Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Porphyria

Volume XIV | Friday, October 30, 1942 | Number 5

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Volume XIV | Friday, October 30, 1942 | Number 5

INDEX

Published for the General Staff Meeting each week during the school year, October to June, inclusive.

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William A. O'Brien, M.D.

I. LAST WEEK

Date: October 23, 1942

Place: Recreation Room
Powell Hall

Time: 12:15 to 1:30 p.m.

Program: "Hyperthyroidism, Pre- and Postoperative Problems"
Charles E. Rea

Discussion
O. H. Wangensteen
G. T. Evans
C. J. Watson
Ralph Knight
Adam Smith
K. W. Stenstrom

Present: 122

Gertrude Gunn,
Record Librarian

- - -

II. BABIES

A daughter, Susan Jane, to Dr. and Mrs. Rodney F. Sturley, Sunday, October 18. (In service)

A son, Richard, Jr., to Dr. and Mrs. Richard Varco, September 13, 1942.

A son, Frederick Eldon, to Dr. and Mrs. Lyle French at St. Mary's Hospital, October 5, 1942.
(In service)

- - -

III. MEETINGS

1. PATHOLOGY SEMINAR

November 2, 1942, at 12:30 p.m. in 104 Anatomy.

"Synovialoma" - J. S. McCartney

- - -

2. ANATOMY SEMINAR

Saturday, October 31, at 11:30 in room 226 Institute of Anatomy.

"The milk factor and leukemia" - Arthur Kirschbaun
"Parasites of the American Elk" - Richard Winger

- - -

3. ANNUAL BANQUET OF THE ST. PAUL SURGICAL SOCIETY

Thursday, November 12, 1942 at 7:30 p.m. at the Minnesota Club in St. Paul.

"The Stage Resection of the Duodenum and Head of the Pancreas for Carcinoma" by Dr. Alexander Brunschwig, Professor of Surgery, University of Chicago.

Please make reservations through Charles Rea.

- - -

4. BACTERIOLOGY SEMINAR

Thursday, October 29, 4:30 p.m., 214 Millard Hall.

"How Bacteria Produce Disease"
Abe Stavitsky.

- - -

IV. WANTED

Physician for locum tenens, November 13 - 20, 1942. Preferably one on obstetrical and gynecological fellowship. Salary open.

A. W. Sommer, Elmore, Minn.

- - -

V. PORPHYRIA

Samuel Schwartz
C. J. Watson

Introduction

There are in medicine a number of diseases which, despite their relatively rare occurrence, have stimulated widespread interest. This stimulation has usually been due not alone to the unique features which the disease may exhibit, but especially to the realization that if its nature could be clarified there would follow a much wider understanding of the fundamental character of a number of other related diseases. Thus it is with the relatively rare condition known as porphyria, the final elucidation of which will contribute much to our knowledge of pigment metabolism and diseases of the liver and blood forming organs.

Definition

Porphyria is a disease of unknown etiology characterized by the excretion of red (or potentially red) urine containing uroporphyrin and related compounds. The abnormal formation of uroporphyrin is to be regarded as a constitutional fault, or an "inborn error of metabolism." (Garrod[1]) This applies to both types of porphyria, the congenital or photosensitive type, and the intermittent acute variety, characterized by abdominal colic and nervous manifestations. (See below)

It may be emphasized that porphyria is to be distinguished sharply from ordinary porphyrinuria, which denotes simply an increase in the excretion of coproporphyrin, a product of normal metabolism. Unfortunately, these terms have often been used interchangeably.

Historical

Hoppe-Seyler, in about 1870, described the formation of hematoporphyrin from hemoglobin by the addition of blood to concentrated sulfuric acid. He noted its characteristic fluorescence in ultra violet light and its typical absorption spectrum. Other investigators described the occurrence of what they thought was the same porphyrin in the urine of patients with various disorders, and especially with what is now termed "porphyria." These early studies were excellently summarized in a monograph by Gunther[2] in 1912.

Most of our present knowledge of porphyrins and porphyria stems from the investigations of H. Fischer.[3] He demonstrated in 1915 that the naturally occurring porphyrins differ chemically from hematoporphyrin, which has never been found to occur in nature. The porphyrin which he named uroporphyrin was isolated from the urine of the case Petry, a very well known case of congenital porphyria, and one that was studied at necropsy in extenso by Borst and Königsdörffer.[4] Uroporphyrin was found to have eight carboxyl groups. A similar porphyrin, coproporphyrin, with but four carboxyl groups was isolated from both feces and urine, and was subsequently shown to be present normally in very small amounts.

It might be here noted that H. Fischer's studies of the porphyrins and porphyria culminated in 1929 with the synthesis of hemin. These studies have served as the basis of our present day knowledge of hemoglobin metabolism and of the porphyrin containing respiratory enzymes.

Classification

In the absence of known etiologic factors, various classifications, based upon either chemical or clinical findings, have been suggested. Without entering into a discussion of these it may be stated simply that there are two main types of porphyria: 1) Intermittent acute, and 2) Congenital. It should be noted, however, that the intermittent acute type may likewise be congenital in the sense that it is unquestionably a constitutional abnormality that is often familial. Furthermore, the urinary findings may be present for years before or after (or even without) an acute attack.

A toxic form of porphyria might be considered a subdivision of the first type. It follows the ingestion of sulfonal, trional, and rarely of other drugs. Over 100 such cases have been reported, with a mortality of over 90%. There is much reason to believe that the drug is simply a precipitating factor in an individual of porphyric constitution.

The present monograph is concerned especially with the intermittent acute type. Only passing attention will be given to the congenital (photosensitive) type of porphyria. The latter condition has been reviewed recently by Turner and Obermayer.[5]

The following are among the principal distinguishing features of the two forms:

- - -

	Intermittent Acute	Congenital
Sex	More common in females (3:1)	More common in males (3:1)
Age of onset	20 -- 40 years	Infancy or early childhood
Symptoms and findings	Abdominal colic	Photosensitivity
	Abdominal colic Neuritis and paralysis	Hydroa estivale, later mutilation of exposed areas.
	Mental confusion, psychoses, and pseudohysteria	Erythrodontia and red bones
	Oliguria and hypertension	
Course	High mortality after acute or subacute course.	Long chronic course.
Cause of death	Bulbar palsy	Intercurrent disease
Urine findings	Uroporphyrin, chiefly type III	Uroporphyrin, chiefly type I
	" " Xinc complex	" " free (?)*
	Porphobilinogen	No porphobilinogen (?)*

*Has been insufficiently studied.

- - -

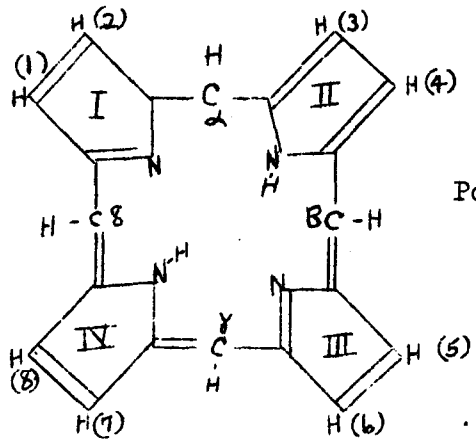
In the intermittent acute type, it is probably best to subdivide the cases into: 1) manifest, and 2) latent, varieties. This separation is based purely upon the presence or absence of acute attacks or other obvious manifestations of the disease, not upon the chemical examination of the urine.

The diagnosis of the latent condition is most commonly made by routine examination of the urine of relatives of patients suffering from an acute attack. Intermittent acute porphyria, according to Waldenstrom, appears to be inherited as a mendelian recessive character.

Our own study embraces a total of 13 cases of the intermittent acute type. Of these 9 were manifest and 4 were latent.

Chemistry

A porphyrin is a chemical substance made up of a ring of four pyrrol nuclei united by methene bridges. For the sake of simplicity all porphyrins may be thought of as derivatives of the synthetic substance, porphin.



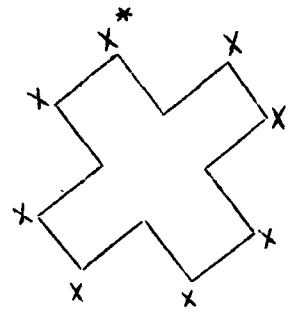
Porphin

In this formula, the following will be noted:

1. The pyrrol nuclei are numbered I through IV.
2. The methene bridges are numbered α through δ (or a thru d).
3. The side chains (only H in the case of porphin) are numbered 1 through 8.

(The above numbering is, of course, omitted in the usual illustration of formulae)

Since the various porphyrins differ only in their side-chain constituents, the following symbol may be used to represent porphyrin formulae.



* X = side chain group.

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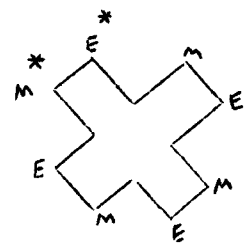
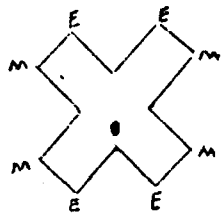
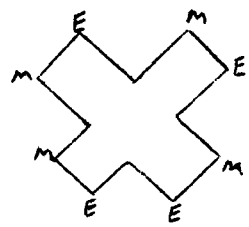
H. Fischer has shown that if four ethyl and four methyl groups are substituted for the hydrogens of porphin, four isomers of so-called aetioporphyrin are obtained.



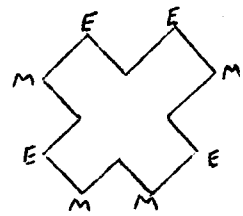
Aetioporphyrin I



Aetio. II



Aetio. III

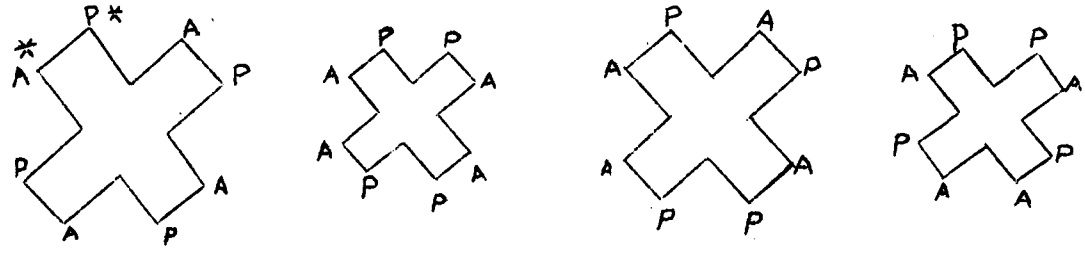


Aetio. IV

* M = Methyl
* E = Ethyl

The aetioporphyrins are purely artificial, do not occur in nature and are of importance only as reference compounds and as a basis for classification.

Similarly, any of the porphyrins having 2 different side groups may be referred to the corresponding aetioporphyrin. Thus,



* A = Acetic acid
* P = Propionic acid

It should be emphasized that of the above porphyrins, only types I and III have been found in nature. H. Fischer, in his postulation of the "dualism" of the porphyrins, has pointed out that one isomer type cannot be converted to the other without destruction of the ring and rotation of pyrrol nucleus IV through an angle of 180°.

Porphobilinogen

According to Waldenstrom and co-workers,[6] porphobilinogen possesses but two pyrrol rings and is therefore a dipyrrylmethene. It is his belief that two molecules may combine in a ring to form uroporphyria, or in a straight chain to form porphobilin.

The identification of these compounds will be discussed in the section on diagnosis, part B.

Diagnosis

A. The diagnosis is suggested by the following clinical features:

1. Abdominal symptoms

   a. Abdominal colic is the most common presenting complaint. Surgery is often resorted to because of an erroneous diagnosis of "acute abdomen." The attack may simulate bowel obstruction, appendicitis, gall stone colic, pancreatitis, or other abdominal conditions. The absence of muscle rigidity and rebound tenderness often aids in excluding inflammatory conditions. Because of pain in the flank and red urine mistaken for hematuria, some cases have been confused with renal colic. In certain instances the pseudohysteric behavior (see below) may lead the clinician to believe that the pain is of hysterical type. In our own series of cases, except for those of latent type, abdominal pain has been a uniform feature at one time or another.

   b. Obstipation is an outstanding feature, and may persist 8-10 days or longer. The stools are characteristically scybala. Diarrhea has been observed in exceptional cases.

   c. Nausea and vomiting are commonly present. (X-ray examination has often revealed areas of intestinal spasm and distension.)

2. Neuropsychiatric symptoms:

   Porphyria may simulate poliomyelitis, encephalitis, hysteria, progressive muscular atrophy, and various other neuropsychiatric states. (See below)

   a. Generalized paresis is characteristically found.

   b. Paralysis of peripheral neuritis type is often present. Landry's ascending paralysis is often cited as the cause of death, but Waldenstrom, who has had the largest experience with this disease

states that the criteria for Landry's paralysis are rarely fulfilled. The paralysis is usually much more irregular in distribution.

c. Psychoses are relatively common. These are of various types ranging from mild mental confusion to acute mania. Hysteria is often simulated. In Sweden, where the disease is especially common in certain regions, porphyria is always looked for in patients presenting hysterical behavior (Waldenstrom).

d. Convulsions and amaurosis may occur. In some instances acute hypertension is undoubtedly a factor. At times optic neuritis is responsible for the blindness.

e. Sensory changes occur very uncommonly, and then only in longstanding cases.

3. Cardiovascular manifestations:

a. Sinus tachycardia, often to 150 or more, is commonly present. It has been suggested that this might be due to a vagus neuritis.

b. Hypertension is usually found.

Among the cases cited by Waldenstrom is one in which the blood pressure during a remission was 100/70. During an acute attack 1/2 year later, the blood pressure rose to 200/110 and the patient complained of headache, vomiting, sudden blindness, and unconsciousness. Within a week the patient improved and the blood pressure fell to 130/80.

4. Renal manifestations:

Oliguria is often present during the acute attack. It is unaffected by forcing fluids or by caffeine diuretics. Carrie[7] believes that it is due to porphyrinopathic vasospasm of the renal arterioles.

5. Blood picture:

According to Waldenstrom, hyperglobulinemia is the only frequent blood change. It has been an almost constant feature of the cases we have studied. Case No. 4, for example, exhibited an albumin/globulin ratio of 2.9/3.9 Anemia is not a feature. There are no characteristic changes in the leukocytes.

6. Skin manifestations:

a. Hydroa aestivale sen vaccinforme. This condition is due to light sensitivity. It is characteristic of the congenital type, but is extremely rare in the intermittent acute form. When it does occur in the latter, it is very mild.

The sequence of events with repeated exposure is: erythema, vesiculation, secondary infection, scarring, and mutilation. The latter may be most extensive, with loss of fingers, partial loss of nose and ears, severe ectropion, conjunctival scarring, corneal ulcers, and eventual blindness, and other changes. Only the exposed surfaces are involved.

Not all cases of hydroa aestivale are due to porphyria. Turner and Obermayer state that there was definite evidence of porphyria in 86 of 200 cases reported up to 1937.

b. Epidermolysis bullosa

This condition is at times associated with either type of porphyria, though it usually occurs independently, often as a familial trait. It is characterized by the formation of large vesicles following slight trauma to the skin, such as rubbing, scratching, or bruising. Light sensitivity need not be associated.

c. Pigmentation

In the congenital form this may be associated with the changes on the exposed surfaces of the skin. Brown pigmentation, at times reminiscent of Addison's disease, or of hemochromatosis, is seen quite commonly in the intermittent acute type. The nature of the pigment is unknown, but the possibility that it is porphobilin deserves further study.

7. Liver function

Liver function is often not obviously disturbed. The frequent report of urobilinogenuria in the older literature is probably mostly erroneous due to the confusion of porphobilinogen with urobilinogen, as will be discussed subsequently.

B. The diagnosis of porphyria is confirmed by laboratory examination of the urine.

1. Color

The color may be normal in the fresh specimen. It becomes red or brownish on exposure to light. Heating in neutral or weakly acetic solution hastens the transition of chromogen to pigment.

2. The porphobilinogen reaction

It has long been known that porphyria urine often exhibits a strongly positive Ehrlich reaction. It was naturally enough believed that this indicated urobilinogenuria. Waldenstrom, however, pointed out that the responsible chromogen differs from urobilinogen, and is indeed the precurser of uroporphyrin and of the associated brown pigment which he terms porphobilin.

We[8] have described the following simple test for this chromogen, the presence of which appears to be pathognomonic of porphyria.

To a few c.c. of urine add an equal amount of Ehrlich's reagents* and a double volume of a saturated solution of sodium acetate. Both urobilinogen and porphobilinogen yield a red solution with absorption maximum at about 565 mu. If this solution is now shaken with chloroform, the red urobilinogen aldehyde is quantitatively extracted, while the porphobilinogen aldehyde remains entirely in the aqueous phase.

3. Porphobilin

Little is known of this compound. It has never been crystallized. Like urobilin it is characterized by a brownish color, and an absorption maximum at about 490 mu. Unlike urobilin, however, it is insoluble in chloroform, and does not exhibit green fluorescence with alcoholic zinc acetate, with which it forms an insoluble zinc salt.

4. Identification of uroporphyrin

A. Absorption studies

The porphyrin is commonly excreted as the zinc complex, with absorption maxima of about 539 and 578 mu. This compound has often been confused with oxyhemoglobin whose absorption maxima are approximately 540 and 580 mu. The two are readily distinguished following the addition of hydrochloric acid. The porphyrin absorption max. shifts to 553 mu. and 596 mu. The HbO_2 bands, similarly treated, disappear in the green, and the weak broad diffuse band of acid hematin appears in the upper red part of the spectrum (Max. 640 mu.).

The normally occurring coproporphyrin has absorption maxima in 10 per cent HCl of about 549.5 and 594 mu., and can therefore be distinguished with reasonable accuracy with the aid of a good

spectroscope. Solubility studies, however, afford the only certain means of separation.

B. Fluorescence Studies:

The porphyrins exhibit an orange to red fluorescence in ultraviolet light of longer wave length (Wood's light: 4700-3600 Å). This fluorescence is usually appreciable in dilutions as high as 1 part in 5 millions. The various porphyrins have characteristic fluorescence spectra. These have been studied extensively.

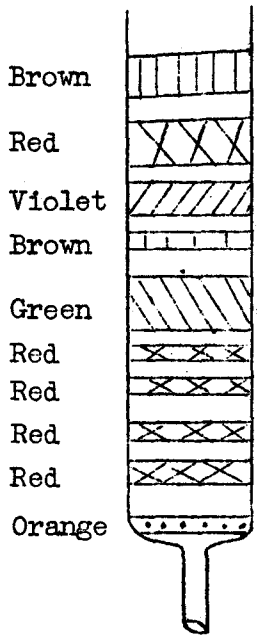
C. Solubility Studies:

The pigments characteristic of porphyria (i.e., uroporphyrin, porphobilin, and porphobilinogen) are insoluble in most organic solvents (i.e., ether, and chloroform). The normally occurring porphyrins, as well as urobilin and urobilinogen, are soluble in at least some of these solvents. Ether extraction from about 5 - 10% acetic acid solution is generally used to separate these two groups of pigments. Uroporphyrins I and III are both quite insoluble in ether. Uro- III, however, may be extracted with ethyl acetate from an aqueous solution acidified just enough to turn Congo paper gray-blue.

D. Chromatographic Analysis:

We have found chromatographic analysis as first described by Tswett and elaborated by Zechmeister and Cholnocky[10] and by Strain[11] to be of much value in the study of the porphyrins. This technique has often permitted their purification in a very simple and satisfactory manner.

Emplying this procedure, it was possible to demonstrate for the first time the excretion of uroporphyrin in the feces of porphyria patients. The following chromatograph was obtained by adsorbing a crude fecal extract on Al_2O_3 and eluting with increasing concentrations of chloroform in petroleum ether.[12]



Stercobilin*,plus?
Uroporphyrin*
Mesobiliviolin
Unidentified
Glaukobilin*
Unidentified porphyrin*
Coproporphyrin*
Protoporphyrin*
Unidentified compound*
Unidentified (Caratinoid?)

*Obtained in crystalline form from the feces of Case 4. Present also in feces from Case 5, but not crystallized.

E. Crystallization:

The porphyrin esters are crystallized from chloroform-methyl alcohol. Crystal form and melting point are usually distinctive. Melting point studies offer the only certain method of distinguishing the porphyrin isomers.

Uroporphyrin I	301°
Uroporphyrin III	255°
Coproporphyrin I	248°
Coproporphyrin III	142°; 166° (dimorphic melting point)

Review of cases investigated in this Laboratory

As noted in the foregoing we have studied in more or less detail, the clinical features and material from 13 patients with intermittent acute porphyria. (Four of these, all related to case 8, were latent in type.)* All were characterized by the excretion of porphobilinogen, uroporphyrin, and porphobilin in the urine. In those instances where the feces were investigated, uroporphyrin was found. In both urine and feces it was excreted chiefly as the zinc complex. Porphobilinogen has not been found in the feces, bile, or duodenal contents. The latter has contained relatively little porphyrin, although the zinc complex has been identified in small amount in some cases. In the first case studied it was of considerable interest that the bile and gall stones obtained at autopsy were entirely free of uroporphyrin, which was present, however, in large amounts in the liver, spleen, kidneys, urine, and feces. The significance of this observation is not clear.

Space does not permit inclusion at this time of more than a few typical case abstracts. A complete report of all of the cases, together with chemical studies, is planned.

Case I.

. T., age 50. Intermittent acute porphyria with cirrhosis of the liver. Admitted to Ancker Hospital 12-7-37. Transferred to University Hospitals 1-4-38. Exitus 1-8-38.

A. History and Physical Examination

1. Patchy pigmentation (4 years). Rhagades about mouth.
2. Red urine. Intermittent 4 years, constant for last two weeks.
3. Progressively increasing ascites, 2 months.
4. Abdominal colic; tympanites, 1 month.
5. Progressive oliguria, 1 month. Uremia 10 days.
6. Increasing jaundice, 3-4 weeks.
7. Increasing apathy and mental confusion, 1 month. Coma, 4 days.
8. No neurological changes.

B. Laboratory Findings:

1. Urine. Deep red color. Strongly acid reaction. Both free and Zn. uroporphyrin present. Strong Ehrlich reaction. Urobilinogen 11.3 mg. per day. Unfortunately we were not aware of the significance of the porphobilinogen reaction at the time this patient was seen. Uro- I ester crystallized. Melting point 298°. Uro- III also identified.

2. Stool:
   Zinc uroporphyrin identified, but not crystallized.
   Urobilinogen 191 mg. per day.

3. Blood:
   a. Zn uroporphyrin in cells, in addition to the normal protoporphyrin.
   b. Two other porphyrins demonstrated in the plasma. One of these is described under section C - 6.

C. Necropsy Findings:

1. Pigmentation, jaundice, ascites (8 liters), and edema.
2. Cirrhosis of the liver (wt. 1200 grams). Diffuse intracellular yellowish brown pigment.
3. Splenomegaly (730 grams).
4. Red normoblastic bone marrow

*We are indebted to Doctors A. R. Hall and John Noble, St. Paul, Minnesota, Doctors C. E. Lynn and A. G. Plankers of Dubuque, Iowa, Dr. W. H. Ford, of Minneapolis, Dr. W. C. Goodpasture and Doctors Canfield of Rockford, Ill., Dr. Docherd of Galveston, Texas, and Dr. E. R. Sternes of St. Paul and Dr. E. J. Kepler of Rochester, Minn. for permission to study cases 1, 2, 3, 6, 7, and 8 respectively.

(shaft of femur).

5. Thickening and blackish pigmentation of cecum and ascending colon; acute phlegmanous inflammation.
6. Porphyrin in various tissues. Zinc uroporphyrin in liver (4+), spleen (1+), kidneys (1+), and bone marrow (trace). None in bile, gall stones, and ascitic fluid.

From the blood plasma, feces, and ascitic fluid a hitherto undescribed porphyrin was obtained. It is characterized by ether solubility, HCl number of <1.0, and chloroform insolubility from 1% HCl. Absorption maxima in 1% HCl at 551 mu. in the visible, and absolute maximum in 404 mu. in the ultraviolet.

Case 5.

,, Male, age 21. Admitted 11-20-4 -

A. History:

1. Red urine intermittently for past year.
2. Severe abdominal pain and constipation past month.
3. Pain in extremities, especially in region of joints of past 3 weeks.
4. Progressive paralysis of both upper and lower extremities for past week.

B. Examination:

1. Restlessness, irritability, thick speech, and swallowing difficulty. Tongue deviates to the left.
2. Flaccid quadriplegia. Absent deep reflexes.
3. Blood pressure ranging from 154/114 to 174/126.
4. Retinal arterioles show irregular attenuation interpreted as spasm. One area of hemorrhage.

C. Laboratory studies:

1. Urine: Zinc uroporphyrin, porphobilinogen, and porphobilin are present.
2. Stool: Uroporphyrin and various other pigments isolated, as shown in chromatograph, section VI-C.
3. Blood:
   a. Normal Hb, Wbc and differential.
   b. Albumin / globulin : 2.9/2.4

D. Course

The patient showed considerable improvement coincident with use of crude liver extract (campolon, 5 cc.) IV.
By April, 1941 he had begun to walk in the pool, pain had disappeared and urinary pigments had markedly decreased in amount. B.P. 114/80. Recurrence on 4-16-41. B.P.135/108. Gradual improvement with campolon therapy. Discharged on 8-27-41.

At the present time the patient has only slight residual paralysis. Can walk without help. B.P. 124/70. Retinal vessels normal. The urine contains fairly large amounts of porphobilinogen, but very little native porphyrin.

Case 8.

- -. - age 25, female.
Admitted 2-14-42, Discharged 4-3-42.

A. History

1. Severe abdominal colic dating back to the fall of 1940. Pain increased during menstrual periods.
2. Appendectomy and removal of right ovarian cyst in December 1940. Followed by hyperthyroidism, with B.M.R. (+) 22.
3. Thyroidectomy in March, 1941.
4. Generalized skin pigmentation

noted soon thereafter. Also numerous bullae on hand, apparently unrelated to trauma. Cortical extract therapy begun under a diagnosis of Addison's disease.

5. Seen at the Mayo Clinic in February 1942. Condition critical. Marked flaccid paralysis of all extremities, facial diplegia (peripheral in type), and almost complete diaphragmatic paralysis. Marked abdominal colic. Diagnosis of porphyria made.

B. Examination: Essentially as noted at Mayo Clinic. B.P. 114/82. Several small scars on hands.

C. Laboratory studies:

1. Red, acid urine containing porphobilinogen, porphobilin, and uroporphyrin III.
2. Zinc - uroporphyrin in feces.
3. Albumin / globulin = 3.4/3.0

D. Course:
Gradual improvement except for brief relapse on 3-21-42. Treatment symptomatic. Only moderate weakness present on discharge.

E. Familial Character

It is of considerable interest that the urines of the patient's mother and 3 relatives showed pigment changes characteristic of porphyria. In none, however, were clinical evidences of porphyria present.

Pathology

1. Anatomic changes:

No well established characteristic anatomical changes have been described. Mason, Courville, and Ziskind[13] found degenerative changes present especially in the coeliac ganglion which they felt might account for the symptomatology of porphyria.

2. Chemical Changes

Diffuse porphyrin deposits are found in both the acute and congenital types. In the latter the bones and often the teeth may be red due to impregnation with porphyrin. Borst and Konigsdorffer have described the porphyrin distribution in necropsy tissues of the case Petry (congenital type). The various porphyrins present were identified by means of micro-cluorescence spectroscopy.

We have demonstrated the occurrence of the Zn uroporphyrin in various necropsy tissues of patients dying of acute porphyria.

Discussion of Symptomatology

The underlying mechanisms in porphyria are but poorly understood. Certain physiological effects of the porphyrins have been well established in experimental animals, but it is not clear to what extent these relate to the clinical picture of porphyria.

1. Light sensitizing effect.

Hausmann[14] in 1909 showed that hematoporphyrin, in the presence of light, is fatal to paramecia and to mice. In the dark it is completely innocuous. His studies have been extended and shown to apply to other animals as well as to man.

The light sensitizing effect is modified by various factors:

a. Wavelengths corresponding to the specific absorption of the porphyrin must be used.

b. The activity of the different porphyrins varies. In general Hemato-> Uro-> Copro-> Deutero-> Protoporphyrin.

c. The porphyrin must be fluorescent. Tappeiner has shown that all photosensitizing substances

are fluorescent. Therefore, the copper porphyrin which is non-fluorescent is also non-photosensitizing. The zinc comples is only moderately fluorescent. Rask and Howell[15], in perfusion experiments, have shown that albumin tends to inactivate the photosensitizing effect of porphyrins (Combination of porphyrin with albumin causes a marked diminution in the fluorescent properties of the porphyrin).

Hill and Holden have reported the denaturization of albumin in the presence of hematoporphyrin and sunlight. Similar changes in fibrinogen have also been described by Howell and by Boyd.

2. Smooth muscle

a. The Intestinal Tract

These effects are independent of light. In general, the porphyrins produce dilatation of the stomach and upper small intestine, and contraction of the lower small intestine and colon, at least in the experimental animal. Vanotti[16] believes that porphyrin acts both by desensitizing the vagus nerve endings, and by stimulating directly the smooth muscle.

b. The Vascular System

Vasospasm has been reported in the experimental animal following the administration of porphyrin. Although nothing certain can be said about the relation of the porphyrins to vasospastic states in human beings, it seems obvious that this question merits further study.

Carrie and others regard the intestinal colic, hypertension, oliguria, retinal vessel spasm, and even peripheral neuritis as "porphyrinopathic" phenomena. It might be noted that they would explain the similar symptoms of lead poisoning (characterized by the excretion of large amounts of coproporphyrin III) on the same basis.

3. The Skeletal System

Frankel has shown that porphyrin is deposited in the bones of growing animals or of adult animals with bone regeneration. The osteoblasts have been shown to be rich in porphyrin. Though most authors feel that porphyrin deposition is incidental and due merely to mechanical adsorption of the porphyrin on calcium phosphate, Lersum believed that porphyrin is essential for bone growth, and claimed that he could prevent or cure rickets by the administration of porphyrin. This claim, however, has not been corroborated.

4. Bone Marrow

The occurrence of large amounts of porphyrin in the erythroblasts of the marrow has been demonstrated by Borst and Konigsdorffer. Further, it has been shown that increased erythropoiesis is associated with an increased coproporphyrin I excretion. The significance of these findings is unknown.

5. The Nervous System

The development of paresis and paralysis of the extremities in photosensitized animals is common. Waldenstrom has pointed out that B-propyl piperidin (a pyridin derivative) causes a motor neuritis simulating that found in acute porphyria and suggested that the abnormal pyrrol metabolism of porphyria might result in the formation of such a pyridin compound.

6. The Endocrine System

a. Sex glands

Rodenwald[17] claims that the administration of hematoporphyrin to castrated mice will ellicit estrus. He has also found that both hemato- and protoporphyrin

stimulate the secretion of gonadotropic (and melanophoric) hormones by the pituitary. Several authors have called attention to the increase in symptoms and porphyrin excretion in the premenstrual and menstrual period.

b. Thyroid

Hinsberg and Mertens claim that porphyrin injection in animals causes an increased basal metabolism. Hyperthyroidism has been described in several instances of "acute" porphyria.

The application of the above noted physiological effects of porphyrins to the problems of porphyria is not a simple one. The fundamental difficulty is this: Several abnormal pigments are present in porphyria, none of which have been adequately studied. Most physiological studies have been made with hematoporphyrin, a substance which does not occur in nature. The natural porphyrins differ quantitatively from it; they may or may not differ qualitatively. The effect of zinc on porphyrin activity, the effects of porphobilinogen, porphobilin, and of other porphyrins which we have found in porphyria, the effects of the different isomers, modifying effects of other substances such as albumin, the relationships of the porphyria pigments and the naturally occurring porphyrins to hemoglobin and the respiratory enzymes - these are all questions which must yet be elucidated. One wonders, too, at the variation in symptomatology present not only in the two varieties of porphyria, but also in different patients with apparently the same urinary findings.

It might be noted here that a physiological porphyria has been described in the fox squirrel by Turner. Several authors have called attention to the natural occurrence of the Cu-uroporphyrin in the feathers of turacos birds of Africa. The protective mechanisms in these two instances is not entirely clear.

On the basis of the physiological studies noted, of the symptomatology of porphyria, and of the role of porphyrins in the respiratory enzymes, one might indulge in considerable speculation concerning the fundamental part played by porphyrins in the human body. Until the above noted questions are answered, however, such speculation is best avoided.

The papers by Dobreiner and Rhoads[18] and by Watson[19] are recommended for further elucidation of the role of porphyrins in human disease.

Therapy

In the absence of known etiology, a rational therapeutic approach is impossible. The following procedures have, however, been used with varying claims of success:

1. Liver Extract

This has been widely used. Carrie, Duesberg, and Vanotti are among those who claim it is of some value. Waldenstrom, who has studied over 100 cases, states that he has never seen a porphyria patient positively improved by liver extract therapy.

We have felt that crude liver extract (Campolon) was beneficial in two of our cases. The last case treated, however, developed an acute exacerbation while receiving the material intravenously.

2. Calcium

The intravenous administration of calcium was first suggested by Massa who found he could prevent porphyrinuria and colic in lead poisoning if calcium were administered with the lead. The porphyrin is supposedly immobilized by adsorption on the calcium salts deposited in the bones.

3. Alkalinization of the Urine

This was first suggested in 1898 by Müller who observed the characteristic acid reaction of the urine during the acute exacerbation. Follow-

ing alkalinization of the urine he found an apparent decrease in porphyrin excretion. Waldenstrom has suggested, however, that the decrease in porphyrin under these conditions is due merely to a reduced oxydation in alkaline urine of chromogen (porphobilinogen), of whose presence Müller was not aware.

Vanotti claims that the increased urine acidity is associated with an elevated calcium excretion. This, in turn, causes an increased excretion of porphyrin. He further states that alkalinization of the urine prevents the carboxylation of coproporphyrin to the more toxic uroporphyrin. He feels that it is best to administer calcium and attempt alkalinization of the urine during the acute stage to immobilize the porphyrin, and then after adequate improvement, to administer 4 - 6 cc. of 25 per cent magnesium sulfate intravenously repeatedly to cause slow mobilization of the porphyrin.

4. Diuretics

These are generally ineffective. Waldenstrom states that salyrgan occasionally appears to be beneficial.

5. Vitamin B Complex, especially riboflavin.

Vanotti claims that riboflavin administration is followed by decreased prophyrin excretion in the acute exacerbation, but is ineffective in toxic cases and in congenital porphyria. In one of our own cases, vitamin B complex and calcium pantothenate intravenously failed to give any benefit.

6. Symptomatic treatment

a. Sedation and analgesia
   1. Bromine compounds are recommended by Waldenstrom
   2. Morphine
   3. Papavenine I. V.
   4. Local heat to abdomen
   5. Avoid barbiturates.

b. Avoid exposure to light in photosensitive patients. Mackey and Garrod suggest that a coating of vaseline offers good protection.

7. Administration of metals

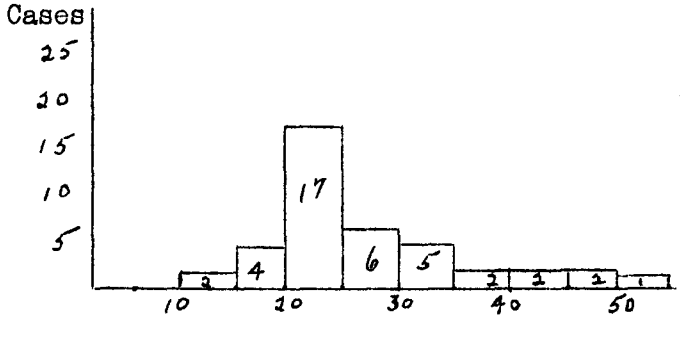
Fischer and Hilger have suggested the administration of copper to form the non-fluorescent Cu-uroporphyrin Derrien and Turchini have suggested the use of zinc because of possible zinc depletion of the body during the acute exacerbation. Neither suggestion, apparently, has ever been tested.

Prognosis

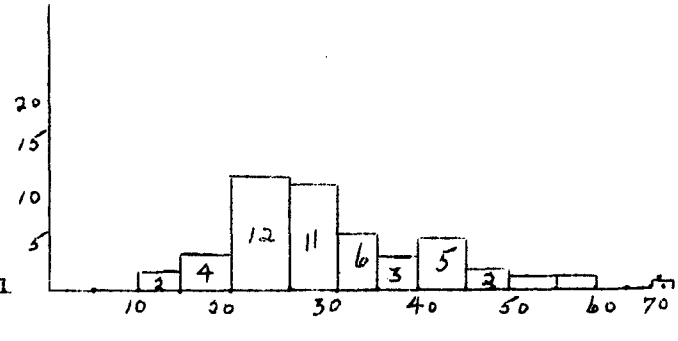
According to Waldenstrom, the prognosis depends primarily upon the chief symptom. Thus, in his series,

26 cases of latent type	0 deaths
24 cases of abdominal type	4 deaths
46 cases of neurological type	41 deaths

The following graphs from Waldenstrom indicate the prognosis in this series.



Age of onset



Age of death

In our own series of cases exitus occurred in 4 patients, all with the manifest disease. Death was due to bulbar paralysis in 3 instances (average age 29 years) and to hepatic coma in one (age 50.).

Summary

The clinical and chemical findings characteristic of porphyria are discussed together with a brief survey of the physiological effects of the porphyrins. Three case abstracts are presented from our series of thirteen patients. Some problems requiring further investigation are noted.

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VI. GOSSIP

In Omaha last week I told the convention about our experience with caloric needs of athletes. Studies in the division of nutrition of the students' health service showed that 5,000 calories a day for basketball players was only a drop in the bucket as most of them ate from 2,000 to 3,000 calories on the side. Feeding our football players is quite a big job as they, too, consume in the neighborhood of 8,000 to 9,000 calories a day. Imagine my surprice to find the Omaha paper stating that "Golden Gophers are not fed pink tea and cakes. University authority states that each athlete receives 90,000 calories a day." It would appear that our overstuffing might have interfered with their performance in the Seahawks and Illinois games. Last week they were apparently back on their normal diet for Michigan....A visitor at the Center for Continuation Study this week came from the University of Texas. He told of a debate which was scheduled by one of their dining clubs on the affirmative and negative of the question, "a chicken is a vegetable." The affirmative won by proving things which were equal to the same thing were equal to each other. The reasoning ran thus: an egg plant is a vegetable, a chicken is an egg plant, therefore, a chicken is a vegetable. I know it's old, but it was not nearly as old as the stories which were told at the Minnesota Hospital Service Association dinner on Tuesday evening at Coffman Memorial Union. The gathering was held in honor of the fact that the association now had over 500,000 members. Member 500,000 and his wife sat at the head table. Either the speeches were bad or the hour was late as the honored one went to sleep. He woke up when they gave him his $25. war bond. Dignitaries near and far included James Hamilton of New Haven, Connecticut, president of the American Hospital Association. A seasoned dinner-goer said that Jim had one of the finest collection of old tales that he had ever heard. One that the audience seemed to enjoy was about Jim's experience in a restaurant when he accidentally spilled some salt on a lady's back. Being an old friend of the family she came over to tell him that she couldn't be caught that way. Governor Stassen was at his best in emphasizing the importance of cooperative ventures in the health field rather than government control. Elmer Sevringhaus, famed endocrinologist, of the University of Wisconsin spoke before the probation and parole course at the Center for Continuation Study on the relation of his field to human behavior. Three days were devoted to the medical aspects of probation and parole. The public health nurses are in now for a 3 day discussion of mental hygiene and community nursing. Monday, Tuesday, and Wednesday of next week former nurses will come back for a quickie in modern nursing procedures. Many are now teaching nursing classes and others are just anxious to see what changes have occurred. The Minnesota Educational Association is also in town this week as well as the association of governing boards of state universities, which is meeting at the Center for Continuation Study....One of our faculty members went hunting for the first time last week. Warned to be extremely careful about his gun and the possibility of stray shots he nearly collapsed when a fire cracker went off at his rear. At the punch board the honorable superintendent with little output of cash won some valuable boxes of shells. Those of us who do not hunt are grateful to those who do for their generosity in sharing their "take." I say this in spite of a dinner to which I was invited, which was scheduled on a night when I was out of town.....At the alumni homecoming program last week, colored motion pictures of mutilating accidents involving the face were shown by Dr. Erich. They were so ghastly that the motion picture operator fainted. His helper was so busy running the machine that he did not have a chance to see them. There is still an opportunity to contribute to the Christmas boxes for our two units. Dr. Clarence Dennis, who thinks of everything and does everything well, is arranging for the presents. Contributors still have a chance to give at Superintendent Amberg's office...Dr. Thomas Francis, Jr., School of Public Health, University of Michigan, was loud in his praise of our hospitality and especially was he impressed by the members of the Phi Beta Pi fraternity who arranged the whole affair..