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Porphyria

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I. PORPHYRIA: CLINICAL MANIFESTATIONS IN RELATION TO CHEMICAL FINDINGS

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1. Introduction

A. Historical[1,2,3,4,5,6]

The porphyrins constitute a group of interesting compounds ubiquitous in nature and fundamentally related to cellular metabolism. Although porphyrins had undoubtedly been recognized by earlier observers it was Hoppe-Seyler who provided the first clear description of a porphyrin and how it might be prepared in vitro from hemoglobin. He believed that the porphyrin which he named hematoporphyrin, and which was subsequently crystallized by Nencki and Sieber, was the underlying, naturally occurring pigment of the hemoglobin molecule. This belief was rather generally accepted and held sway for many years. Porphyrins subsequently observed in the excreta under a variety of conditions were generally referred to as hematoporphyrins. The disease which is now known as porphyria to which major emphasis will be given in this review was first designated by Günther[2] in 1911 as hematoporphyria. The earlier confusion of the artificial hematoporphyrin with the naturally occurring porphyrins[1,2,3] was largely due to the fact that the latter had not been prepared in pure form and that the spectroscopes available to the earlier investigators were not sufficiently sensitive to detect the minor differences between their various absorption spectra. The spectra of hemato- and coproporphyrin are particularly close[7] and it is not surprising that they were confused for so many years. Protoporphyrin and uroporphyrin exhibit greater variations in their spectra and, in addition, are quite distinct in their solubility characteristics[7]. Thus, all but uroporphyrin are ether-soluble. Copro- and hematoporphyrin are extracted from ether by very dilute hydrochloric acid while protoporphyrin requires higher concentrations[7]. Proto- and hematoporphyrin are both chloroform soluble while their sodium salts are water insoluble[7]. Exactly the reverse is true with respect to copro- and uroporphyrin in respect to these solvents. In spite of these various differences which are quite clear-cut, the distinction of the naturally occurring porphyrins from hematoporphyrin was only achieved with the work of Hans Fischer, the results of which were first apparent in 1913. Fischer had the unique opportunity to study a case of congenital or photosensitive porphyria during life and after autopsy[8,9]. His study, which has now become a classic in the annals of porphyrin investigations, clearly reveals how much of general importance can be learned from the investigation of but one patient, even though that patient is suffering from a rare disease. The feces and urine of this patient yielded crystalline copro- and uroporphyrin, respectively. These were so named because it appeared to Fischer that there was no uroporphyrin in the feces and but small amounts of coproporphyrin in the urine. As a matter of fact, one of the very misleading aspects of this study was the belief which then held sway for many years that uroporphyrin does not occur in the feces in cases of porphyria

Only within the last decade was it shown in this laboratory that the feces of porphyria patients also contain uroporphyrin[10], sometimes in considerable amounts, although as a rule much less than is found in the urine. In the famous case Petry (the name of the individual studied by Fischer and co-workers), the viscera and bones contained large amounts of porphyrin[9]. So much uroporphyrin was present in the bones that they were actually red in color, a feature which has been noted in other cases of this type. It was most curious that the scapula of Petry contained the copper salt of uroporphyrin. This substance is also known as turacin, a normal constituent of the wing feathers of the Turacus, a bird which is found in both Africa and South America.

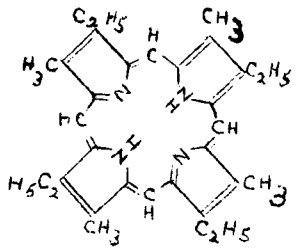
Following the isolation of these porphyrins from the case, Petry, Fischer went on to show that coproporphyrin is a normal constituent of the feces and urine[11,12]. He believed that uroporphyrin was present in the normal urine in traces. In the early twenties he and his group succeeded in crystallizing a porphyrin which Kammerer[13] had previously observed in feces containing blood and which had also been found in egg shells ("ooporphyrin"). It soon became clear that this was in fact, the underlying porphyrin of the hemoglobin molecule. Fischer named it protoporphyrin because of its widespread representation in nature. He and his associates carried out the brilliant synthesis of protoporphyrin and hemin in 1929[13].

B. Chemical structure and dualism of the porphyrins[7].

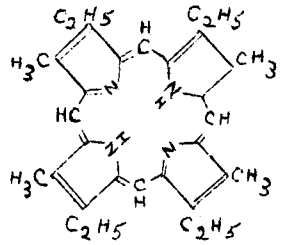
The porphyrins are characterized by a porphyrin skeleton consisting of four pyrrol nuclei connected by four methene or CH bridges. The different porphyrins vary depending upon the character of the substituent groups on the eight free corners of the four pyrrol nuclei (see Fig. 1). The number of porphyrin isomers of any given type depends upon the number of different substituent groups. Thus, with the coproporphyrins there are two different substituents, namely methyl and propionic acid groups and consequently four possible isomers, all of which were synthesized by Fischer and his associates[7]. In the case of the protoporphyrins there are three different types of substituent groups, namely two vinyl, two propionic acids, and four methyl[7]. Fifteen different isomers of this type are theoretically possible but only one of these has been isolated or synthesized, namely the type nine isomer, according to Fischer's classification[7]. This is the underlying porphyrin of many iron porphyrin enzymes of respiratory type such as cytochrome and catalase, as well as hemoglobin. Fischer's classification of the porphyrins depends primarily on the four artificial aetioporphyrins which have only methyl and ethyl groups on the porphyrin skeleton[7]. Depending upon the relative position of these groups there are four possible isomers and all other porphyrins are classified according to which one of these their configuration corresponds. In determining this the substituent group with the larger number of carbon atoms corresponds to the ethyl groups of the aetioporphyrin and that with the smaller number to the methyl groups. This relationship is seen in Fig. 1. Fischer clearly recognized that there was a dualism of the porphyrins in nature. Of the four possible isomeric types only one and three are naturally occurring and type three is preponderant to a very great extent, especially under normal circumstances.

Uroporphyrin differs from the coproporphyrin in having four acetic groups rather than the four methyl groups. It is, therefore, an octacarboxyl porphyrin while coproporphyrin is a tetracarboxyl variety[7].

C. In recent years some information has been gained about the physiological and pathological significance of the coproporphyrins, but there are many unanswered questions. The excretion of the coproporphyrins in the urine and feces has been studied by a host of investigators over the past quarter of a century. The method employed has usually been a modification of the ether and acetic extraction procedure described by Fischer[7,11] and first



$C_{32}H_{38}N_4$



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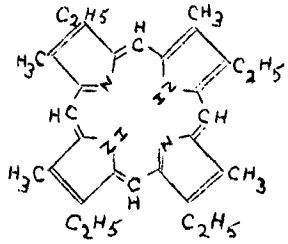

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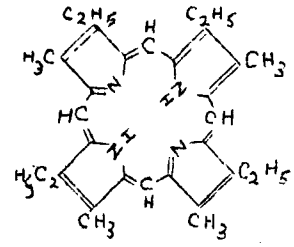
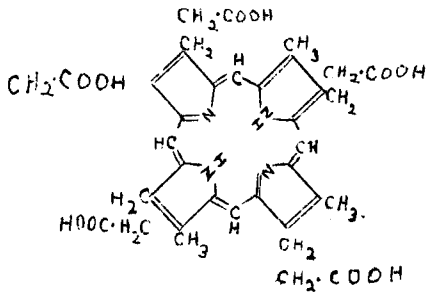


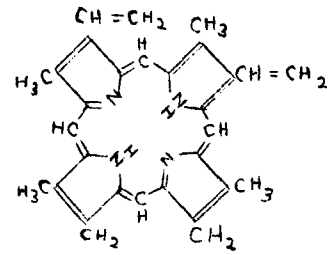
$C_{32}H_{38}N_4$

The Four Aetioporphyrins (artificial)



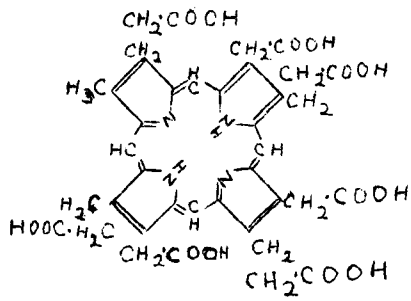
$C_{36}H_{38}O_8N_4$

Coproporphyrin I



$C_{34}H_{34}O_4N_4$

Protoporphyrin 9, (type III)



$C_{40}H_{38}O_{16}N_4$

Uroporphyrin I

Figure I

used in quantitative fashion by Fikentscher[14]. The Fikentscher method, slightly modified[15], has been used in this laboratory for a number of years but has been superseded during the past year by a much simpler and more reliable technique[16]. With the older method 100 cc. of urine were extracted repeatedly with ether and after suitable purification and concentration the coproporphyrin, dissolved in dilute hydrochloric acid, was quantitated by virtue of its red fluorescence in ultraviolet light. The new method[16] employs but 5 cc. of urine and is much more sensitive principally by virtue of the use of a new type of fluorimeter which incorporates an electron multiplier tube. With the old method, as used in this laboratory, the normal range of total coproporphyrin in the 24 hour urine was from 20 to 100 micrograms[17]. In certain other laboratories employing what was believed to be the same technique, a somewhat higher range was observed and the reason for this was not at first apparent. It has now been explained mainly on the basis of two factors: 1) the presence of a chromogen or precursor of coproporphyrin in the urine[16,18]. Light, heat, and air promote the conversion of this chromogen to the porphyrin. It is colorless and does not exhibit red fluorescence in ultraviolet light. Consequently, prior to its conversion it is not included in the quantitative determination. If the old method of ether extraction is carried out rapidly and expeditiously, somewhat lower values are obtained than when it is carried out slowly with more exposure to air and light, (because with the latter there is greater conversion of chromogen to porphyrin)[18]. The other important factor is that of the pH of the urine during the period of collection[16]. It has now been established that a considerable deterioration, often amounting to from 50 to 75 per cent of the total coproporphyrin occurs when the pH is below 6.0. The optimum pH for preservation of the porphyrin is from 7.0 to 9.0. This is readily effected by placing 5 grams of sodium carbonate in the bottle in which the collection is to be made. With the new 5 cc. method carried out on urines collected in this way and in which chromogen is converted to porphyrin by means of small amounts of iodine, the values obtained are much higher than with the modified Fikentscher procedure previously used. The upper limit of normal with the new method is approximately 300 micrograms per day with a mean of about 170[16,19].

Of even greater interest than the total amount of coproporphyrin excreted is the variation of the isomer ratio in disease states. A method of isomer analysis worked out in this laboratory several years ago[15] has permitted acquisition of a large amount of data[6b,17,20,21,22,23]; the results are summarized in Table I.

Table I

Urinary Coproporphyrin (UCP) Isomers in Disease

(Type I normally preponderant, 60-80%)

UCP increase due to:	
Type I	Type III
Mechanical (obst.) jaundice	Chemical and heavy metal poisoning
Infectious hepatitis	Cirrhosis in chronic alcoholics
Cirrhosis in non-alcoholics	Refractory or aplastic anemias
Hemolytic jaundice	Poliomyelitis
Pernicious anemia	Many cases of Hodgkin's disease
Leukemia	
- - - - - - - - - -	- - - - - - - - - -
Photosensitive porphyria, with uroporphyrin I	Intermittent acute porphyria, with the Waldenström porphyrin

The origin of the coproporphyrins is not well understood but recent studies have yielded considerable insight into the problem. It has been known since Van den Bergh's original discovery in 1928[24] that the erythrocytes contained free protoporphyrin. It was discovered only recently, however, that very small amounts of coproporphyrin are also present[25,26,27]. Conditions associated with increased erythropoiesis and increased hemoglobin synthesis in the bone

marrow are characterized by an increased concentration of the ECP (erythrocyte coproporphyrin). Considerable evidence has already accumulated that the ECP is a sensitive indicator of the rate of hemoglobin synthesis in the bone marrow[26,27]. It has been found very recently that under many conditions of increased erythropoiesis the bone marrow coproporphyrin is much larger than that in the circulating erythrocytes[28]. This and other evidence discussed elsewhere[27] appears to support the view that coproporphyrin III is a normal precursor of the hemoglobin protoporphyrin rather than a side product as previously believed. The final proof of this concept, however, has not been provided.

It is now reasonably clear that in disturbances such as lead and other heavy metal poisoning, chemical poisoning, and certain other toxic states, the excessive type III coproporphyrinuria is related to a disturbance in hemoglobin synthesis in the bone marrow with overproduction or faulty utilization of the type III prophyrin. It is also quite clear that at least a major fraction of the type I coproporphyrin normally excreted in the feces and urine is to be regarded as a side product of hemoglobin synthesis of questionable, if any, physiological significance.

On the other hand there is considerable reason to believe that the coproporphyrins are not formed solely in the bone marrow but are related to cellular metabolism much more broadly, and in this connection at least the liver and the central nervous system deserve special consideration. Thus, in hepatic cirrhosis, the urinary coproporphyrin excretion is usually increased[22] often markedly so and as noted in Table I the isomer ratio varies considerably with the type of cirrhosis[22]. In these cases no evidence has thus far been found to indicate that the excessive porphyrin excretion is related to formation in the bone marrow though this possibility has not yet been excluded with complete certainty. In poliomyelitis and in certain other diseases of the nervous system, the possibility exists that the excessive type III coproporphyrinuria[21] is related to the formation of this porphyrin in the white matter of the nervous system itself. Klüver[29] first showed that the white matter of the nervous system of warm-blooded animals regularly contains small amounts of coproporphyrin. This has been tentatively identified both in his and our laboratory as the type III isomer. Klüver has pointed out that the absence of this porphyrin in the nervous system of cold-blooded animals may indeed relate the coproporphyrin to a temperature regulating mechanism. This is an intriguing possibility deserving of much further investigation. It has thus far not been possible to alter the central nervous system porphyrin experimentally. Lead and barbiturate intoxication in rabbits and dogs have not produced any demonstrable change in the coproporphyrin concentration of the brain. At the same time, the possibility of a much more rapid turnover cannot be excluded. It has been impossible to increase the porphyrin concentration of the dog's brain by injection of large amounts of coproporphyrin into the internal carotid artery. This supports the view that the porphyrin of the central nervous system is formed in situ rather than being brought to it from another site of formation.

D. <u>The chemistry and possible physiological role of uroporphyrin and related compounds</u>.

As mentioned in the foregoing, uroporphyrin is an octacarboxyl porphyrin which was first isolated from the case of Petry by Fischer. This was the type I isomer. Later Waldenström[30] described a similar porphyrin, also ether insoluble and indistinguishable spectroscopically, but extracted in part by ethyl acetate and with methyl ester melting point of 258 - 260° C. (the melting point of uroporphyrin I methyl ester is 284°). On decarboxylation Waldenström obtained what was believed to be coproporphyrin III from this porphyrin and hence designated it as the type III uroporphyrin isomer. This belief was rather generally accepted but it was later shown in this laboratory[31,32] that when the Waldenström or 260 prophyrin is submitted to chromato-

graphic analysis it may or may not behave as an entity. In some cases it is separable into two porphyrins, one with methyl ester melting point of 284 which, on decarboxylation, yields coproporphyrin I, and the other with methyl ester melting point of 208 which, on decarboxylation, yields coproporphyrin III. Repeated determinations of the number of carboxyl groups in the 208 porphyrin have given a value of 7 as compared with 8 in uroporphyrin I[33]. In other instances the 260 porphyrin behaves as an entity on the calcium carbonate column. Recent studies of this porphyrin by means of paper chromatography have also failed to resolve it into two components[34,35]. Nevertheless, the finding that the 260 porphyrin is mainly composed of type I isomer has been repeatedly confirmed[34, 35,36]. Thus, to date, there has been no demonstration of the occurrence in nature of a type III uroporphyrin. The theory of porphyrinogenesis, recently proposed by Neuberger and associates[37], gives the key rôle to uroporphyrin III. It supposes a primary formation of uroporphyrin from smaller building blocks, namely alphaketoglutaric acid and glycine. These combine to yield specific dipyrry l methenes which, in turn, couple to produce uroporphyrin III. The scheme of porphyrin biosynthesis which these investigators have envisioned would explain the failure of appearance in nature of types II and IV and would thus account for Fischer's dualism of the porphyrins. Thus far, however, the uroporphyrin III, which is an essential link in their hypothesis, has not been demonstrated. In this respect it is noteworthy that a recent study still in progress in this laboratory[38] has shown the occurrence of a uro-type porphyrin in the bone marrow of rabbits with experimental lead poisoning. Since, as already mentioned, there is a concomitant marked increase of coproporphyrin III one may, perhaps, speculate that the uro-type porphyrin which has been observed in these animals may, in fact, be the missing uroporphyrin III. This possibility is receiving intensive study at the present time.

2. Definition, classification, and principal features of the main forms of porphyria.

Sir Archibald Garrod's inclusion of porphyria as one of the "inborn errors of metabolism"[39] appears to be fully justified, both on the basis of congenital and familial occurrence of the disease. It is a common experience to find that other members of the family of a case having outspoken manifestations of the disease, exhibit latent porphyria. They may have had no symptoms at all or their symptoms may have been so minor as to escape previous observation. Yet, careful examination of the urine reveals the presence of abnormal pyrrol compounds or porphyrins.

The possibility certainly exists, also, that there are many individuals with a latent porphyria trait, but in whom no abnormality in porphyrin excretion can be found. This seems all the more likely because of certain exceptional cases of the intermittent acute type in which, during remission, the porphyrin excretion has returned to within the normal range, uroporphyrin and porphobilinogen having disappeared from the urine.

The physiological and pathological excretion of the coproporphyrins as referred to in the foregoing is best regarded as a symptomatic or secondary porphyrinuria rather than a form of porphyria. Nevertheless, there is a very real question as to the existence of an acquired state of porphyria. The two substances most characteristic of porphyria are uroporphyrin and porphobilinogen and on occasion either one or both of these substances are observed in association with other disease. For example, we have had under observation during the past two years a patient with systemic sporotrichosis. When first seen with the disease in a very active form the urine contained a relatively large amount of uroporphyrin and porphobilinogen yet there were none of the ordinary symptoms of porphyria. This question will be considered again in the following. It is clear, at least, that under ordinary circumstances these substances are

characteristic of a constitutional or inborn error of metabolism but the possibility must be reckoned with that under certain circumstances porphyria may be secondary rather than primary.

The classification of porphyria offers considerable difficulty even when the term is restricted to a constitutional meaning. Our experience with 80 cases during the past 15 years has lead to the following classification:

Table II

Classification of Porphyria

I. Photosensitive (congenital, infantile) (Porphyria erythropoietica)

More common in males
Hydroa aestivale, scarring and mutilation
Erythrodontia
Hypertrichosis
Splenomegaly and hemolytic anemia
Large amounts of free uroporphyrin I and coproporphyrin I in excreta
No porphobilinogen

II. Intermittent acute

More common in females beyond menarche
Abdominal and nervous manifestations
Death often due to bulbar or respiratory paralysis
Skin pigmentation at times
Porphobilinogen and porphobilin in large amounts during attacks
Zn complex of Waldenström uro-type porphyrin (methyl ester M.P. 258-260° C.)
Excessive coproporphyrin III

III. "Mixed" (Cutanea tardive) (Porphyria hepatica)

Photosensitivity appearing first in adult life
Vesicles of skin also follow trauma and at times heat
Purplish facies (Brunsting)
Skin pigmentation
Jaundice and liver functional impairment, or outspoken cirrhosis
Abdominal pain
Nervous manifestations

- - -

The alternative names for the photosensitive and mixed types, as underlined at the right in each instance in Table II, are believed to be justified both on fundamental and clinical grounds. This will be discussed again in the following.

Of the 80 cases which form the basis of the present survey, and of the classification given in Table II, 28 were studied in the University Hospitals, 5 at the Minneapolis Veterans Hospital. The remainder were cases of other physicians or clinics who provided us with protocols and urine samples.

3. Manifestations of porphyria in relation to chemical findings.

Methods have only recently become satisfactory for the study of the porphyrins of the red blood cells, serum or plasma, bone marrow, or liver obtained by biopsy. The following discussion, therefore, will be concerned mainly with urinary findings and even in the case of the urine the study of our first few cases was fragmentary because of lack of knowledge at that time of the porphobilinogen reaction which we first began to employ extensively in 1939. The simple test for porphobilinogen described in 1941[40] has been useful as a screening method in the diagnosis of porphyria. This is simply the modified Ehrlich aldehyde reaction to which is added the test as to chloroform solubility of the resultant red aldehyde compound. Porphobilinogen aldehyde is insoluble while urobilinogen aldehyde is readily soluble. Although the test cannot be regarded as strictly pathognomic, it is quite reliable and a positive result clearly indicates a strong possibility of porphyria. Active abdominal and/or nervous manifestations were present in 44 of the cases of intermittent acute porphyria and in every one of these porphobilinogen was readily demonstrable, usually in strong concentration. Sixteen cases of this type were studied during a remission in which there was complete freedom from symptoms. All of the sixteen had previously had attacks. Porphobilinogen was still demonstrable in fifteen of the sixteen but in one the reaction was very faint. In seven of these cases in which it was possible to carry out serial studies marked diminution was noted as the patient went from a relapse into a complete remission (see Table III). The amount of uro-type porphyrins declined similarly during remissions of the disease (see Table IV).

Table III

Urinary prophobilinogen in relapse and remission of intermittent acute porphyria

Case	Relapse	Remission
1.	++	+
2.	45 units/d.	12 units/d.
3.	56 units/d.	23 units/d.
4.	++	0-2 units/d.
5.	51 units/d.	0-2.5 units/d.
6.	40 units/d.	8 units/d.
7.	+	neg.

- - - - -

Table IV

Urinary uro- type porphyrin in relapse and remission of intermittent acute porphyria

Case	Relapse	Remission
1.	14.9 mg./d.	0.34 mg./d.
2.	0.3 " "	0.1 " "
3.	34.0 " "	2.1 " "
4.	9.5 " "	0.03 " "
5.	30.0 mg./d	0.3 mg./d.
6.	22.6 " "	1.0 " "
7.	2.0 " "	0.06 " "
8.	10.2 " "	0.6 " "

- - - - -

Porphobilinogen was absent in all five cases of the "pure" photosensitive or erythropoietic type and in the mixed cases ("cutanea tardive" or hepatic type) except when abdominal pain or neurologic disturbances were present, and at these times it was always observed. The intermittent acute type was regularly characterized by the Waldenström or "260" porphyrin, occurring as the zinc complex, while the pure photosensitive type in all instances exhibited uroporphyrin I and coproporphyrin type I in the free state. It has been noted that the porphyrin in the mixed cases is also excreted as the zinc complex even in the

absence of abdominal or nervous manifestations. Thus, it is doubted that the latter are related to the complexing with zinc, nor is there any basis for thinking that the zinc complex protects against light sensitivity. In two cases of the mixed type observed recently photosensitivity and skin lesions were prominent at a time when all of the porphyrin in the urine was excreted as a metal complex.

Waldenström[30b,41] called attention to certain cases in which the urine contained large amounts of porphobilinogen with relatively little or even no demonstrable increase of porphyrin and in rare instances no demonstrable uroporphyrin. It has been evident in our own material that there is a lack of correlation between the amount of porphyrin in the urine and abdominal or nervous manifestations. We have seen cases with outspoken symptoms in which the urine contained surprisingly small amounts or even no increase of porphyrin at all, in the presence of considerable porphobilinogen. These observations strengthen the belief that porphobilinogen or some close relative, is related to the manifestations of the intermittent acute form. In this connection it is pertinent to mention a case studied quite recently. This was a young woman who has had no less than ten laparotomies because of recurrent abdominal pain. She was about to be discharged with a diagnosis of functional disease or neurosis when Dr. Thomas Gibbons thought to carry out a porphobilinogen reaction on the urine. This was found to be positive, but no uroporphyrin could be demonstrated and there was no increase in the excretion of coproporphyrin. The feces were also carefully examined without finding any significant increase in porphyrin excretion. The blood serum, however, was found to contain nine micrograms per 100 cc. of coproporphyrin, all in the form of chromogen (only apparent after treatment of the ethyl acetate extract with iodine). This amount was undoubtedly significant as we have never been able to demonstrate any porphyrin in normal human serum. The fundamental significance of these findings is not at all clear but the clinical and practical implications are obvious. Some years ago Van den Bergh[41] reported a case of "porphyrinemia" without porphyrinuria. In this instance, however, no mention was made of the urine Ehrlich reaction, so that the possibility of occurrence of porphobilinogen cannot be determined. Van den Bergh's case differs from the one just reported, however, in that the bile and feces contained a great excess of coproporphyrin.

We are beginning to acquire information as to the probable site of formation of the porphyrins in porphyria. It has thus far been possible to examine the liver and bone marrow in four cases of what are believed to represent the "mixed" form of the disease. The first of these, as it happens, was also the first case in our entire series and was studied in this hospital in 1937. The patient had a cirrhosis of the liver at autopsy and the liver contained large amounts of a zinc complex of a uro-type porphyrin. The bone marrow, on the contrary, contained only traces of porphyrin. It should be noted that in those days our methods of purification and identification were by no means as sharp and decisive as at present so that only the gross difference between liver and bone marrow deserves record at this time. In three other cases of the mixed type studied recently by means of liver and bone marrow biopsy the liver was regularly found to contain a large amount of porphyrin while the bone marrow did not show any evidence of increase. These findings are in striking contrast to results which have been obtained recently in a case of pure photosensitive or congenital type in a young girl[43]. Here the bone marrow was remarkably rich in porphyrin content, the normoblasts containing a large amount of at least three porphyrins, probably proto, copro, and uroporphyrin. The circulating red blood cells also contained a large amount of porphyrin and, in fact, it was possible to isolate crystalline uroporphyrin and coproporphyrin I from the erythrocytes of this girl. The porphyrin content of the liver, however, was not as striking. This little girl had a severe hemolytic anemia with splenomegaly.

Splenectomy has thus far resulted in a remarkable remission of her disease. There has been no recurrence of anemia over a period of 15 months and the photosensitivity which was formerly severe has almost entirely disappeared. On but one occasion in the 15 month interval since splenectomy has there been a vesicle which might be ascribed to photosensitivity. During this period she has been able to play and become tanned in the sun, which she had not been able to do before because of prompt and severe vesicle formation (hydroa aestivale). It appears clear that the reduction in hemolytic activity produced by the splenectomy also resulted in a marked reduction of erythropoiesis and, hence, of porphyrin formation. It may be recalled that Borst and Königsdörffer[44] found that the nucleated red blood cells of the bone marrow in the famous case Petry were rich in porphyrin content. As already mentioned at the outset the Petry bones were deeply stained with porphyrin. It should be noted, however, that the findings of uroporphyrin in bone itself does not signify an osseus origin. Fraenkel[45] showed many years ago that if uroporphyrin is injected into a young animal it is deposited rapidly in the growing bone. This is also true in a callus and it seems not unlikely that this is simply a matter of absorption of the porphyrin on calcium phosphate as suggested by Rimington[46]. There can be little doubt, however, that the finding of large amounts of uro- and coproporphyrin in the developing red cells of the bone marrow as well as in the circulating red cells, denotes a close relationship to erythropoiesis. From the comparisons of liver and bone marrow which have been alluded to, it seems not unlikely that the pure photosensitive or congenital type of porphyria is fundamentally related to erythropoiesis. In fact, the name "porphyria erythropoietica" would seem to be peculiarly suitable for this form. In the mixed form, in which liver disease is so often encountered and in which the livers contain large amounts of porphyrin, while the bone marrow fails to show increases, the term "porphyria hepatica" would seem to be justified. Information as to the ordinary intermittent acute form is not yet adequate to hazard a statement as to the site of formation of the porphyrins. Some of our cases have had relatively large amounts in the liver and thus far we have not observed any with significant increases in the bone marrow or circulating erythrocytes. Thus, it appears fairly clear that this form is sharply separated from the erythropoietic type. Further work is necessary, however, to determine the significance of other sites such as the central nervous system.

4. The porphobilinogen problem.

The term porphobilinogen was proposed by Wandenström[41a] to designate a colorless chromogen which he believed to be limited in occurrence to the urines of porphyria patients. Waldenström emphasized that while this substance gives an Ehrlich reaction similar to that of urobilinogen, the chromogen itself is not extracted from urine by ether as is true of urobilinogen. Of even more significance from a practical standpoint is the chloroform insolubility of the Ehrlich aldehyde compound of porphobilinogen[40], in contrast with the ready solubility of urobilinogen aldehyde. This difference usually permits a ready distinction of the two substances and has become of the utmost help in screening urines with respect to the diagnosis of intermittent acute porphyria. As has already been noted porphobilinogen is regularly found in association with abdominal or nervous manifestations but not with skin lesions. The porphobilinogen reaction is probably not entirely pathognomic for porphyria though its relative reliability was shown by Hammons and Welcker[47] who found the reaction negative in 1,000 random urine samples from as many different hospitalized patients with various disorders. A case of sporotrichosis was mentioned in the foregoing, in which the urine contained porphobilinogen and uroporphyrin. A case of hepatic cirrhosis has been observed in which death was due to hepatic coma; the urine on certain occasions contained uroporphyrin and porphobilinogen; at others only marked

excesses of coproporphyrin. It has not been determined whether either of these individuals were suffering from latent porphyria to which the other diseases were added or coincidental or whether the occurrence of porphobilinogen and uroporphyrin was secondary to the sporotrichosis in the one or the hepatic cirrhosis in the other. In a few cases of other types weak porphobilinogen reactions have also been encountered which were rather difficult to interpret, but in the main the reaction has denoted porphyria.

Waldenström and Wahlquist[41] offered evidence that porphobilinogen is a dipyrrlmethene, in other words, a substance with but two pyrrol nuclei in its molecule and hence a molecular weight one-half that of a porphyrin. Their studies indicated that when an acidified urine containing porphobilinogen is heated, two molecules of the substance couple to yield one molecule of uroporphyrin. Heating in an alkaline urine was said to produce porphobilin which was regarded as a straight chain polymer of dipyrrlmethene molecules without porphyrin characteristics. This substance is dark brownish red, relatively insoluble, without red fluorescence in ultraviolet light and without any porphyrin absorption spectrum. It exhibits broad diffuse absorption from 500 mu. downward into the violet. There is no doubt that porphobilin is responsible in large measure for the brownish-black color of the urine of cases of intermittent acute porphyria. This darkening often develops only as the urine stands exposed to the light and air and it should be emphasized that the urine in this type of porphyria may be normal in color when freshly voided, becoming red, brown, and almost even black on standing for a number of hours or days.

In the foregoing section on the coproporphyrins (I,c) reference was made to the importance of a chromogen of coproporphyrin. Evidence has also been obtained that uroporphyrin is excreted partly as a chromogen and that this chromogen differs from the porphobilinogen which is responsible for the Ehrlich aldehyde reaction. Quite recently, by means of the method of Sveinsson and Rimington[48], it has been possible to separate the Waldenström uro-type porphyrin and its chromogen from porphobilinogen. When porphobilinogen is completely freed of porphyrin or chromogen, it is then impossible to convert it to porphyrin by means of heating in an acid medium. As result of this work porphobilinogen is regarded as the chromogen or precursor of porphobilin only, not of the Waldenström porphyrin. The colorless precursor or chromogen of the porphyrin does not give an Ehrlich aldehyde reaction. Curiously enough, this chromogen differs from coprophyrinogen in that it is but poorly converted to porphyrin by means of iodine, while heat is much more efficient. Quite to our surprise it has now been found that a very great proportion of the uro-type porphyrin may be overlooked unless the urine is heated. In some instances the amount has been observed to increase as much as 50 fold after heating for twenty minutes at 80 to 85°C. (in the boiling water bath). Gibson and Harrison[35] have also recently reported a considerable augmentation by heating, although not of this magnitude.

5. Idiopathic coproporphyrinuria.

This survey would not be complete unless some reference were made to an interesting but poorly understood group of cases to which we have given the name of idiopathic coproporphyrinuria. Two cases of a massive, symptomless form have recently been reported from this laboratory[49]. The condition in both instances was discovered quite by accident. In both, the urine, bile, and feces were found to contain large amounts of coproporphyrin type III, neither uroporphyrin nor porphobilinogen being demonstrable. The porphyrin content of the red blood cells and serum was normal. The cause of formation of the tremendous excesses of coproporphyrin III in these cases was not at all clear. There was no evidence in either of chemical or heavy metal toxicity, although this was carefully sought.

We have now studied, in addition, a number of individuals having abdominal pain, several of whom had had laparotomies without the finding of any pathology, and whose urines were subsequently determined to contain excessive coproporphyrin III. It is attractive to consider that the abdominal pain in these cases is causally related to the increased formation of coproporphyrin, as it is known that coproporphyrin in remarkably dilute solution causes prolonged small bowel spasm in animals. Nevertheless, many other individuals have been observed, including the two symptomless cases just referred to, in which even greater excesses of coproporphyrin III were being formed without production of pain. It is recognized that the amount found in the urine and feces may not give an adequate picture of the concentration in the viscera or blood and it is certain that much more study is needed with particular reference to the significance of coproporphyrinogen and of possible combinations of coproporphyrin with proteins or other substances in the viscera which might have an important effect insofar as physiological activity is concerned. For the time being the simple recognition of this group must suffice without any attempt to define its significance in fundamental terms.

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II. MEDICAL SCHOOL NEWS

Coming Events

Nov. 27 - Dec. 1	Continuation Course in Child Psychiatry for General Physicians and Pediatricians
December 7 - 9	Continuation Course in Clinical Chemistry for General Physicians, Internists, and Pediatricians
December 15 - 16	Continuation Course in Obstetrics for General Physicians
January 4 - 6	Continuation Course in Geriatrics for Physicians

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Student Health Service Building Dedicated

Dedication of the new Student Health Service Building of the University was celebrated on November 7. This modern structure is situated across Church Street from the Out-Patient wing of the University Hospitals and directly south of the Botany Building.

One of the most striking features of the building is the full-length picture windows which give a beautiful view of the Mississippi River to those sitting in the waiting room. Well-needed space has been provided for the Mental Hygiene Unit, special diet kitchen and dining room, x-ray department, and pharmacy service.

Principal speaker at the dinner in the main ballroom of the Coffman Memorial Union was Dr. William P. Shepard, Vice President of the Metropolitan Life Insurance Company and Director of its Health and Welfare Division for the Pacific Coast area. Dr. Shepard, who is also a graduate of the University of Minnesota Medical School, spoke on the subject "Student Health and Public Health."

Other speakers included Mr. Ray Amberg, Director of the University of Minnesota Hospitals, Dr. Ruth E. Boynton, Director of the University Health Service, Dr. Harold S. Diehl, Dean of the Medical School, and Dr. Malcolm M. Willey, Vice President of the University Academic Administration. Rev. Wallace Pomplun gave the Invocation.

Dr. Boynton outlined the growth of the Student Health Service and the changes which have occured during the past years in the type of service being given to University students.

* * *

Faculty News

Dr. Charles D. Creevy, Professor of Surgery and Head of the Division of Urology, is the author of a book, "An Outline of Urology," recently issued by the Burgess Publishing Company.

Mr. Ray Amberg, Director of the University Hospitals, was elected a trustee of the American Hospital Association at its recent meeting in Atlantic City, New Jersey. He addressed the annual meeting of the Minnesota Hospital Association on the subject, "Federal and State Legislation Affecting Hospitals."

Dr. Henry E. Michelson was recently elected President of the American Dermatological Association at its annual meeting in Jasper Park, Alberta.

Dr. C. J. Watson, Professor and Head of the Department of Medicine, has recently been appointed to the National Advisory Council on Arthritis and Metabolic Diseases for the United States Public Health Service. A major function of the Council is to advise the Surgeon General of the United States Public Health Service on the distribution of public funds for medical research, training of scientific personnel, and for the construction of research and training facilities.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome
November 19 - 25, 1950

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Sunday, November 19

University Hospitals

9:00 - 10:00 Surgery Grand Rounds; Station 22.

10:30 - Surgical Conference; Todd Amphitheater,

Monday, November 20

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109 U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Seminar; Etiology: Spondylolysis and Spondylolisthesis as Causes of Scoliosis; Jose Montero; E-101, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 12:50 Physiology Seminar; Studies of Cardiac Output Using the Ballistocardiograph; Henry Taylor; 214 Millard Hall.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - 5:00 Pediatric Seminar; Feeding of the Premature Infant; Eldon Berglund; 6th Floor West, U. H.

4:00 - Public Health Seminar; 113 Medical Sciences.

4:30 - 5:30 Dermatological Seminar; M-436, U. H.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staffs; Powell Hall Amphitheater.

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Lowry; 5th Floor.

1:00 - 2:00 Staff Meeting; Classroom, 4th Floor.

Monday, November 20 (Cont.)

Minneapolis General Hospital (Cont.)

2:00 - 3:00 Journal Club; Classroom, Station I.

Veterans Administration Hospital

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; Conference Room; Bldg. I.

1:00 - Metabolic Disease Rounds; N. E. Jacobson and G. V. Loomis; Bldg. I.

4:00 - Therapeutic Conference; Conference Room, Bldg. I.

Tuesday, November 21

Medical School and University Hospitals

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:00 Physiology-Surgery Conference; Hypothermia: Experimental Tolerance and Certain Metabolic Effects; Allan Hemingway; Todd Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by General Hospital Staff; Drs. Lipschultz and Stansbury; Eustis Amphitheater, U. H.

*8:00 - Minnesota Pathological Society Meeting; Primary Hyperparathyroidism: A Study of 100 Consecutive Cases; Lewis B. Woolner; Medical Science Amphitheater.

Ancker Hospital

1:00 - 2:30 X-ray Surgery Conference, Auditorium.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Dr. Adams; 4th Floor.

8:30 - Pediatrics Allergy Rounds; Dr. Nelson; 4th Floor.

9:00 - 10:00 Pediatric Rounds; F. H. Top; 7th Floor.

Veterans Administration Hospital

8:45 - Surgery Journal Club; Conference Room; Bldg. I.

Tuesday, November 21 (Cont.)

Veterans Administration Hospital (Cont.)

8:30 - 10:20 Surgery Conference; Seminar Conference Room, Bldg. I.

9:00 - Infectious Disease Rounds; W. Hall.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell.

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Chest Surgery Conference; J. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

1:30 - Liver Rounds; Samuel Nesbitt.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, November 22

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109 U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

11:50 - 12:50 Radio-Isotope Seminar; The Literature Review; 113 Medical Sciences.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Powell Hall Amphitheater.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

8:00 p.m. Dermatological Pathology Conference; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Lowry; 5th Floor.

12:15 - Staff Meeting; Classroom, 4th Floor.

2:00 - 4:00 Infectious Disease Rounds; 8th Floor.

Wednesday, November 22 (Cont.)

Minneapolis General Hospital (Cont.)

3:00 - 4:00 Pediatric Rounds; E. J. Huenekens; 4th Floor.

4:00 - 5:00 Infectious Disease Rounds; Classroom, 8th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans and Bernard O'Loughlin; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, November 23 -- HOLIDAY

Friday, November 24

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Antabuse Therapy for Alcoholics; Jack Wallinga; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

2:00 - 4:00 Physiology Conference; 214 Millard Hall.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U. H.

4:15 - 5:15 Electrocardiographic Conference; 106 Temp. Bldg., Hospital Court, U.H.

5:00 - 6:00 Urology Seminar; Technique of Ureterosigmoidostomy; B. A. Smith; Powell Hall Amphitheater.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Friday, November 24 (Cont.)

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Lowry; 5th Floor.

9:30 - Surgery-Pediatric Conference; O. S. Wyatt and T. C. Chisholm; 4th Floor.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

1:30 - Chest Conference; Wm. Tucker and J. A. Myers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

Saturday, November 25

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; Wallace H. Cole and Staff; M-109, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Forrest Adams; 4th Floor.

9:00 - 10:00 Pediatric Rounds; F. H. Top; 7th Floor.

Saturday, November 25 (Cont.)

Minneapolis General Hospital (Cont.)

11:00 - 12:00 Pediatric Clinic; Charles May; Classroom, 4th Floor.

Veterans Administration Hospital

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.

* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.