

CHAPTER VIII

HÆMATOPORPHYRIA CONGENITA

(Congenital Porphyrinuria)

THE porphyrins form a group of coloured compounds, akin to hæmatin and to bilirubin. They differ somewhat widely in percentage composition, but agree in the possession of a molecular nucleus built up upon four pyrrol rings, each of which supplies one of the nitrogen atoms of their empirical formulæ. The best-known members of the group are the hæmatoporphyrins prepared by Hoppe-Seyler and Nencki and Sieber from hæmatin, but a closely allied pigment, phylloporphyrin, has been obtained from chlorophyll by Schunck and Marchlewski. Church obtained yet another from turacin, the copper-containing pigment of the red feathers of the plantain-eaters, but did not succeed in preparing his turacoporphyrin free from copper. Solutions of the several porphyrins are indistinguishable in tint; they yield spectra more complex and characteristic than those of any other animal pigments, and so much alike that they can only be differentiated by accurate measurement of their absorption bands.

Whereas in the laboratory the porphyrins have only been prepared by the action of powerful reagents, in the animal body they are formed by the gentler methods of metabolism. Pigments of this class are present in traces in normal human urine, fæces, bile and meconium, and in larger amounts, but still traces, in the excreta of sufferers from many maladies.

Until recently the metabolic pigments of the group were

thought to be identical with the laboratory products, and were always spoken of as hæmatoporphyrin. Hans Günther, who has contributed much to our knowledge of the porphyrins as metabolic products, and who first recognized the existence of the anomaly now to be described, assigned to it the name of hæmatoporphyrin congenita, and thereby emphasized the fact that the excretion of urine rich in porphyrin is only one of the symptoms which result from the presence of excess of such pigment in the tissues. Although there is much to be said in favour of Hans Fischer's proposal that the excretion of urine rich in porphyrin should rather be described as porphyrinuria, it seems better, in view of Günther's priority, to retain for this inborn error of metabolism the name which he assigned to it. Accordingly the title 'Hæmatoporphyrin Congenita' has been placed at the head of this chapter.

In the latter years of the last century a number of investigators studied the occurrence of hæmatoporphyrin in urine and fæces, and amongst them McMunn, Stokvis, Salkowski, Hammarsten, Riva and Zoja, Sallet, and the present writer. The minute quantities in morbid urines were first detected by McMunn, and my own observation that traces are present in normal human urine and in meconium, has since been confirmed by others, and most recently by Günther. Stokvis first found traces in normal fæces and Otto Neubauer in the bile.

In the study of the minute quantities in normal and ordinary morbid urines one has to rely upon spectroscopic evidence alone. The amounts present do not suffice, as a rule, to modify the colour of the urine, but it is sometimes possible for a trained observer to detect the characteristic absorption bands in the spectrum of untreated morbid urines, and more often those of the acid spectrum after addition of hydrochloric acid. Günther suggests that any urine which shows the bands, after acidification, in a layer

five centimetres thick, may be regarded as containing hæmatoporphyrin in abnormal quantity.

Upon a wholly different plane are cases in which the urine has a deep red colour, like that of port wine, and is rich in porphyrin and other abnormal pigments of which as yet we know little. This phenomenon was first described by Baumstark and Neusser, and many patients who pass such urine have taken sulphonal or an allied drug over considerable periods, as in the early cases investigated by Stokvis, Salkowski, and Hammarsten. Although intermediate cases are met with it is convenient to restrict the name of hæmatoporphyrinuria, or porphyrinuria, to cases in which the colour of the urine is conspicuously abnormal.

In a monograph published in the year 1911 Hans Günther¹ passed in review the cases of such hæmatoporphyrinuria previously recorded, and others which he had himself met with, and grouped them under four heads.

In his first class he included cases of acute onset, in which the symptoms could not be ascribed to the administration of any drug, and some of which were recorded before sulphonal came into use. In many such cases the excretion of red urine is associated with severe toxic symptoms, of which abdominal pain is the most common and a form of ascending paralysis is the most grave. Some patients have suffered from repeated attacks at longer or shorter intervals, and in a family described by Barker and Estes² several members suffered from such attacks, some of which proved fatal.

In the second class are placed the cases due to sulphonal or trional, in which similar grave associated symptoms are usually present, and in which a fatal ending is the rule. The patients have often taken the drug for months or years, with apparent impunity, prior to the development of the hæmatoporphyrinuria.

¹ *Deutsches Archiv f. klin. Medizin*, 1911, cv. 89.

² *Journal of the American Medical Association*, 1912, lix. 718.

In the two remaining classes are placed the cases in which hæmatoporphyria persists over long periods. In such cases the acute toxic symptoms are wanting, but there is evidence of a greatly exalted sensitivity of the tissues to light. Günther pointed out that in some such cases, including one which he recorded, the hæmatoporphyria is congenital and persists through life, and to him belongs the credit of having recognized the very remarkable inborn error of metabolism under discussion, which, both in its physiological and clinical aspects, is one of the most interesting of the series. The remaining cases of long duration he classes under the head of chronic hæmatoporphyria. This is, as he himself admits, the least convincing of his four classes, and it is probable that some at least of the cases so named, in which the diagnosis rests only upon the alleged time of onset of the symptoms, were, in reality, examples of congenital hæmatoporphyria.

In a more recent paper³ the same author puts forward the view that a constitutional anomaly, which he styles 'porphyrim', underlies acute and chronic cases alike; that individuals who exhibit this anomaly are liable to develop the symptoms of hæmatoporphyria under any suitable provocation, and that one such provoking cause is prolonged administration of sulphonal. Whether we accept this hypothesis or not, there can be no doubt of the existence of a congenital metabolic anomaly of which porphyrinuria is one of the symptoms.

Although no medical witness has testified, as yet, to the occurrence of porphyrinuria in the earliest days of life, the evidence available appears to me sufficient to carry conviction. The mother of a child whose case was recorded by Mackey and myself⁴ stated that the very first urine passed by the child was red, and that it had been so ever

³ *Deutsches Archiv f. klin. Medizin*, 1920, cxxxiv. 257.

⁴ *Quarterly Journal of Medicine*, 1922, xv. 319.

since. She took pains to obtain confirmation of this statement, upon which we place reliance. In this case the first attack of hydroa vacciniforme, an eruption which results from exposure of the skin to light, occurred when the infant was three months old. The mother of Günther's patient noticed the colour of his urine when he was twenty months of age, and hydroa first appeared at the same time. Vollmer's ⁵ patient, a woman aged 45 years, dated her skin disease from her first year, and had passed red urine as long as she could remember. It may be noted that, in this connexion, the date of onset of the red urine is of more importance than that of the cutaneous affection, the occurrence of which is dependent upon exposure to bright light. The very first case in which a porphyrin was found in the urine, described by Schultz ⁶ and Baumstark ⁷ in 1874, was probably, as Günther pointed out, a member of this group, but the cutaneous lesions were ascribed to lepra bullosa; and a case recorded by Gagey, ⁸ in 1896, diagnosed as one of xerodermia pigmentosa with hæmoglobinuria, may also be included with some confidence. The description of the eruption suggests hydroa; it is stated expressly that no albumin could be detected in the urine, and the spectroscopic appearances were such as porphyrin urines not infrequently present. In Vollmer's case the skin lesions were ascribed to congenital syphilis, but there are ample grounds for revision of that diagnosis also. The close resemblances of the published pictures of McCall Anderson's, Vollmer's, and Günther's patients, leave little doubt of the identity of their cutaneous lesions.

With the possible exception of cystinuria, hæmato-

⁵ *Archiv f. Dermatologie u. Syphilis*, 1903, lxxv. 221. See also Nebelthau, *Zeitschrift f. physiol. Chemie*, 1899, xxvii. 324.

⁶ *Inaugural Dissertation*, Greifswald, 1874.

⁷ *Archiv f. Physiologie* (Pflüger), 1874, ix. 568

⁸ *Thèse de Paris*, 1896, no. 567.

porphyria congenita is the most deleterious in its effects of the six anomalies dealt with in this book. It gives rise to horrible disfigurement, and in some cases to blindness, and although Vollmer's patient reached the age of 65 years, Linser's⁹ died at 50, and Ehrmann's¹⁰ was alive at the age of 48, there is clear evidence that the expectation of life of the victims of this anomaly is far below the average. Anderson's patients died, as I am informed, at 30 and 31 years respectively, and one of their sisters, who is reputed to have been similarly affected, at the age of 15 years. Tuberculosis figures so largely in the histories of such patients as to suggest a special liability to that infection.

The attacks of hydroa vacciniforme tend to recur year after year with the return of summer, unless special precautions are taken to avoid exposure to bright light. Presumably a subject who led a troglodyte existence, and only went about after sunset, would escape damage to his superficial tissues and suffer little inconvenience.

The eruption is confined to the exposed regions, the face and neck, backs of the hands, and in children the knees. Some parts of the face, and especially the chin, are almost immune, and the hair usually affords adequate protection. The exposed surfaces of skin are apt to become abnormally pigmented, as if for protection of the underlying parts, and in some cases, notably in those described by Cappelli,¹¹ and by Arzt and Hausmann,¹² affected children have developed conspicuous hirsuties of the exposed parts.

Bullæ of various sizes first appear upon the exposed areas of skin, some with colourless and others with blood-stained contents. Permanent scarring results in the sites of the bullæ, and areas of redness which do not fade on pressure,

⁹ *Archiv f. Dermatologie u. Syphilis*, 1906, lxxix. 251.

¹⁰ *Ibid.*, 1905, lxxvii. 163; 1909, xevii. 75; and Gross, *ibid.*, 1910, cv. 266.

¹¹ *Giornale Italiano d. Malattie venere e della Pelle*, 1914, lv. 481.

¹² *Strahlentherapie*, 1920, xi. 444.

with patches of milium and the pigmentation already referred to. After repeated attacks there is loss of substance and mutilation of the ears and nose. In the hands, in addition to the cutaneous scarring, the nails are shed from time to time, and grave deformities are produced, which are due to stiffness of the joints and atrophy of the terminal phalanges. On account of the incapacity so caused the index fingers of Günther's patient were eventually amputated.¹³

The formation of bullæ upon the conjunctivæ, and destructive lesions of the eyes which in the end result in blindness, are amongst the most serious results of congenital hæmatoporphyria.

However, hydroa vaccini-forme is not an inseparable accident of congenital hæmatoporphyria, as is shown by the case of a 'bearded woman' described by Hegler, Fraenkel, and Schumm,¹⁴ who was said to have passed red urine all her life, and who died of pulmonary tuberculosis at the age of 33 years. Her face was conspicuously pigmented, as by an exaggerated chloasma uterina, but she showed no bullous eruption or scarring. In this case the growth of a beard had probably no connexion with the hæmatoporphyria. Sobernheim¹⁵ also recorded the case of a boy, aged 13, who was admitted to hospital with enteric fever and passed red urine, rich in porphyrin, during the attack and after his convalescence. It may well be that his porphyrinuria was congenital, for inquiry showed that the colour had been noticed for some years previously at least, but there is no mention of any skin eruption, nor of scarring.

In its sex incidence (males 63.3 per cent.),¹⁶ family occurrence and incidence in childhood, hydroa vaccini-

¹³ Hans Fischer, *Münchener med. Wochenschrift*, 1916, lxiii. 377.

¹⁴ *Deutsche med. Wochenschrift*, 1913, xxxix. 842; *ibid.*, 1916, xlii. 1242

¹⁵ *Ibid.*, 1892, xviii. 566.

¹⁶ Günther, *Dermatologische Wochenschrift*, 1919, lxviii. 203.

forme closely resembles hæmatoporphyria congenita, but on the evidence available it is not at all probable that hæmatoporphyria is the only cause of that affection. On the other hand it is likely that not a few cases with porphyrinuria are included in the records of hydroa cases, in the majority of which no mention is made of the urine; and indeed the amount present, although abnormal, may be hardly sufficient to attract attention.

One of the most remarkable features of congenital hæmatoporphyria is a deep brown pigmentation of the bones of its subjects, which is due to deposition of porphyrin. A similar pigmentation of the bones of two pigs was described by Tappeiner in 1885, and a number of such observations have since been recorded in swine and cattle. In a paper published by Schmey,¹⁷ in 1913, a *résumé* is given of the examples recorded down to that date. Of the symptoms exhibited by the affected animals practically nothing is known, but one cow is stated to have passed blood-stained urine. In several cases porphyrin has been extracted from the dark brown bones. This phenomenon has been called ochronosis of cattle, a most unfortunate use of a name already appropriated to an entirely different condition.

The bones of the patient of Hegler, Fraenkel, and Schumm, the bearded woman, showed such pigmentation in an extreme form, and those observers describe the striking contrast between the dark brown bones and the untinted articular cartilages. Schumm extracted a porphyrin from these bones. Schultz also described pigmentation of the bones of the skull-cap in his case, and those of the amputated fingers of Günther's patient also were deeply stained.

That the bones of our patient are deeply pigmented Mackey and I were able to convince ourselves by the very

¹⁷ *Frankfurter Zeitschrift f. Pathologie*, 1913, xii, 218.

simple method of trans-illumination of the hands by an electric bulb-lamp. The shadows of the bones of the hands of normal individuals, even adults, are faint and indistinct, and the most conspicuous shadows seen are those of the contents of the dorsal veins, whereas the bones of the child with hæmatoporphyria threw dense, dark, rod-like shadows, quite unlike those shown by normal controls. But, as was to be expected, an X-ray picture showed no abnormal density of the bony structures, and the only abnormality to be noticed was an obvious delay in the ossification of some of the carpal bones such as was found by Arzt and Hausmann in one of their cases. Thus we are provided with means of detecting the pigmentation of the bones of living subjects, which should prove useful in the investigation of future cases.

The most striking feature in our case was the pigmentation of the enamel of the milk teeth, which has, hitherto, not yet been observed in any other. The child cut his first tooth at the age of nine months and it was pink in colour. When Mackey first saw him he was twenty-two months old, and had twelve teeth, all of a pinkish-red colour almost indistinguishable from that of the gums. Now, at the age of six years their tint is best described as brown-pink. When the milk teeth shall be shed we hope to examine them further, and it will be interesting to see whether the permanent teeth will be similarly pigmented. Pigmentation of the enamel is a rare phenomenon. A pink colour may result from injury to the pulp of a tooth and extravasation of blood, and staining by bile-pigments has been described by Thursfield and Langmead in children suffering from chronic jaundice. Even in congenital porphyria it is evidently an exceptional sign, for Cappelli, whose patient was of the same age, describes the milk teeth as irregular, rather large, and with some erosion of the crowns, but makes no mention of any peculiarity of tint.

The teeth of Günther's patient are described as yellowish-white, but the root of one which was extracted was deeply stained, and from it porphyrin was obtained; and a similar staining of the roots of the teeth was present in the case recorded by Hegler and Fraenkel. There can be no doubt that the dental staining is of the same nature as the pigmentation of the bones, and is due to deposition of porphyrin.

In some of the cattle with pigmented bones the enamel of the teeth has also been coloured. Thus Schenk¹⁸ observed a chocolate-brown staining of the enamel in a cow, and Colberg¹⁸ described a calf three days old of which the bones and teeth were dark brown in colour, but it would not appear that in either instance the pigmentation of the bones was proved to be due to porphyrin.

Schumm¹⁹ was able to detect traces of porphyrin in the blood-serum of Günther's patient, and estimated the quantity at about 0.001 gramme in 100 c.c.

The fæces have been examined in only a few cases of congenital hæmatoporphyria. In Günther's case and ours the stercoporphyrin of Hans Fischer was found in considerable amounts, and the mother of our patient had noticed that in his infancy the child's fæces had stained the napkins red, apart from any admixture of urine. It is important that such examinations should be carried out in all future cases, and also in cases of hydroa without obvious porphyrinuria, since there is reason to believe that stercoporphyrin plays an important part in the causation of hydroa vacciniforme.

The colour of the urine varies from time to time, and in one of McCall Anderson's cases it was said to be normal in the intervals between attacks. The colour is usually like that of port wine, but occasionally it is rather brown than

¹⁸ Quoted by Poulsen, *Beiträge zur pathol. Anatomie u. z. allgem. Pathologie*, 1910, xlviii. 487.

¹⁹ *Zeitschrift f. physiol. Chemie*, 1916, xcvi. 123.

red. The detection of porphyrin in the urine is not always so easy as might be expected. When the untreated urine is examined with the spectroscope the porphyrin bands are sometimes much obscured by a more general absorption due to other abnormal pigments which may also mask the red colour. In my experience this is more often the case with the sulphonal urines than with others. The urine of the patient of Mackey and Garrod shows the bands of alkaline porphyrin with great distinctness, and when hydrochloric acid is added shows those of the acid spectrum equally well, for even acid urines yield the so-called alkaline spectrum. Some urines show only two bands, very like those of oxy-hæmoglobin, but if albumin be absent the presence of that pigment may be excluded. This is usually called the metallic spectrum, but Günther believes that it is due to the action of heat upon hæmatoporphyrin, and prefers to speak of it as the 'warm-spektrum'.

For the detection of porphyrin in normal urine special methods are required, such as precipitation of the pigment upon the phosphate sediment which is thrown down by the addition of 200 c.c. of 10 per cent. solution of sodium hydrate to a litre of urine,²⁰ and extraction of the porphyrin from the sediment by means of a small quantity of alcohol acidified with hydrochloric acid. Saillet²¹ showed that the pigment might be extracted by shaking the urine with acetic ether, and by this method also the normal traces may be detected. For the extraction of porphyrin from the red urines Nebelthau's²² method of precipitation by the addition of glacial acetic acid, in the proportion of 5 c.c. of acid to 100 c.c. of urine, is by far the best. However, in exceptional cases the pigment fails to be so precipitated and resort must be had to other methods.

²⁰ *Journal of Physiology*, 1894, xvii. 349.

²¹ *Revue de Médecine*, 1896, xvi. 542.

²² *Zeitschrift f. physiol. Chemie*, 1899, xxvii. 324.

There is nothing characteristic in the blood-picture in congenital hæmatoporphyria. In some cases there has been diminution of red corpuscles, but in others of long standing there has been no evidence of excessive hæmolysis. A conspicuous eosinophilia has been observed in some cases, such as often accompanies bullous eruptions of other kinds, but in others, including that recorded by Mackey and Garrod, the eosinophil corpuscles have not been increased in number.

A conspicuous feature in some cases is enlargement of the spleen. In Schultz's case the lower border of that organ was below the level of the umbilicus. In Günther's case the spleen was not palpable when the patient was under his observation, but at a later stage it was found by Hans Fischer to be clearly palpable, and in an additional note on the condition of Ehrmann's patient, at the age of 48, Günther describes the spleen as palpable. The splenic enlargement, which has not been found in affected children, would appear to be a late development.

Congenital hæmatoporphyria would appear to be one of the rarest of inborn errors of metabolism, for even if alleged cases in unseen members of affected families be included, the known examples do not exceed twenty in number. The red urine, the hydroa and its effects, and the pigmentation of the bones are all very conspicuous features which are little likely to escape observation, and the last of these could not be overlooked at an autopsy. Even if all cases of hydroa should be found to be of this nature, and also every case of long-standing porphyrinuria, it would still be sufficiently rare. On the other hand it is no easy matter to determine whether certain cases should or should not be included in this group. The information supplied by patients or their friends as to the time of onset of symptoms is often not at all reliable, and a classification based upon such information cannot be wholly satisfactory. Nor is the appearance of the urine a safe guide, for in some cases the red colour

has been intermittent, and in others, such as those recorded by Arzt and Hausmann, is at no time conspicuous. Their patients were brothers, aged 2 and 11 years respectively (children of a marriage of first cousins), both of whom suffered from hydroa. On some days their urine had a reddish colour, but as a rule its tint was normal; but the absorption bands of a porphyrin were almost always visible when a layer 5 cm. in depth was examined with a pocket spectroscop. No porphyrinogen was found, nor could porphyrin be extracted from the fæces. Nevertheless these cases cannot be excluded from the list of examples of congenital hæmatoporphyrin.

The sex and family incidence of the anomaly have been discussed in an earlier chapter, and resemble those of other inborn errors of metabolism.

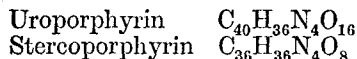
The work of Hans Fischer²³ upon the excreta of the patient whose case Günther had previously recorded has placed our knowledge of the metabolic porphyrins upon a new and satisfactory footing, for he was able to extract the pigments in quantities sufficient for investigation by strictly chemical methods.

From the precipitate thrown down from the urine by glacial acetic acid, and from the fæces, he prepared crystalline methyl-esters of the porphyrins from both sources, and showed that the urinary product, which he named 'urinary porphyrin', and the fæcal product 'kot-porphyrin', differed conspicuously in their chemical composition, and that both differed from the hæmatoporphyrin and mesoporphyrin of Nencki and Zalewski. In accordance with our usage I shall speak of these substances as 'uroporphyrin' and 'stercoporphyrin' respectively.

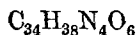
The methyl-esters of the two pigments melted, with

²³ *Zeitschrift f. physiol. Chemie*, 1915, xcvi. 34; *ibid.*, 1916, xcvi. 109, 148; *ibid.*, 1916-17, xcvi. 14, 78; *Münchener med. Wochenschrift*, 1916, lxxiii. 377.

decomposition, at 290° and 249–250° respectively. The method of micro-combustion enabled the percentage composition of both to be ascertained, and various derivatives of both, which threw light upon their molecular structure, were prepared and studied. These investigations enabled Fischer to assign to them the following empirical formulæ :



whereas the formula of the hamatoporphyrin of Nencki is :



The differences of the formulæ of the metabolic products are due to the fact that whereas stercoporphyrin has three carboxyl groups uroporphyrin has seven. In each of the three compounds each of the four nitrogen atoms forms part of one of the pyrrol rings in the molecular nucleus.

Otto Schumm,²⁴ who has directed much study to the spectroscopic differences of the several porphyrins, using a grating spectroscope and solutions of uniform acidity and alkalinity, is convinced that these pigments can be differentiated by differences in the positions of their absorption bands. We may hope that it will be found possible, by working with large quantities, to determine the nature of the porphyrin of normal urine by this method.

The absorption bands of the alkaline spectrum of uroporphyrin in decinormal potassium hydrate lie nearer to the violet end of the spectrum than those of stercoporphyrin, and the relative positions of the bands are somewhat different. In the spectrum of solutions in 25 per cent. hydrochloric acid, on the other hand, the bands of uroporphyrin lie nearer to the red end.

Schumm gives the following measurements of the middle

²⁴ *Zeitschrift f. physiol. Chemie*, 1914, xc. 1 ; *ibid.*, 1916, xcvi. 123 ; *ibid.*, 1919, cv. 158 ; *Münchener med. Wochenschrift*, 1913, xl. 1853.

lines of the several bands in wave lengths, but it should be noted that these measurements are only strictly comparable with those obtained with a grating spectroscope, and with solutions of uniform acidity or alkalinity.

	I.	II.	III.	IV.	V.
Uroporphyrin in 25 per cent. HCl	596.7	577	553.4	526.3	511.8
Stercoporphyrin in 25 per cent. HCl	593.1	573.5	549.9	524.5	509.3
Hæmatoporphyrin (Nencki)	595.3	574.5	552	526	511
	I.	II.	III.	IV.	
Uroporphyrin in n/10 KOH	611.3	559.4	538.4	501.8	
Stercoporphyrin in n/10 KOH	617.5	565.5	538.3	503.3	
Hæmatoporphyrin in n/10 KOH	618.5	566	541	504	

We are not yet in a position to assert that the same porphyrins are always present in the urine and fæces, but it is at least highly probable that this is the case. Chemical examination of the urine and fæces of the child described by Mackey and myself are being carried out, on Fischer's lines, by E. N. Allott, and the melting-points of the respective methyl-esters render it almost certain that the urinary pigment is uroporphyrin, and that the less abundant pigment in the fæces is stercoporphyrin. Ellinger and Reisser²⁵ found uroporphyrin in the urine in a case of porphyrinuria due to trional, and Schumm in a sulphonal case. Schumm also found uroporphyrin in the deeply pigmented bones of the patient of Hegler and Fraenkel. Again, Löffler²⁶ found uroporphyrin in the urine and stercoporphyrin in the fæces in a case of acute non-toxic porphyrinuria with ascending paralysis.

On the other hand, Schumm,²⁷ who has examined, by his spectroscopic method, the urine of patients with lead poisoning, in which, as is usually the case, porphyrin was present in some excess, was led to the unexpected conclusion that, judging from the positions of the absorption

²⁵ *Zeitschrift f. physiol. Chemie*, 1916, xcviii. 1.

²⁶ *Biochemische Zeitschrift*, 1919, xcviii. 105.

²⁷ *Zeitschrift f. physiol. Chemie*, 1922, cxix. 139.

bands, the pigment present in such urines is not uroporphyrin but stercoporphyrin.

Hans Fischer believes that the porphyrins of the urine and fæces are derived from a common parent substance, and that from it stercoporphyrin is first formed in the organism, and from this again uroporphyrin, which is more readily excreted in the urine. In the urine stercoporphyrin is excreted in small amount, together with a much larger quantity of uroporphyrin, but in the fæces stercoporphyrin apparently occurs alone. He succeeded in converting the urinary into the fæcal pigment by removal of hydroxyl groups.

Biological experiments lent strong support to Fischer's views. Thus he found that when uroporphyrin was injected subcutaneously into a rabbit it was excreted wholly in the urine, whereas stercoporphyrin, so injected, appeared mainly in the fæces, and only in small amount in the urine. Moreover when Fischer himself took uroporphyrin by the mouth he recovered that pigment unchanged from his stools, and no reduction to stercoporphyrin had been brought about in the alimentary canal. He estimated that the patient with congenital porphyrinuria, whose excreta he investigated, passed, on an average, some 0·3 gramme of uroporphyrin and some 0·1 gramme of stercoporphyrin daily, i. e. some 0·4 gramme of porphyrins in all.

In the year 1874 Baumstark found, in the urine of Schultz's patient, a porphyrin which he called uro-rubro-hæmatin, and another dark-coloured pigment, uro-fusco-hæmatin, which yielded no characteristic absorption bands. In almost all, if not in all, cases with red urine, the colour is in part due to such other pigment (the urofuscine of Günther) which is precipitated by baryta mixture, leaving the filtrate yellow.

At present our knowledge of urofuscine is very scanty, and my own experience leads me to believe that several

distinct colouring matters are included under that name. In some cases a purple pigment, which shows a broad, ill-defined absorption of the green and yellow portions of the spectrum, has been isolated by myself and others. Even from the pink urines, which show the porphyrin bands very clearly, acetic acid precipitates the porphyrin but leaves the filtrate more or less deeply coloured.

Günther believes that urofuscin is a precursor of porphyrin, with which it is so closely associated, but the development of the porphyrin spectrum in solutions of urofuscin may be due to the presence of the colourless porphyrinogen which is met with both in urine and fæces.

We cannot hope to solve the problems of hæmatoporphyrin until our knowledge of the place of the porphyrins in animal metabolism is far more advanced. Stokvis²⁸ suggested that some at least is formed in the alimentary canal, from hæmoglobin, muscle pigment, and even from the chlorophyll of vegetable foods. This view met with no wide acceptance, and in a number of observations, carried out some thirty years ago, I failed to detect any influence upon the normal traces in the urine of changes from a meat diet to one of vegetables or of milk foods only. The traces were present after long periods during which only milk was taken, in the urine of sucklings and in that of a life-long vegetarian. Snapper,²⁹ on the other hand, has recently found that considerable quantities of porphyrin are present in the fæces after hæmorrhages into the alimentary canal, but with no corresponding increase of the output in the urine, whereas in the stools of three out of four cases of acute non-toxic porphyrinuria he found little or none.

Whether or not an actual exogenous formation of porphyrin occurs, that some of the porphyrin in the animal tissues and excreta is endogenous cannot be doubted.

²⁸ *Zeitschrift klin. Medizin*, 1895, xxviii. 1.

²⁹ *Berliner klin. Wochenschrift*, 1921, lviii. 800.

Nor, seeing that traces of such pigment are present in normal urine, fæces, bile, and meconium,³⁰ can we deny it a place among the endogenous products of normal metabolism. In this connexion the presence of porphyrin in meconium is of special significance.

More than twenty years ago I called attention to its presence in the meconium of newly-born and still-born infants, and Günther³¹ has confirmed this by a more elaborate investigation. In dried meconium he found some 2 mg. of porphyrin per 100 grammes, and some 0.7 mg. in 100 grammes of the undried material. The pigment was present prior to the appearance of bacteria in the intestine, and the growth of neither aerobic nor anaerobic bacteria had any influence upon its amount. On the other hand, in the yellow intestinal contents of an eight months fœtus none was found.

The metabolic products which suggest themselves as likely parent substances of the porphyrins are hæmoglobin and bilirubin. Although bilirubin differs so widely from the porphyrins in its properties it is allied to them in *chemical composition, and possesses the nucleus of four pyrrol rings*. Its empirical formula is $C_{33}H_{36}N_4O_6$, and it is undoubtedly formed from hæmoglobin.

It has been suggested that the porphyrin may be an intermediate product in the anabolism of hæmoglobin, but there is no direct evidence to support such an hypothesis, nor is there any obvious reduction of hæmoglobin formation in cases of porphyrinuria. Nor does it appear likely that bilirubin is the parent substance, although Snapper is inclined to think that the presence of bile in the intestine favours the formation of porphyrin therein.

It is far more probable that it is derived from hæmoglobin,

³⁰ *Lancet*, 1900, ii. 1328.

³¹ *Ergebnisse der allgem. Pathologie und path. Anatomie* (Lubarsch und Ostertag). 1922 xx. *Abtheilung* 1, 643.

and there is much to be said in favour of Hans Fischer's suggestion that the metabolic porphyrin, or a precursor thereof, is an intermediate product in the conversion of hæmoglobin into bilirubin.

All the available evidence tends to show that an excessive excretion of porphyrin does not imply excessive hæmolysis. Sufferers from hæmolytic diseases, such as pernicious anæmia and paroxysmal hæmoglobinuria, do not excrete porphyrin in excess, and what is far more significant, patients who pass red urine, rich in porphyrin, over long periods usually show no signs of excessive hæmolysis. For example, in our case of *congenital porphyrinuria, red urine* had been passed continuously from birth onwards, and the fæces also were rich in porphyrin, but at the age of six years the child had a red corpuscle count of 4,480,000 per c.mm. and the hæmoglobin percentage was 90; in Cappelli's case a child of the same age had 4,800,000 erythrocytes per c.mm., and at the age of 33 Günther's patient had 4,148,000 red corpuscles and 90 per cent. hæmoglobin.

The results obtained in cases of acute hæmatoporphyrria tell the same story, nor does the fact that in some cases there has been obvious anæmia invalidate the evidence of those in which there is none.

If the metabolic porphyrin be an intermediate product on the path from blood-pigment to bile-pigment, and if, as in other inborn errors, the lack of a specific enzyme causes an arrest at this intermediate stage, it is not necessary to invoke any excessive hæmolysis to account for the excretion of porphyrin in the quantities observed.

Fischer pointed out that in his case the arrest was certainly not complete, seeing that the patient formed bilirubin; but, on the other hand, an output of some 0·4 gramme of porphyrin per diem represents a large fraction of the daily output of bilirubin, which Abderhalden

estimates at 0.5 gramme. Whether, and if so how far, the formation of bilirubin is diminished in these cases we do not know. Nor do we know whether excessive hæmolytic causes increased excretion of porphyrin by a porphyrinuric, as it should do if this hypothesis be correct.

There is some clinical and experimental evidence which tends to support the above hypothesis, or at least to show that some process which has its seat in the liver is at fault. Riva and Zoja's³² clinical observations led them to conclude that hepatic disorders, functional as well as organic, are mainly responsible for the appearance of abnormal amounts of porphyrin in the urine; Keyzer,³³ a pupil of Stokvis, formed the same opinion, and my own observations, carried out at about the same date, supported this view. Thus in valvular heart disease an increased output is closely associated with passive congestion of the liver, as manifested by enlargement and tenderness of that viscus, and speaking generally it is rather upon the study of individual cases, and on the contributory factors at work, than on statistical tables, that this opinion is based. In many cases of grave hepatic disease there is no obvious increase of urinary porphyrin.

Suner³⁴ found that hæmatoporphyrin, prepared by Hoppe-Seyler's method, when injected into a dog did not appear in its urine, but when the animal's liver was damaged by the administration of small doses of phosphorus for a fortnight, injected hæmatoporphyrin did so reappear. Moreover, he found that when finely minced liver substance was incubated at 37° to 40°, for 24 to 36 hours, with a dilute solution of hæmatoporphyrin in normal saline, the colour of the liquid was discharged and the spectrum was no longer

³² *Gazzetta medica di Torino*, 1892, xliii. 423, and *Archivio Italiano di Clinica Medica*, 1893, xxxii. 63.

³³ *Ueber Hæmatoporphyrin im Harn*, Dissert., Freiburg, 1897.

³⁴ *Journal de Physiologie et de Pathologie générale*, 1903, v. 1052.

visible ; whereas in a control from which the liver substance was omitted, the colour and spectrum persisted unchanged. Hence he concluded that the normal liver has the power of destroying hæmatoporphyrin.

Stokvis, Otto Neubauer, and A. Perutz have produced porphyrinuria in rabbits by the continued administration of sulphonal, whereas other experimenters have failed to obtain this result. The differences may be due to variation of technique and dosage, or to idiosyncrasy of the animals experimented upon. Perutz³⁵ found that when the urine of a rabbit thus rendered porphyrinuric was incubated with the minced liver of a normal rabbit the porphyrin spectrum disappeared, and bilirubin was found in solution ; but when the liver of a sulphonal rabbit was used in place of normal liver the absorption bands persisted and no bilirubin was found. These experiments have the advantage over those of Suner that the pigment employed was a metabolic and not an artificial porphyrin.

Günther³⁶ also has made experiments with the livers of guinea-pigs and with glycerine extracts therefrom. When the liver substance was incubated with a solution of uroporphyrin the spectrum of the latter disappeared, but the glycerine extract proved to be inactive. Whence he concludes that no ferment which can be extracted by glycerine is concerned in the reaction. The reaction did not take place at room temperature. The liver of the frog and that of *Arion* had no such action. Pulps of other organs, such as spleen and kidney, also failed to destroy uroporphyrin, and in this connexion it is interesting to note that I found the normal trace of porphyrin in the urine of three patients upon whom the operation of splenectomy had been performed.³⁷

Obviously, we have still much to learn as to the source

³⁵ *Archiv f. Dermatologie und Syphilis*, 1918, cxxiv. 531.

³⁶ *loc. cit.*, sub 31, p. 659.

³⁷ *Lancet*, 1900, ii. 1329.

and origin of the metabolic porphyrin, but such knowledge as we possess is consistent with the view that hæmoglobin is its parent substance and the liver the seat of its formation, and with the hypothesis that what is lacking in the subjects of congenital hæmatoporphyria is an enzyme which is responsible for one of the stages in the conversion of blood-pigment into bile-pigment.

Among the problems which congenital hæmatoporphyria presents, none is of greater interest than that of its relationship to hydroa vacciniforme, with which it is so closely associated.

Some twenty years ago it was discovered, by Tappeiner³⁸ and Raab,³⁹ that certain fluorescent pigments, of which eosin is one, induce hypersensitiveness to light in lowly organisms, such as paramecium. When a solution of such a pigment is added to a culture of the organisms they are killed by exposure to sunlight, but remain unharmed in a shaded portion of the same vessel. W. Hausmann⁴⁰ showed that hæmatoporphyrin, which has likewise the property of fluorescence, exercises this photo-sensitizing power not only with paramecium and red blood corpuscles, but also when injected into higher animals, such as white mice. With infusoria and red corpuscles the effect is only obtained when the pigment is exposed in contact with the organisms, and hæmatoporphyrin which has been previously exposed to light exerts no such action in the dark.

Hausmann found that when 0.01 gramme of Nencki's hæmatoporphyrin was injected into a white mouse subcutaneously the animal shows no ill effect so long as it is kept in the dark, but when exposed to bright light it dies within a few hours. When smaller doses are given, or when

³⁸ *Münchener med. Wochenschrift*, 1900, xlvii. 5.

³⁹ *Zeitschrift f. Biologie*, 1900, xxxix. 524.

⁴⁰ *Biochemische Zeitschrift*, 1911, xxx. 276; *ibid.*, 1914, lxvii. 309.

the animals are kept in feeble light, a definite syndrome, a true light disease, is presented.

The earliest symptom is irritation of the nose and ears, which are swollen and acquire a bluish-red tint, and later on undergo necrosis and are shed. Another sign is loss of hair over wide areas. The effect of the injection wears off in time, and, if the animal be kept in the dark long enough, subsequent exposure produces only slight symptoms or none at all.

That similar effects are produced in human subjects was proved by Meyer-Betz,⁴¹ by means of a bold experiment upon himself. Injection of 0.2 gramme of hæmatoporphyrin into a vein rendered him hypersensitive to light for two or three months, long after it ceased to be possible to detect the pigment in his blood. A few hours after the injection he exposed an area of skin upon his arm to the light of a Finsen lamp, with water-cooled lens, for forty minutes. Upon a normal subject such exposure causes nothing worse than a blister, but on the following day the exposed area was indurated and the skin around it was œdematous. The exposed portion of skin became almost black and there developed superficial necrosis with a sharply defined border. After detachment of the crust a deep ulcer remained, which healed in a few weeks but left a permanent scar. Exposure to sunlight produced giantœdema of his face, followed by peeling and pigmentation; and, even after he was no longer hypersensitive, exposure to sunlight caused undue amount of pigmentation. Hæmatoporphyrin could be detected in his blood during the first few days.

All the above experiments were carried out with artificial hæmatoporphyrin, but the natural porphyrins produce similar, although less intense effects.

Hausmann⁴² found that the urine of Ehrmann's patient,

⁴¹ *Deutsches Archiv f. klin. Medizin*, 1913, cxii. 476.

⁴² Ehrmann, *Archiv f. Dermatol. u. Syphilis*, 1905, lxxvii. 163; *ibid.*, 1909, cxvii. 75.

which was rich in porphyrin, did not sensitize paramecium or blood corpuscles, but the pigment extracted by the sodium hydrate method did so. Hans Fischer⁴³ sensitized mice by injection with the natural porphyrins, but failed to sensitize paramecium and blood corpuscles. Hausmann's⁴⁴ later experiments led him to the conclusion that the same porphyrin may occur in both photo-sensitizing and inactive forms, and lays special stress upon the fact that the porphyrin which was found by McMunn in the integument of certain earthworms (*Eisenia foetida*) serves as a protection from light, and is non-fluorescent, whereas when extracted with alcohol acidified with hydrochloric acid it fluoresces and has strong photo-sensitizing power. Fischer found that the natural porphyrins differed in their action; that when injected into mice uroporphyrin was the more strongly toxic, whereas stercoporphyrin induced greater sensitiveness to light. He suggests that the character and severity of the symptoms in cases of hæmatoporphyria may depend upon the amount of stercoporphyrin, or the precursor thereof, present in the organism, and upon the ability of the organism to convert it into uroporphyrin by addition of hydroxyl groups, and so to facilitate its excretion in the urine. He suggests that if large quantities of uroporphyrin are formed acute toxic symptoms may ensue, as in cases of sulphonal porphyrinuria, but if the conversion of the stercoporphyrin be complete, whilst the resultant uroporphyrin is not excessive in amount, there may be no symptoms, toxic or cutaneous. When on the other hand, as in his case, some 0.4 gramme of porphyrin is excreted in the 24 hours, and one quarter of it in the form of stercoporphyrin, we may expect to see the classical syndrome of porphyrinuria with hydroa.

This view gains support from the observations of Rodelius

⁴³ *Münchener med. Wochenschrift*, 1916, lxxiii. 377.

⁴⁴ *Biochemische Zeitschrift*, 1916, lxxvii. 268.

and Schumm⁴⁵ on a case of chronic porphyrinuria without hydroa or toxic symptoms, in which they failed to find porphyrin in the fæces. Snapper also found little or none in the stools of several cases of acute hæmatoporphyrin with abdominal symptoms. On the other hand Arzt and Hausmann⁴⁶ found no porphyrin in the fæces of their patients with hydroa, who also excreted much less than the usual quantities of the pigment in their urine.

How the photo-sensitizing action is brought about is still unknown. Some of the symptoms produced by injection of porphyrins in animals and in man, recall those of protein poisoning; Günther⁴⁷ also calls attention to the resemblance of the acute fatal attacks in injected mice to protein shock, and it is conceivable that a condition of sensitiveness may be maintained by the normal traces. If so, animals born and bred in the dark should be comparatively immune, an experiment which has not been tried. As lending some support to such an hypothesis some recent experiments by Howell⁴⁸ may be quoted. They show that when, instead of a living organism, a solution of fibrinogen, to which hæmatoporphyrin has been added, is exposed to light the fibrinogen becomes converted into a protein soluble in water, not precipitable by heat, and not coagulated by thrombin. Howell suggests that the pigment acts as a catalyst which starts or aids the action of light upon the protein.

At first sight these observations seem to supply a simple explanation of the association of hydroa with porphyrinuria. In the tissues of the congenital porphyrinuric there is present a pigment which is proved to possess the property of photo-sensitization, and such an individual is liable to develop a

⁴⁵ *Zeitschrift f. Urolog. u. Chirurgie*, 1914, iii, 112.

⁴⁶ *loc. cit.*, sub 12.

⁴⁷ *loc. cit.*, sub 31, p. 671.

⁴⁸ *Archives internationales de Physiologie*, 1921, xviii, 269.

cutaneous eruption upon any exposed surface, the occurrence of which is obviously due to exposure to light. But on further examination the matter is shown to be much less simple. The effects of exposure to light in animals injected with porphyrin, and those observed by Meyer-Betz in himself are of quite a different nature, and in no such experiment has hydroa been produced. Even in sufferers from hydroa, with or without porphyrinuria, it is not at all easy to produce the eruption by irradiation of a protected area, and many such attempts have failed completely. Magnus Moller⁴⁹ found that repeated exposures were necessary, and in Freund's case there was a considerable latent period after the exposure. Those who have succeeded agree in attributing the effect to radiations of short wave length, and Freund's⁵⁰ conclusive observations prove that, in his case at least, the ultra-violet rays were the most potent in producing hydroa.⁵¹

Howell also found the violet and ultra-violet rays to be the most active in bringing about the change in fibrinogen, but Hausmann showed, by convincing experiments, that the effects observed in the injected mice are mainly due to *visible* rays in the region of λ 500, which is the region of maximum absorption in the porphyrin spectra.

Yet, although the natural cutaneous eruption and the symptoms induced experimentally in animals are obviously not comparable phenomena, we cannot doubt that the sensitiveness to light which results from the presence of porphyrins in the tissues is the cause of the hydroa, and the failure to reproduce the natural syndrome is presumably due to faulty technique.

The absence of hydroa in some cases of congenital hæmatoporphyria may be due, as Fischer suggested, to

⁴⁹ *Der Einfluss des Lichtes auf die Haut*, Stuttgart, 1900.

⁵⁰ *Wiener klinische Wochenschrift*, 1912, xxv. 191.

⁵¹ See Arzt u. Hausmann, loc. cit., sub 12, p. 450.

lack of stercoporphyrin in such cases, or perhaps with greater probability to the presence of the porphyrin in an inactive form.

It is more difficult to explain the apparent discrepancies between the degree of porphyrinuria and the severity of the hydroa. In the cases described by Arzt and Hausmann the amount of porphyrin in the urine was far less than in other recorded cases of congenital hæmatoporphyria, so much less that it is with some hesitation that the diagnosis is accepted. In some cases, and notably in one of McCall Anderson's, the urine is said to have been of normal colour between the attacks, and in others also it would seem that exposure to bright light causes both the porphyrinuria and the hydroa.⁵² Moreover in some instances irradiation of an area of skin has been followed by a deeper coloration of the urine.⁵³

Fischer suggested that the explanation of such observations may lie in the presence in the tissues of a chromogen of the porphyrin, a colourless reduction product, which, as he found, does not sensitize them to light. Sallet first demonstrated the occurrence of such porphyrinogen in urine, and it is also found in fæces. Moreover Schumm⁵⁴ has shown that it is promptly converted into the pigment by potassium permanganate, and slowly by the action of light.

Further evidence bearing upon this point is supplied by some observations of Perutz⁵⁵ upon two cases of hydroa vacciniforme, in which porphyrinuria was present at times, whilst at others the presence of porphyrinogen could be demonstrated by the permanganate method. He states clearly that in one case attacks of hydroa occurred at

⁵² Radaeli, *Giornale Italiano delle Malattie vener. e della Pelle*, 1911, lii. 93.

⁵³ Linser, loc. cit., sub 9.

⁵⁴ *Münchener med. Wochenschrift*, 1913, lx. 1853.

⁵⁵ loc. cit., sub 35.

times when the urine did not show the spectrum of porphyrin.

So the matter stands at the present time, and it is obvious that much remains to be done. The study of past records of cases of congenital hæmatoporphyria can carry us no farther, and only by the investigation of fresh cases, in the light of the knowledge which is now at our disposal, can we hope to solve the problems still outstanding.