sumably later developed (hence great tolerance of belladonna by young children), and thus fail first in dissolution.

It is well known that in pernicious diabetes sugar disappears from the urine during febrile ailments, the explanation being, I suppose, that the dilated hepatic arterioles do not then get so much blood as when general arterial tension is normal. (If the splanchnic nerves are divided before experimental injury to an animal's "diabetic centre," there is no glycosuria.) It is known, too, that in febrile diseases epileptic attacks usually cease. I suppose that in this condition, arterial tension being relaxed, or during the stage of febrile disease when it is relaxed, the semi-stagnant patch—"discharging lesion"—in the cortex gets less blood. Is it possible that the good effects of a seton in some cases of epilepsy are owing to the induction of a slight, miniature febrile condition? I suppose that nitroglycerine is given in epilepsy to produce general arterial relaxation. I have as yet but little experience of this remedy. Increase of arterial tension would be another reason for diminishing in an epileptic's diet the quantity of highly-nitrogenised food; for during high arterial tension, which much food of that kind may induce, the "semi-stagnant patch" may get more blood than if the patient has a simpler diet. On the great importance of degrees of arterial tension in epileptics Dr. Broadbent insisted strongly in his Croonian Lectures (1886), and since hearing them I have paid very particular attention to states of the pulse in epileptics. Besides ordinary care of the bowels and dietetics, we may give occasional small doses of blue pill when there is undue arterial tension. We should in such cases not give strychnine.

In cases of epilepsy the patient should "avoid excitement." But in young people we may err in being too strict; we may narrow a young epileptic girl's life too much by forbidding the amusements proper to her age. If she have a fit soon after a hearty game or a dance, it is, I think, only the premature development of a fit nearly due.

ON THE EXCRETION OF REDUCTION PRODUCTS OF HÆMATIN IN DISEASE.¹

By C. A. MACMUNN, M.A., M.D. Dub.,
Wolverhampton.

I MUST apologise for having brought a subject under your notice which may appear to be more of interest to pathological chemists than to medical men. I should not have presumed to do so were it not that some of the facts to which I wish to call attention have such an obvious bearing on pathogenesis, that they may be considered really more of medical than of chemical interest.

The subject is a difficult one, and to many may appear very dry, but that is not the fault of the subject, but is due to the fact that very few care to make themselves acquainted with the methods of spectrum analysis, and are not, therefore, in a position to understand the results.

For twelve years I have devoted much of my leisure time to the application of the spectroscope to biology in general, and, when I have had material to work upon, to that special branch of biology with which we are all concerned. During that time many new and interesting facts have presented themselves which, when their full significance is understood, must help to throw light on many now difficult problems.

In the present paper I wish to direct attention to the occasional presence of reduction products of hæmatin in pathological urine. In order to make this subject clearly understood it will be necessary to go somewhat into detail, and to refer incidentally to other kindred subjects.

Every medical man is more or less interested in the chemistry of urine, and most of us would like to know the cause of the increase of colour which that fluid undergoes in disease, or the actual change of colour from pale yellow to brown and black, which it often shows under certain conditions. It is easy enough to detect bile-colouring matter or blood-colouring matter by our rougher chemical tests; but there are other colouring matters present which cannot be detected by any other method but the spectroscopic one.

It may be asked, "And if you find out that a certain colouring matter is present, of what use is that knowledge?" So far,

indeed, as the mere presence of a colouring matter is concerned, if we had to do only with that colouring matter, its detection could not add much to our knowledge, because we know that pigments in themselves are not poisonous substances. But if we can tell how these things are produced in the organism, we have a clue to the processes by means of which other things with which the pigments are associated are produced; and, considering how little we do really know of these processes, in other words, of the metabolic changes which characterise disease, anything must be considered of importance which will help us to understand these changes. If we know that a certain colouring matter can only be produced out of the body by a very energetic reduction or oxidation process, we know that in the body it must be produced in the same way. These pigments are, in fact, finger-posts, indicating accurately the metabolism that is taking place in the organism under normal and diseased conditions.

A definite and accurate knowledge of the colouring matters of urine will help the diagnosis of disease also, but we have a great deal to learn yet. We must not be content with a superficial examination of urine by means of the spectroscope. The colouring matters must be isolated, and the changes which their solutions undergo on the addition of different reagents must be studied patiently and carefully. The most apparently trifling differences have to be noted, for it is these things which teach us so much. The accusation of being careless in things chemical is frequently brought against the medical profession, and often with good reason; and yet if a man tries to bring in more refined methods of analysis, and devotes his time to their study, he is, on the other hand, liable to be called theoretical and a scientific enthusiast.

Most of the pigments in man's body are derived from the red colouring matter of the blood, hæmoglobin, either immediately or remotely, by destructive metabolism—catabolism; while others are built up from simpler radicals by a constructive metabolism—anabolism. Among the former are the colouring matters of bile, and some of those of urine, with others such as melanin (but it would appear that melanin may sometimes owe its source to other things). Among the latter, or those not derived from hæmoglobin, are the lipochromes or colouring matters of fat, formerly known as aureins, apparently the yellowish-red pigment of muscle, which I discovered and named "myohæmatin,"² and a class of pigments found in various tissues and organs, also discovered by me and named "histohæmatins." The products of decomposition of indoxyl-sulphate of potassium—indigo-blue and indigo-red, the derivatives of skatol and other pigments—also owe their origin to another source than hæmoglobin.

That bilirubin, the red colouring matter of bile, is derived from blood is proved by the fact that an identical substance occurs in old blood extravasations which is known as hæmatoidin, and that biliverdin, or the green colouring matter of bile, is also often directly derived from blood is proved by the fact that it occurs in the placenta of the bitch, also in the egg-shells of some birds, where it is often accompanied by hæmatoporphyrin (Sorby). Dr. Carter, of Birmingham, once sent me a bright green specimen of hydrocele fluid, the colour of which I found was due to biliverdin, and in that case its origin was definitely traced to an old hæmorrhage into the tunica vaginalis.³ A curious proof was afforded of the truth of this assertion by an examination of the common red sea anemone, *Actinia mesembryanthemum*.⁴ In this lowly organised animal I found that a substance occurred in ectoderm and endoderm which could be made to show the bands of reduced hæmatin by appropriate treatment, and between these layers is a bright green deposit, which I found to consist of a pigment which was quite indistinguishable from biliverdin. Hence, although the examination of the lowest animals may seem at first sight superfluous, yet we often come upon facts, during such examination, which throw a vivid light upon questions of physiology and pathology.

Colouring Matters of Urine.—If you will take up almost any book on the chemistry of urine, you will find a very confused account of the colouring matter of that fluid. Some of the German textbooks are not included under this statement, as doubtful matters are as a rule left out of them. In some of these manuals you will find Heller's test for "urophain" and tests for "urohæmatin," although these substances are only of historical value.

² MacMunn: Researches on Myohæmatin and the Histohæmatins, *Philos. Trans. Roy. Soc.*, Part I, 1886.

³ MacMunn: Observations on the Colouring Matters of the so-called Bile of Invertebrates, etc., *Proc. Roy. Soc.*, No. 226, 1883.

⁴ MacMunn: Observations on the Chromatology of Actiniae, *Philos. Trans. Roy. Soc.*, Part II, 1885.

¹ Read before the Staffordshire Branch.

as Hoppe-Seyler has long since shown. In fact, the darkening which takes place on treating urine with strong mineral acids, and with these aided by heat, is due to the oxidation of several chromogens, not to the change of one, such as indican (=indoxyl-sulphate of potassium), urobilin, urochrome, and what Udranszky⁹ calls the "humus substances," and probably in some cases skatol compounds, and other bodies mostly belonging to the aromatic series. We only possess definite knowledge of a few urinary colouring matters. Among these I will here refer to the urobilin series only. Thudichum's urochrome does not belong to that series, as I have satisfied myself, and I am not, therefore, called upon to say anything about it.

In 1880⁶ I published a paper in the *Proceedings of the Royal Society*, in which I endeavoured to show how some of the urinary colouring matters could be definitely traced back to, and artificially prepared from, hæmatin and the bile pigments, and are therefore derived ultimately from hæmoglobin. I have recently gone over the same ground again, provided with better appliances, and I have confirmed the results contained in that paper so far as I have gone, but I have also found that our present views as to the identity of hydrobilirubin and urobilin, and on some other points, require considerable modification.⁷ Some of these points will be referred to further on.

If you examine normal urine with the spectroscope, you may or may not see that a shading or band is present at the F line. It may be necessary to add a little acid to the urine, such as hydrochloric or nitric, when as a rule it comes into view. When you examine high-coloured urine, such as you find in febrile cases, this band is generally very dark. Jaffé⁸ was the first who described the colouring matter to which the band is due, and he called it urobilin. He found that it was often absent in normal urine when freshly passed, but that on standing it appeared. Hence, he argued, there is a colourless substance or chromogen present in normal urine, which on standing exposed to the air becomes oxidised into urobilin. I thought I had evidence of the presence of two chromogens in urine; one that of normal, the other that of pathological urobilin, but it may be that the continued action of reducing substances in the urine may account for this. The matter is, however, not exactly as Jaffé described it. Immediately after the urine is passed the band may be seen, shortly afterwards it becomes invisible, because the pigment becomes reduced by some reducing substance in the urine; when acid fermentation begins in the urine it again becomes visible, owing to the influence of oxidation; and it may again disappear when the urine undergoes ammoniacal fermentation. Jaffé found this colouring matter most abundantly in febrile urine. He also found that a body of similar spectroscopic characters could be obtained from bile by the action of hydrochloric acid.

Maly⁹ next succeeded in converting bilirubin into a substance which he took to be urobilin. He obtained it by acting on bilirubin with sodium amalgam, and he called this new substance hydrobilirubin, assuming that one molecule of hydrogen and one of water were added on to the bilirubin. Vaulair and Masius,¹⁰ and Maly¹¹ subsequently, stated that the colouring matter of fæces—named stercobilin by the two first observers—was identical with Jaffé's urobilin.

Lastly, Hoppe-Seyler¹² found that a substance with the same optical and other characters as urobilin could be obtained by the action of tin and hydrochloric acid on hæmatin. It is unnecessary to quote the observations of others, which are numerous. These observers based their conclusions as to the identity of the above-mentioned pigments on the following characters: (1) On the presence of a band at F in acid solutions of the respective pigments; (2) On the green fluorescence which neutral solutions assume when treated with ammonia and zinc chloride; (3) On the shifting of the band at F towards the red end of the spectrum under the influence of caustic alkalis or on the addition of zinc chloride and ammonia; and (4) On the solubility of these pigments.

But these observers, and others also, did not notice the absorp-

tion bands which occur in the red half of the spectrum, not only in neutral solutions, but also in those to which ammonia, ammonia and zinc chloride, zinc chloride alone, and caustic soda have been added.

I called attention to these bands in the papers referred to below.¹³ At first it was supposed these bands were due to the presence of impurities, but it would now appear that they are not, and that they belong to the same pigments which give the band at F. The solutions have to be examined first in deep, then in less deep, and finally in shallow layers; it is only by doing so that we can see all the bands of each spectrum.

I have found, and I believe my conclusions may be accepted as true, that observers have included under the name urobilin at least three pigments, namely, 1, normal urobilin; 2, pathological urobilin; and 3, urohæmatoporphyrin. These conclusions are based, not on the mere examination of urine itself, but on the examination of solutions of the isolated pigments. In every instance the pigment was isolated as follows: The urine was treated with neutral and basic lead acetate until the filtrate was free from colour, the precipitate was acted on by rectified spirit and sulphuric acid (in the proportion of 3 c.c. H₂SO₄ to 17 rectified spirit), and again filtered; the filtrate was now diluted with water and agitated in a separating funnel with chloroform, the chloroform when it had separated was removed, and evaporated on the water bath. Sometimes it may be necessary to wash the chloroform again with water. If normal human urine be treated in this way we find that although the pigment in naked-eye appearances resembles very closely pathological urobilin, yet in its solutions certain differences are apparent when these are examined with the spectroscope. In neutral or acid solutions only one band at F is seen, none are seen in the red half of the spectrum. This band at F is not nearly as dark as the corresponding one of pathological urobilin: it has washed-out edges, and it is not merged into a less shaded band extending towards the violet end of the spectrum as is the corresponding band of pathological urobilin. Then, again, if we treat its alcohol solution with the reagents mentioned above, we find that it differs from pathological urobilin in many particulars.

From this description it may be inferred wherein the principal differences between normal and pathological urobilin lie, but besides, ammonia, ammonia and zinc chloride, zinc chloride alone, and caustic soda develop in alcohol solutions of pathological urobilin certain absorption bands, which are not seen in similar solutions of the normal pigment, and which prove that in the majority of cases pathological urobilin is derived from hæmatin by a reduction process. The third colouring matter which observers had confused with those just mentioned is one which is of very great importance from a medical point of view. I named it urohæmatin¹⁴ at first, but finding afterwards that it is closely related to hæmatoporphyrin, which is a decomposition product of hæmoglobin or hæmatin, and got from these by the action of strong sulphuric acid, I changed its name to urohæmatoporphyrin.¹⁵ In acid solutions this also gives a band at F, but also two others very characteristic—one narrow at D, another in the green; and in an alcoholic solution, after adding ammonia, no less than five characteristic absorption bands. Now all of these colouring matters are very easily distinguished from each other, and yet all give a band at F in acid solution; all give a green fluorescence with zinc chloride and ammonia, and correspond to the description of urobilin given by the above observers.

Artificial Preparation of these Colouring Matters.—In a paper already referred to I made the following remarks:¹⁶ "It is probable that a knowledge of how the urinary pigments can be prepared artificially will be of great use in enabling us to understand how they are produced in the body. Thus the knowledge of the fact that the spectrum of urobilin varies according to the amount and kind of oxidation, or reduction, or both, to which it has been subjected in the body, which I shall endeavour to show is the case, is of great importance, especially as we can produce in the laboratory pigments (from bile and blood-colouring matter), by a greater or less amount of oxidation or reduction, or of both combined, which can be made to resemble exactly pigments obtained from urine in health and disease." It is evident that we may meet with pigments in urine which do not correspond exactly to either of those mentioned, but intermediate between

⁹ Udranszky: *Zeit. f. Physiol. Chem.*, Band xi, Heft 6, 1887; and Band xii, Heft 1 and 2, 1888.

⁶ MacMunn: Further Researches into the Colouring Matters of Human Urine, etc., *Proc. Roy. Soc.*, No. 208, 1880.

⁷ MacMunn: *Proc. Physiol. Soc.*, Oxford meeting, March, 1888.

⁸ Jaffé: *Centralbl. f. d. Med. Wiss.*, 1868, No. 16; *Arch. f. Pathol. Anat.*, Bd. xlvii, s. 1.

⁹ Maly: *Ann. Chem. Pharm.*, Bd. 161, s. 368, and Bd. 163, s. 77.

¹⁰ Vaulair and Masius: *Centralbl. f. d. Med. Wiss.*, 1871, Nr. 24.

¹¹ Maly: *Centralbl. f. d. Med. Wiss.*, 1871, Nr. 54.

¹² Hoppe-Seyler: *Handbuch der Phys. und Path. Chem. Analyse*, 4 Auflage, s. 214, and *Med. Chem. Unter.*, Heft 4, s. 534.

¹³ MacMunn, *Proc. Roy. Soc.*, Nos. 206 and 208, 1880.

¹⁴ *Ibid.*

¹⁵ MacMunn: Observations on some of the Colouring Matters of Bile and Urine, etc., *Journ. Physiol.*, Nos. 1 and 2, vol. vi.

¹⁶ MacMunn: *Proc. Roy. Soc.*, No. 208, 1880, p. 206.

any two of them, but even then there is no difficulty in saying definitely how they have been produced in the organism, and I think this is a great advance, for we cannot say as much for other constituents of urine; so that here we see how the spectroscopic has outstripped other methods of analysis.

It would *a priori* seem likely that normal urobilin should follow the same law, as for instance, urea, and be a complete metabolite of hæmoglobin, as urea is that of proteids, and a metabolite produced by an oxidation process, for in health oxidation overbalances reduction. All the experiments which I have made do in truth point to this conclusion. I was first led to this conclusion by studying the Gmelin-Heintz reaction¹⁷ with the spectroscope. This, as every medical man knows, is the test by means of which we recognise the presence of bile pigment in pathological fluids. If we add impure nitric acid (containing nitrous) to a solution containing bilirubin, a series of colour changes are produced, the fluid becoming green, blue, violet, red, and lastly yellow, then colourless. If the fluid be examined with the spectroscope while these colour-changes are in progress, a band will be seen to appear before D; then this darkens, and another appears at F. Another then appears after D, and now all these bands are visible together. Soon the band after D fades away, to be followed by that before D. The band at F is very dark at one stage of the reaction, fainter as it progresses, until it finally disappears. It seemed to me that the dark band at F was like that of pathological urobilin, and the fainter one into which the dark one changed like that of normal urobilin; and so it proved. The pigment which gives the fainter band at F is that known as choletelin, and, on isolating this substance, I found that it bore a very striking resemblance to normal urobilin. I failed to prove that the pigment which gave the dark band was identical with pathological urobilin, but, on reducing choletelin with sodium amalgam, I found that it did closely resemble pathological urobilin. Hence I was led to think that normal urobilin is a fully oxidised body, and pathological urobilin a less oxidised one. It may appear paradoxical that pathological urobilin should be an intermediate product of oxidation of bile-pigment, and a product of reduction of hæmatin, yet such is the case. Liebermann also has concluded that the continued reduction of choletelin produces a similar substance to hydrobilirubin. Further, I found that, if you shake human bile with chloroform, you obtain a solution free from bands; but, if you let it stand, the same bands as those seen in the Gmelin-Heintz reaction come gradually into view. And I afterwards found that human bile contains a substance which is easily changed into a urobilin-like pigment by oxidising agents such as peroxide of hydrogen. But I found that I could obtain an artificially-prepared substance from hæmatin with greater ease than from bile-pigment, and this bore even a more striking resemblance to normal urobilin.

If blood—preferably from the sheep—be treated with rectified spirit acidulated with sulphuric acid and filtered, a solution of acid hæmatin is obtained. If to this solution peroxide of hydrogen¹⁸ be added until the bands of acid hæmatin have disappeared, and then water be added, and the solution agitated in a separating funnel with chloroform, the chloroform separated off and evaporated on the water-bath, a residue is obtained bearing a most striking likeness to normal urobilin. Its solutions—especially if acid be added—show a faint band at F; and, if a rectified-spirit solution be treated with ammonia and zinc chloride, we can see a fine green fluorescence. Sometimes it may be necessary to reduce the pigment in the rectified-spirit solution for a short time with sodium amalgam, as it is not easy to know until afterwards whether the right quantity of peroxide of hydrogen has been added; then acidulate with sulphuric acid and agitate with chloroform as before, and evaporate this. The pigment thus obtained cannot be distinguished from normal urobilin either spectroscopically or as regards solubility. By further reduction with sodium amalgam, it can be made to resemble pathological urobilin—in this point resembling choletelin.

Hence normal urobilin must be an oxidation product, and its origin in the body can be explained. It is needless to say that this has a most important bearing on medicine. Suppose we have a bile-pigment, such as bilirubin, present in the blood, and that there is not enough oxygen present to convert it into a lower metabolite, we should then have jaundice produced, provided

the bile-pigment is not excreted fast enough. Some years ago,¹⁹ I tried to show that cases of so-called hæmatogenous jaundice, in which no obstruction to the flow of bile into the intestine can be found, might be explained by the oxidation theory. But, in some cases included under this name, it would appear that the rapid destruction of red blood corpuscles may lead to the formation of such a relatively large quantity of bilirubin in the blood itself that, even if the oxidising process were not interfered with, the tissues could hardly escape being deeply stained. Besides, the presence of any detectable amount of bilirubin in human blood is very doubtful. The blood-serum of the horse contains bilirubin, according to Krukenberg, but then the horse does not possess a gall-bladder.

In accounting for the presence of pathological urobilin in urine, we meet with greater difficulties. If Maly's view be true, that urobilin—by which Maly really means hydrobilirubin—is produced by reduction of bilirubin, pure and simple, then it cannot well be an intermediate product of oxidation (of bilirubin). But I find that Maly's hydrobilirubin is not identical with either normal or pathological urobilin. If pathological urobilin be ever derived from bile-pigment, it is a more complete metabolite than is hydrobilirubin; the latter seldom occurs in urine, and, when it does occur, it is probably present in those cases where the patient is recovering from jaundice, when absorption of relatively large quantities of bile-pigment from the tissues is taking place. In working at hydrobilirubin, I found—strange to say—that sodium amalgam leads to the formation of bodies similar to those which form during the Gmelin-Heintz reaction; for instance, during one stage bilicyanin is formed, and this, we know, is considered to be an oxidation product. Hoppe-Seyler has, indeed, tried to show that nascent oxygen plays a considerable part in the action of sodium amalgam. Whether this be so or not, there are absolute proofs in support of my view that neither pathological nor normal urobilin is identical with hydrobilirubin; and Le Nobel²⁰ has come to a similar conclusion. I hope to publish results shortly which will place this matter beyond doubt.

I have shown elsewhere that stercobilin,²¹ the colouring matter of feces, bears a very close resemblance to pathological urobilin, and may be its source in some cases. If this be so, then we can easily explain the depression of spirits, the languor, pain in the limbs, and other well-known symptoms which frequently accompany its presence in urine, for stercobilin cannot well get into the circulation without being accompanied by various poisonous alkaloids—ptomaines which we know arise during the action of the digestive and putrefactive ferments on food-products. But in many cases I find that what at one stage of my knowledge I should have taken for pathological urobilin can be proved by appropriate treatment to be a direct derivative of hæmatin, and closely connected with the next pigment which we have to consider.

This third pigment, to which I previously referred as urohæmatoporphyrin, is one of great importance. I cannot here say anything very definite as to its relationship to pathological urobilin, although, according to Le Nobel,²² it can be converted into a urobilin-like body, "urobilinoidin," by further reduction, but I hope shortly to publish some results which will show this connection more clearly.

To appreciate the activity of the morbid chemical process by which urohæmatoporphyrin is produced in the body, let us for a moment consider how hæmatoporphyrin is produced. It is produced by dissolving hæmatin, which is itself a decomposition-product of hæmoglobin, in strong sulphuric acid, filtering through asbestos, pouring the filtrate into water, and adding ammonia, when flocks of hæmatoporphyrin separate out, which can be filtered off, and purified. Urohæmatoporphyrin is obtained by the action of zinc and sulphuric acid on hæmatin, aided by heat, and the process is not completed for a considerable time. We may, therefore, wonder how such an energetic process can go on in the body. Of course this pigment is produced in the body, where it never arises in sufficient quantity to be excreted as such in the urine, except under pathological conditions, by the action of an energetic fermentation attended by reduction, and we may safely suppose that other things, such as leucomaines, must be produced with it, by means of the same active reduction, which things are not quite so harmless as it is. I presume that in the majority of

¹⁷ MacMunn: Spectroscope in Medicine, 1880, and *Proc. Roy. Soc.*, No. 208, 1880, p. 215, etc.

¹⁸ MacMunn: *Proc. Roy. Soc.*, No. 208, 1880, p. 226.

¹⁹ MacMunn: On Urobilin, etc., *Dub. Journ. Med. Sc.*, 1884.

²⁰ Le Nobel: Ueber die Einwirkung von Reduktionsmitteln auf Hæmatin und das Vorkommen der Reduktionsprodukte in pathologischem Harn, *Archiv. f. d. Ges. Phys.*, Band xl, 1887.

²¹ MacMunn: *Jl. Physiol.*, Nos. 1 and 2, vol. vi.

²² Le Nobel: *loc. cit.*

cases it is formed from hæmoglobin, but it may also be formed from the colouring matters which I referred to before as myohæmatin and the histohæmatins. I have two good reasons for saying so: (1) I procured hæmatoporphyrin²³ from these pigments; (2) hæmatoporphyrin occurs as such in the integument of some invertebrates²⁴ in which no hæmoglobin but a histohæmatin is present, for example, slugs, star-fishes, and the mollusc *Solecirtus strigillatus*, as I have shown.

Urohæmatoporphyrin is not confined to the urine of acute rheumatism, as I at one time supposed;²⁵ for although it is found in the urine of that disease in greatest abundance, and in its most typical condition, I have found it also present in the following, and perhaps other diseases, namely, so-called idiopathic pericarditis, Addison's disease, cirrhosis of the liver, croupous pneumonia, Hodgkin's disease, measles, typhoid fever, meningitis, and peritonitis.

From a careful consideration of the conditions under which this pigment may appear in urine, I conclude that it may be present (1) when an excessive destruction of hæmoglobin or the histohæmatins is taking place, the glands which are concerned in the further downward metabolism of these effete pigments being unable to deal with the excess of effete pigments present in the blood; (2) where the pigment-metabolising glands are diseased, as in Addison's disease and cirrhosis of the liver. The products of destructive metabolisms of these colouring matters—hæmoglobin and the histohæmatin—are got rid of as bile pigments and urobilin under normal conditions, but under diseased conditions the urobilin is replaced altogether, or it may be supplemented, by urohæmatoporphyrin. Probably an increased destruction of hæmoglobin takes place in inflamed organs, and the altered pigment being in a condition of chemical instability comes under the influence of some energetic reducing ferment. It might be suggested that bacteria are the agents concerned in this fermentation, for we know some of these organisms exercise a reducing, others an oxidising, action, but no bacteria are present in some of those diseases in which urohæmatoporphyrin is found.

Le Nobel, of Leyden,²⁶ has repeated my experiments on urohæmatoporphyrin, and although he differs from me in a few minor details, he has fully confirmed these results. He thinks that the above pigment, whether in urine or prepared artificially, is a mixture of two, but he did not study the action of ammonia on the band at F. This is the only point of difference between us worth mention. He objects to the name urohæmatin, which I abandoned in 1885, and another criticism of his is based on a mis-translation of one of my papers. Le Nobel has also found that hæmatoporphyrin is converted into urohæmatoporphyrin by the action of acetone or aldehyde, and he suggests that it is by the action of these that derivatives of blood-colouring matter may arise in the body, but this is "not proven," and the explanation is rather far-fetched. He also suggests that a reduction product of hæmatin, what he names "urobilinoidin," may have been mistaken for urobilin by Kunkel,²⁷ who shows that the latter is increased in amount after the absorption of large blood extravasations,²⁸ and that the increase of urobilin in fever which Leube and Stokvis²⁹ attributed to increased destruction of hæmoglobin, may have been due to an increased excretion of urobilinoidin also. I myself am quite satisfied, as I said above, that what has been taken for pathological urobilin, and so named by myself, is in many cases a direct metabolite of hæmatin produced by an energetic reduction process. I would here protest against the prevalent idea that the occurrence of (pathological?) urobilin is diagnostic of the existence of pelvic hæmatocele. It may have been present in some cases, but it is just as likely to be absent in others.

Besides urohæmatoporphyrin, other metabolites of hæmoglobin may be present in urine. In the urine of a case of purpura hæmorrhagica, my friend Dr. Armitage and I found a substance

present which, on the addition of one drop of sulphide of ammonium, changed into reduced hæmatin; had hæmoglobin or met-hæmoglobin been present, reduced hæmoglobin would have been obtained. Here evidently the circulating hæmoglobin had undergone some profound change.

Lately Drs. Lewin and Posner³⁰ have found such hæmatin-like pigments in urine; but they are wrong in supposing that in the majority of such cases the hæmatin has a renal origin; nothing but prolonged contact with acid urine could change hæmoglobin into hæmatin, and if freshly passed urine shows the reduced hæmatin bands when treated with a trace of ammonium sulphide, the blood has probably undergone some change before it has reached the kidney.

The interesting observations of Mr. Bond,³¹ of Leicester, show that the hæmoglobin of the blood is more prone to crystallise, and is therefore more chemically unstable in some diseases than in others.

In intermittent hæmoglobinuria I have found in every instance, where it was not due to a vasomotor disturbance in the kidney itself, that all the blood-colouring matter present in the urine had been changed into methæmoglobin. If the statement of Hoppe-Seyler³² be correct that when the urine contains methæmoglobin it also frequently contains bile acids, we have a clue to the causation of intermittent methæmoglobinuria. For if we suppose, that through some vasomotor disturbance of the hepatic circulation, some poison, such as an incompletely metabolised product of digestion or active ferment or the bile acids could pass over into the blood of the hepatic vein and thence into the general circulation, it could hardly fail to change a part of the circulating hæmoglobin into methæmoglobin, the latter would then become dissolved in the plasma—as is the case in methæmoglobinuria—and be excreted by the kidney.

There is one point in connection with urohæmatoporphyrin to which I should like to refer; it is this: The presence of this colouring matter in the urine of a case which is suspected to be of rheumatic origin should intensify our suspicion. It is almost always present in acute rheumatism. Hence the spectroscope may help one at times to settle a doubtful diagnosis.³³

Another fact which cannot fail to strike anyone is that in febrile cases we have a reduction product of hæmatin present in the urine; we have been taught that the febrile process is accompanied by increased oxidation; but it is just the opposite—it is characterised by increased reduction.

For maps of spectra mentioned here the various papers referred to in the foot-notes can be consulted, where the other characters of those pigments, so far as I have been able to study them, are given.

WHAT IS STONE IN THE BLADDER? A REJOINDER.

By SIR HENRY THOMPSON, F.R.C.S., M.B.Lond.,

Consulting Surgeon to His Majesty the King of the Belgians; Consulting Surgeon and Professor of Clinical Surgery to University College Hospital, etc.

A FEW lines will, I hope, suffice to deal once more with the simple question I proposed above, and also with the long article raising numerous side issues—extremely tempting to reply to, if I had either time or taste for controversy—which Dr. Freyer has thought it necessary to write.

I must remark that the first statement he makes begs the question. He says: "Hitherto the universally accepted definition of stone in the bladder was any calculous formation, no matter of what size, which failed to pass out of the bladder spontaneously, and for the removal of which an operation was necessary."

But this is precisely the matter in dispute, and the contrary is in my opinion the fact. Surely it is notorious that small concretions and even large ones have been washed out, and removed from the bladder by forceps from time immemorial. But the procedure has never taken rank as "an operation for stone." I have operated for them thus and also by crushing them, many more than a hundred times, recording operations for "gravel" or "concretion," rigidly excluding them from my series of stone

²³ MacMunn: Further Observations on Myohæmatin and the Histohæmatins, *Jl. Physiol.*, vol. viii. No. 2.

²⁴ MacMunn: On the Presence of Hæmatoporphyrin in the Integuments of Certain Invertebrates, *Jl. Physiol.*, vol. vii. No. 3; and On the Hæmatoporphyrin of *Solecirtus strigillatus*, *Jl. Physiol.*, vol. viii. No. 6.

²⁵ MacMunn: *JOURNAL*, December 1st, 1883.

²⁶ Le Nobel: *loc. cit.*

²⁷ Kunkel: *Virch. Arch.*, vol. 79; quoted by Le Nobel, *loc. cit.* Cf. Ziegler's *Pathological Anatomy*, by MacAlister, vol. i. art. 68, and vol. ii. art. 268. This book contains many references to the subject.

²⁸ In two cases of this kind of which I have examined the urine, I have found pathological urobilin in large amount. In one I could prove that it had been derived from hæmatin, that is, the pigment closely resembled urobilinoidin.

²⁹ Leube: *Die Lehre vom Harn*; Stokvis: *Besprechungen*; *Deutsches Archiv für Klin. Med.*, 1893.

³⁰ Lewin and Posner: Zur Kenntniss der Hæmaturie, *Centralb. f. d. Med. Wiss.*, No. 20, 1887.

³¹ Bond: A Contribution to the Pathology of the Blood, *Lancet*, September 10th and 17th, 1887.

³² Hoppe-Seyler: quoted by Charles in his book on *Physiology and Chemistry*.

³³ *JOURNAL*: December 1st, 1883, and February 4th, 1888.