain-Barre syndrome may be mimicked. Cerebral spinal fluid is usually normal except for minimal protein elevation. The cranial nerves may be attacked with facial weakness or ocular paralysis. Pain in the legs to suggest diabetic neuropathy may occur

before or with the paralysis. The degree of pain will vary with the degree of peripheral neuritis. Despite the presence of paresthesias, sensory changes are generally absent. Coma, convulsions and epileptiform attacks may occur. The mental changes possibly embrace the field of psychiatry. As a matter of fact, Waldenstrom discovered most of his cases of porphyria by simply testing the urines of a large number of patients in Swedish mental hospitals. Before the acute attack comes on, the patient may have had a long history of psychoneurosis.

Porphyria cutanea tarda resembles the porphyria erythropoietica because of the skin lesions and photosensitivity. However, the age of onset is from 40 to 60 years and the skin lesions, though similar, are less mutilating and hepatic dysfunction is often present. If the cutaneous lesions are present in addition to neurologic or abdominal manifestations, then these cases are referred to as *mixed porphyria;* and if the patient appears to be well but yet excretes porphobilinogen or uroporphyrin in the urine, the patient is said to have *latent porphyria.*

An important point must now be raised regarding porphyrinuria as opposed to porphyria. It should be emphasized that the finding of an excessive amount of coproporphyrin in the urine does not make the diagnosis of porphyria by itself. This merely represents porphyrinuria or, to be more specific, coproporphyrinuria and is merely a manifestation of another disease process. Coproporphyrinuria has been found in a large variety of diseases such as infectious hepatitis, obstructive jaundice, pernicious anema, hemolytic anemia, poliomyelitis, Hodgkin's disease, Laennec's cirrhosis and in

		PORPHOBILINOGEN	UROPORPHYRINS	COPROPORPHYRINS
NORMAL		NEGATIVE	NEGATIVE	Total 100-300 MCG Type I (60-80%) and Type III
PORPHYRIA ERYTHROPOIETICA		NEGATIVE	Type I	Type I
PORPHYRIA	ACUTE INTERMITTENT	POSITIVE	Type I	Type III
PORPHYRIA	PORPHYRIA CUTANEA TARDA	NEGATIVE	Type I	Type III
HEPATICA	"MIXED" PORPHYRIA	MAY BE POSITIVE	Type I	Type III
HEPATICA	"LATENT" PORPHYRIA	INTERMITTENTLY POSITIVE	Type I Intermittently	Type III Intermittently
COPROPORPHYRINURIA		NEGATIVE	NEGATIVE	Types I and III

TABLE I

SUMMARY OF THE URINARY PORPHYRIN EXCRETION IN THE PORPHYRIAS

infection processes such as pneumonia. Porphobilinogen is usually present in the urine of symptomatic cases of acute intermittent porphyria, present intermittently

in latent porphyria and may be present in mixed porphyria. It is not present in porphyria cutanea tarda and porphyria erythropoietica. All the forms of porphyria hepatica may show coproporphyrin III and a uroporphyrin which is usually referred to as Waldenstrom's uroporphyrin and is probably uroporphyrin type I, although it is claimed by others to be type III. Uroporphyrin I is found in the urine of porphyria erythropoietica. Regarding the color of the urine, grossly, it is usually thought that the urine must be colored to suggest a diagnosis; though actually porphobilinogen is colorless and the other porphyrins excreted will color urine only when excreted in large quantities such as in porphyria erythropoietica. From a practical standpoint then, a normal colored urine does not exclude the diagnosis of porphyria.

From the standpoint of treatment, splenectomy and protection from the sun in the porphyria erythropoietica are indicated, and screening from the sun would be indicated in the porphyria cutanea tarda. For the varied manifestations of acute intermittent porphyria in the form of abdominal neurologic or psychic symptoms, a wide variety of agents has been tried, and it is probably more important to know what not to give these patients. Alcohol and barbiturates are definitely contraindicated since they have been reported to precipitate an episode of porphyria.[5] For the relief of pain and sedation, Demerol, Chloral Hydrate and Paraldehyde are effective and apparently do no harm. At various times intravenous calcium, crude liver extract, Tetraethyl-ammonium Chloride, Cortisone and ACTH have been recommended, all with varying degrees of success. Chlorpromazine has recently been reported to be helpful.[6] Schrumpf[7] and Peters[8] have reported good results in the treatment of acute intermittent porphyria with BAL (Dimercaprol). Peters noted in some of his cases that an increased amount of zinc was present in the urine. BAL was given in an attempt to aid in the excretion of the zinc. The chelating agent disodium calcium versenate has been recommended and apparently may be effective on a similar process. An increased amount of zinc may be important in producing an enzyme lesion possibly by blocking to some extent the transformation of the porphobilinogen to the purines. BAL was chosen as the agent to be tried in the case of acute intermittent porphyria now to be discussed.

Patient (LH) a 43 year old, white housewife was admitted to another hospital on February 9, 1957, complaining of mid-abdominal pain which had been present for 2 days and was associated with nausea and constipation. The past medical history was negative. The pain persisted for 6 days, requiring narcotics at regular intervals. The pain disappeared then but was followed by development of pain in the legs and progressive weakness of the arms and legs. A Watson test for porphobilinogen was positive and the patient was transferred to Henry Ford Hospital on February 21, 1957.

The physical examination on admittance here was normal except for the neurologic findings. The patient was extremely lethargic. She would respond briefly to questioning but was unable to remain alert for any sustained period. There was a flaccid quadriplegia, and brain stem involvement was present with facial diplegia, ocular weakness and dysphagia. Sensation appeared intact.

On admission the urine was dark brown, gave a yellowish green fluorescence under a Wood's lamp and was positive for porphobilinogen. The hemoglobin was 12.8 grams, white count 12,200. Spinal fluid was negative except for slightly elevated protein of 57 mgm%. No cells were seen in the spinal fluid. An electroencephalogram showed a diffuse depression of electrical activity. Skull x-rays were negative.

The patient was started on BAL in a dose of 100 mgm every eight hours on February 23, 1957. An elective tracheotomy was done for retained secretions, and the patient was also begun on tube feeding via the Barron pump. Within 24 hours the patient was able to converse with the attending physicians and even stated a desire to go home, although the paralysis remained as before. She remained on BAL until March 15, 1957. During this period she was also given Chlorpromazine 25 mgm every 6 hours, as necessary, for moderate extremity pain which she was experiencing. The muscle power in the extremities gradually improved until discharged on April 13, 1957. At that

time the patient was getting out of bed in a chair for short periods and was noting increasing ability to move the extremities and had begun to feed herself.

The important aspects of physiotherapy and measures for rehabilitation in this patient were conducted throughout her hospital stay by Dr. William Schaefer and his staff in the Division of Physical Medicine and Rehabilitation.

Other laboratory data accumulated during the patient's illness were reported as follows: Cephalin cholesterol 1 plus, thymol turbidity 1 plus, thymol floculation negative, zinc sulfate 7 units, serum sodium 128 milli-equivalents per liter, serum chloride 106 milli-equivalents per liter, uric acid on two occasions was 1.3 mgm % and 2.2 mgm % and a 24 hour urine uric acid was 547 mgm (normal equals 500 mgm to 1000 mgm a day). The low figures for serum uric acid and 24 hour uric acid excretion lends some credence to the hypothesis that porphyria represents a block in the conversion of delta-aminolevulinic acid metabolism towards the purine metabolism. BSP showed 17% retention at 45 minutes, serum bilirubin a total of 0.5 mgm %, direct 0.125 mgm %. The sed rate was 2. Urinalysis was negative, non-protein nitrogen 28 mgm %, direct and indirect Coombs tests were negative, prothrombin time 16 seconds 90%, reticulocyte count 6%. Electrocardiograph was normal except for sinus tachycardia, and chest x-rays were negative.

On February 25, 1957, the 24 hour urine contained 21.8 mgm of porphobilinogen, 6000 micrograms of coproporphyin and 1750 micrograms of uroporphyrin. Daily quantitative determinations of porphobilinogen and coproporphyrin were done until March 2, 1957, and the quantity of these two compounds fell slowly so that on March 2nd the urine contained only 1.8 mgm of porphobilinogen and 1,680 micrograms of coproporphyrin. No further determinations of coproporphyrin were made, but the quantity of porphobilinogen continued to fall until it was absent within three weeks after admission and remained absent for the remainder of her hospital course. The urine color varied from dark brown to light straw. There was no appreciable change with exposure to light.

A niece of the patient gave a history of a very similar illness diagnosed as acute intermittent porphyria several years ago. The niece furnished a 24 hour urine for tesing, and it gave a positive reaction for porphobilinogen. The niece had no symptoms at that time, but interestingly enough, the patient who was bedridden by the same disorder was then passing urine which was negative for porphobilinogen.

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