**Hæmatoporphyrinuria and its relations to the source of urobilin / by David Fraser Harris.**

# Hæmatoporphyrinuria and its Relations to the Origin of Urobilin.

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The chief pigment of normal urine is known as urobilin (seeing that this name indicates a relation to "bile," "urochrome" would be a better term, not connoting any view as to genetic relationship). The name for the chromogen "urobilinogen" would become "urochromogen." Other pigments are or may be present in normal urine, *e.g.*, the indigo-blue pigment whose ancestor is intestinal indol, and "uroerythrin" genetically related, it is believed, to skatol, while, according to some physiologists, traces of "pathological urobilin" (which might be better called para-urochrome) and even of hæmatoporphyrin are recognisable in healthy urine.

Certainly, in some morbid urines, urohæmatoporphyrin has been the chief pigment replacing urobilin, while, in a few very rare ones, a pigment allied to it, but, according to M'Munn, less deoxidised, has appeared. This substance, like urobilin and urohæmatoporphyrin, is a proteid-free, iron-free pigment, as yet unnamed. I propose to call it meio-de-oxyhæmatoporphyrin. Urobilin is amber-coloured, urohæmatoporphyrin makes the urine of orange tint, while the rarer ally gives it a deep port-wine colour: urines containing this last do not decompose for many weeks.

I lately encountered meio-de-oxyhæmatoporphyrin in the urine from a case of rare skin-disease, Dermatitis herpetiformis bullosa.* Both these hæmatoporphyrins have absorption-spectra resembling that of alkaline hæmatoporphyrin, and each, on the addition of strong sulphuric acid, is changed to the characteristic two-banded acid-hæmatoporphyrin.

In what way is urobilin related to these rarer and less deoxidised pigments? Let us dispose, in the first place, of the biliary theory of the formation of urobilin, which is, that bilirubin or biliverdin in the intestine is acted upon by nascent hydrogen,

* M'Call Anderson, *Scot. Med. and Sur. Jour.*, Feb. 1897.

and thereby reduced to a body resembling the artificial hydrobilirubin which, absorbed from the intestine, traverses the liver, and so, by the lungs, reaches the arterial stream for the kidney. Against this theory may be urged the following considerations:—

1. In animals with a biliary fistula the urine has urobilin.

2. In Copeman and Winston's case* of human biliary fistula, where the fæces were "clay-coloured," the urine contained urobilin, on some days in excessive quantity.

3. A body constantly present is made to depend upon a fluctuating quantity like "nascent hydrogen."

4. Why, if bilirubin, formed in the liver is at once excreted from it in the bile, should hydrobilirubin pass through the liver unchanged, or pass through it at all into the blood for the right auricle?

5. In fevers, whereas the amount of bile is diminished, urobilin is increased.

The fate of the bile-pigments will still further determine the site of the source of urobilin. The bile-pigments, acted upon in the intestine by some *de-oxidising* agent either contained in pancreatic juice† or acting in its presence, forms stercobilin, the brown fæcal pigment thus eliminated; for (1) before the pancreas secretes we have meconium (thick fœtal bile-pigment unaltered); and (2) although bile be secreted, if the pancreas is diseased or its duct occluded, stercobilin is absent from the faeces; (3) in vigorous catharsis, when bile-pigment is hurried through the intestine, it may be yellow (bilirubin) and not brown (stercobilin).

[Recently it has been suggested, from the spectroscopic affinities between stercobilin and pathological urobilin, that the presence of the latter in urine may be due to an abnormal absorption of the former from the bowel.]

Unquestionably hæmoglobin *via* hæmatin (normally) is the parent of both the bile-pigment and the urinary pigment, and it is most probable both are the offspring of hæmatin of the same generation.

Thus, though the BILIARY origin of urobilin must be given up, there is much to point to its *hepatic* origin; that the liver is the

* *Jour. of Phys.*, x. p. 21.

† T. J. Walker, *Med.-Chir. Trans.*, Lond., vol. lxxii., 1890.

chief seat of the formation from hæmatin of the immediate antecedent of urobilin there can be no doubt, for—

(1) Increased destruction of red blood-discs in the liver, such as follows from injecting into the portal vein any substance which liberates $HbO_2$, leads to an increase of urinary pigment.

(2) In pernicious anæmia much iron is deposited in liver cells, and the urobilin is increased, indicating an exaggerated destruction of $HbO_2$; in such urines the band at F can be seen (without concentrating the urine), sometimes pathological urobilin, a more de-oxidised pigment, is formed due to the abnormally intense de-oxidative hepatic katabolism of $HbO_2$.

Since M'Munn made urobilin by oxidising acid-hæmatin by per-oxide of hydrogen, and then briefly de-oxidising with sodium-amalgam, he has suggested that "urobilin is formed by nascent oxygen in the tissues." As to the *modus operandi* of its formation there are, then, two theories: (1) The reduction theory; (2) The oxidation theory. Though most probably both reduction and oxidation occur in the formation of uroblin, neither is alone the method; and as it was unsatisfactory to attribute the reduction to intestinal nascent H, so it is unlikely that nascent oxygen in the tissues performs the oxidation. The living protoplasm of the tissues craves oxygen for itself, and fixes it interstitially. If the liver is the great source of urobilin formation, it is, as we should expect, pre-eminently a region of *de*-oxidations.

All other pigments are artificially produced by processes of more or less complete reduction, thus:—

(1) Hæmatin acted on by nascent H = Hæmatoporphyrin.

(2) Hæmatin (but not bilirubin) acted on by zinc + $H_2SO_4$ to full reduction, yields pathological urobilin, intermediate stages in this process giving "urobilinoidin" (le Nobel), the chromogen of urohæmatoporphyrin.

(3) Urobilin reduced yields pathological urobilin (para-urochrome).

From these facts and other considerations we may follow M'Munn in believing that the order of the pigments as to degree of de-oxidation is as under:—

(1) Oxy-Hæmoglobin.

(2) Hæmoglobin.

(3) Hæmatin.

(4) Hæmatoporphyrin.

Meio-de-oxyhæmatoporphyrin.
Urohæmatoporphyrin.
Urobilinoidin.
Urobilin.
Urobilinogen.
Para-urochrome (pathological urobilin).
Para-urochromogen.

We have then to account for processes of decomposition, oxidation, and reduction in the transformation of blood-pigment to urinary-pigment. I believe it may be done thus:—

Taking the liver in health, oxyhæmoglobin reduced is first decomposed to hæmatin by separation of the proteid globin; the hæmatin is, by separation of its iron, further decomposed into some antecedent of urobilin, perhaps its chromogen.

This substance, secreted "internally" by the liver, passes on to the heart, and thence to the lungs, where it becomes oxidised to urobilin (hence the urobilin band in blood-serum*), and is then swept on into the arterial stream, to be (some of it) rapidly reduced at the moment of renal excretion; hence we are prepared to find in urine *some* urobilin and *some* urobilinogen, which latter, as the urine stands, becomes oxidised to the pigment—a process hastened by the acid fermentation, or by the action of potassium permanganate, HCl or $HNO_3$ on the urine.

In pernicious anæmia the initial amount of this hepatic katabolism is increased, or is excessive in the degree of de-oxidation (as above indicated). On this view M'Munn's oxidation-stage by $H_2O_2$ has its analogy in the lungs, and his "brief reduction" by Na-Hg in the kidneys.

But there are probably other than hepatic sites of urobilin formation, and tissues other than the liver can to a certain extent transform hæmoglobin. The blood of old clots (cerebral, aneurysmal, or of corpora lutea) often shows crystals of a proteid-free, iron-free pigment hæmatoidin (identical in analysis with bilirubin); blood effused into the peritoneum and other sites causes an increase

* M'Munn, *Proc. Roy. Soc.*, 1881, p. 231.

of urobilin or pathological urobilin, which also occurs in acute muscular rheumatism and in other fevers.

[The presence of an increase of urobilin in febrile urine may possibly be due not only to an excessive initial production of pigment-antecedent normally oxidised to urobilin, but also to a diminished reduction to chromogen by the relatively inactive renal epithelium.]

Tissue, other than hepatic, can katabolise blood-pigment, but urobilin is not always the end-product—the initial reduction may not proceed so far as that. These other tissues may be included under three heads:—

I. muscles; II. skin; III. connective tissues, with bones, cartilages, etc. Now, it is of blood from these three systems, in addition to the hepatic supply, that the blood in the right auricle may be *chemically* viewed as constituted: blood from these four sources contributes to arterial and therefore renal blood.

Under certain diseased conditions of one or more of these three systems, urohæmatoporphyrin replaced urobilin in the urine, notably in acute rheumatism (muscular and articular), effusion of blood into the peritoneum, and Addison's disease; but the following is a complete list of M'Munn's cases,* with the seats of depraved metabolism indicated (as above numbered):—

Acute rheumatism (I. and III.)

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| Pericarditis | (III.) |
| Peritonitis | |
| Meningitis | |
| Cirrhosis of liver | |
| Peritoneal blood effusion | |

Croupous pneumonia.

| | |
|---|---|
| Typhoid fever | (II.) |
| Measles | |
| Addison's disease | |

Hodgkin's disease.

Sulphonal overdosing.†

The less de-oxidised ally, meio-de-oxyhæmatoporphyrin, has appeared as *the* pigment on one or two occasions—twice in obscure

* *Journal of Physiology*, vol. x.

† Oswald, *Glas. Med. Journal*, 1895.

neurotic fatal cases in women, and once in a case with grave cutaneous lesion (reported above). It is noteworthy that in muscles we have a hæmoglobin derivative, myo-hæmatin, whose spectrum is very similar to urohæmatoporphyrin. Whatever else it is, it is a reduction product, for oxidation causes its bands to disappear. We might note the anæmia in Addison's and Hodgkin's diseases; and as to System II., that if it be *destroyed* over a pretty extensive area, as in a severe "burn," we have hæmoglobinuria—a paralysis of $HbO_2$-transforming power.

Normally, then, we may regard muscles, skin, and connective-tissues as seats of a subsidiary formation of urobilin from a hæmatin derivative, which, if it be excessively reduced, gives rise to pathological urobilin; if, owing to as yet most obscure deviations from healthy metabolism in these systems, it be only imperfectly reduced, we then have, in not a few cases, urohæmatoporphyrin, and in very rare ones its less reduced dark red ally. The degree of completeness of the initial reduction determines which of these hæmatin derivatives is to appear, for the amount of subsequent pulmonary oxidation and renal reduction is probably the same for all.

[In certain diseases this would, of course, not be so, as in pneumonia, where pulmonary oxidation is deficient, more, the[illegible] of the chromogen and less of the pigment from the system in which the prominent lesion existed would be excreted.]