UROBILIN EXCRETION IN DISEASED CONDITION

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Various theories have been propounded to explain the source of urobilin in urine. In health it is believed to be derived from bilirubin by the action of bacteria present in the alimentary canal. In vitro this change has been accomplished successfully; but the point has not been settled whether one special microbe does it or whether there are several varieties capable of effecting the change. Again, urine containing a large amount of bile does not show any urobilin band when inoculated with faecal microbes, so the production of urobilin from bile-pigments by the action of faecal microbes is not possible under these conditions. The same experiment performed with ox-gall broth and similar germs, neither gives the urobilin band nor can urobilin be extracted with amyl alcohol from the mixture. Bacterial action is surmised to be responsible for the production of urobilin on account of the fact that meconium is rich in bile and urobilin is absent, while it appears soon after birth. However, various changes take place in the alimentary canal of the new-born besides the appearance of the bacteria. Thus the different glands of the canal are called into activity by the presence of the milk in it. For this reason it is quite as logical to attribute the presence of urobilin to the action of the secretion of these glands on bile-pigments as to the presence of bacteria. Vaughan Harley (1) found that urobilin in faeces was increased along with the aromatic sulphates in the urine of certain dogs.

This seems to show that bacterial agency may be responsible for the increase of urobilin as the same is true for the increase of aromatic sulphates. The following observations, unfortunately, do

not show any such constant relationship between increase of urobilin and indican in urine.

Thus in 124 cases where urobilin was found to be copious, only 54 (*i.e.*, 43·2 per cent. of cases) had copious indican also, while the rest had traces.

On the other hand out of 126 cases with copious indican only 53 (*i.e.*, 42·0 per cent.) had copious urobilin also. Thus, whether we look for increased indican in cases of copious urobilin or *vice versa*, the fact remains that in diseased condition at least in more than 50 per cent. of cases the reverse happens to be true.

Again, out of 188 cases with traces of urobilin 67 (35·5 per cent.) had copious indican; while out of 157 cases of traces of indican 53 (*i.e.*, 33·8 per cent.) had increased urobilin. These observations show a higher percentage in favour of the correlation theory of Vaughan Harley. However, we must take into consideration this fact that both these constituents are found in traces under ordinary circumstances in the urine, consequently in those cases where either of the substances is scanty the other ingredient may be scanty also, although the cause of the production may not be the same.

Again, in a case of chronic constipation where one finds copious indican, according to the views of Vaughan Harley one ought to find copious urobilin also; however, in such a case urobilin was actually found in traces only.

On the other hand in a case of chronic diarrhoea indican was found in traces while urobilin was copious and free. In a case of phthisis where the urine was repeatedly examined to see if any relationship was to be noticed between these two constituents of urine, indican was constantly found to be in traces while urobilin was copious and free, except on two occasions when the patient had indigestion followed by diarrhoea, when indican was found to be moderately increased while urobilin was copious as usual. In a case of puerperal septicaemia although indican was copious, urobilin was found to be in traces only. In a case of enteric fever urobilin was found to have increased considerably although indican was found in traces. The

same was true in a case of Gaertner infection during convalescence. On the other hand in two cases of coli infection urobilin was in traces although indican was increased.

Thus, whether one takes the statistics of several cases or looks to individual cases where indican is in excess, it is evident that no definite relationship exists between urobilin and indican present in urine.

In these observations urobilin was extracted with 10 c.c. amyl alcohol from 30 c.c. urine. The spectrum of pure urine as well as of the extract was examined, and those cases where a deep band was seen between the green and blue parts were considered as having copious urobilin. In many of these cases the band was found in pure urine. Alcoholic solution of zinc chloride and ammonia was subsequently added to the amylic extract, and the amount of fluorescence noted as control. Indican was tested by mixing 15 c.c. urine with equal parts of pure hydrochloric acid, and to this one drop of either fresh hydrogen peroxide or 0.5 per cent. solution of nitrite of sodium was added and the colour of the chloroform extract was noted for the amount of indican. Some specimens of urine do not require the oxidising agent at all—rather the reverse.

Urobilin was also looked for in various diseases, with a view to determine whether the increase is due to any particular disease or otherwise, so that this fact may be used for differential diagnosis. These observations agree with those of others in several respects; however, in some cases this does not hold true.

In enteric fever it has been generally stated that urobilin is not increased. In twenty-one cases of this disease only three had increased urobilin, but two of these cases had complications which must have been responsible for the increase, while the third had increased urobilin during convalescence only. In a case of enteric the patient developed croupous pneumonia as a complication; still no increase of urobilin was noticed for the succeeding five days, after which it showed a good deal. No complication of the liver had arisen during this period. In a case where the patient's blood did not respond to the Widal test for *B. typhoid* but to that of *B. gaertner*, urobilin was found

increased during convalescence ; and in two other cases where agglutination was obtained with *B. coli*, urobilin was found scanty. In a case where the blood clumped both *B. coli* and *B. gaertner*, urobilin was scanty. Finally a case which did not clump any bacilli of the typho-coli group but clumped a bacillus isolated from the patient's urine, showed only traces of urobilin on several occasions. This microbe belongs to the typho-coli group with certain special characters which will form the subject of another communication. In the three cases of Gaertner and coli infection it is interesting to state that indican was copious.

In diseases of the respiratory system it was found that both croupous and broncho-pneumonia had copious urobilin in all cases (seventeen) ; while asthma, pleurisy, and bronchitis (five cases of each disease) did not show any increase. In a case of croupous pneumonia, urobilin was found to be normal during the convalescent stage. In a case of tubercular pleurisy it was copious. Here again indican was in traces.

In phthisis (fifty-seven cases) it was found increased in 75.5 per cent. of cases. In very early cases it was not increased. Here it may be stated that in two out of three cases of leprosy it was found to have increased considerably. This increase of urobilin in phthisis is interesting because it has been observed that injection of tuberculin has a similar effect (2).

In diabetes it has been stated by Schäfer (3) that 'urobilin was increased as a rule.' In only six cases have I found it to be increased out of twenty-five cases of this disease.¹ One of the cases with increased urobilin died, and at the *post mortem* examination chronic tuberculosis was found to be present. The pancreas was not diseased. In another case the patient had a severe crop of boils at the time when urobilin was copious, and it was only in traces after recovery from this complication ; the amount of sugar was 5 per cent.

It is curious that in a large number of cases of uric acid diathesis

1. It may be suggested that as in diabetes the amount of urine is considerably increased, the quantity used must be proportionately larger than that used for other diseases. With this object, in two cases 100 c.c. of such urine were extracted with 10 c.c. amyl alcohol. Urobilin was not found in sufficient quantity to give even a faint band.

urobilin has been found rarely increased. The samples examined were loaded with urates and were high coloured, yet this constituent was only found increased in five out of twenty-five cases. On the other hand indican was found to be copious in thirteen out of twenty-five cases of the same complaint. This also shows that in a large number of cases of increased intestinal putrefaction, urobilin is not necessarily increased.

In six cases of acute dysentery urobilin was scanty, and in four cases of sprue the same was true. Out of three cases of appendicitis only one had excess of urobilin, while a case of acute peritonitis had traces of urobilin. Again, eighteen cases of renal calculi and pyelitis had only traces of urobilin. Out of seven cases of acute rheumatism urobilin was found to be copious in six cases, while the seventh case had traces only. This last case had copious uric acid also, while the others had ordinary amount of uric acid, so it is likely that the disease was more of the nature of uratic deposit in the joints rather than rheumatic fever. However, it is not likely that uric acid prevents the excretion of urobilin, as in some cases of phthisis and other diseases both urobilin and uric acid were copious in the same sample of urine.

On the other hand in six cases of scurvy both urobilin and indican were copious. It seems that in these cases the destruction of the effused blood in the tissues is responsible for the urobilin, while the intestinal putrefaction was responsible for the indican.

It has been stated that in acute Bright's disease urobilin is not excreted by the kidneys. Out of twelve such cases three had copious urobilin, though the urine was loaded with casts, both hyaline and granular.

These observations show that urobilinuria can exist in cases of albumen with casts in the urine. Again from the records of other diseases where both albumen and urobilinuria were looked for, I find that in many other diseases also this holds true. Thus in case of phthisis out of twenty-five cases where albumen was found in traces, sixteen had copious urobilin and more had traces only. Besides that, in one case of phthisis with copious albumen (varying between three

and eight parts per 1,000), urobilin was also copious on every occasion that the urine was examined (thirteen samples examined).

In enteric fever as a rule urobilin is not increased ; however, three cases with copious urobilin had albumen also. In one of these cases perhaps the pus present in the urine might have been the cause of albumen. In malaria, out of four samples with albumen three had copious urobilin, one of these had granular casts also. Relapsing fever cases with albumen in the urine showed copious urobilin in three samples, while in two such cases the urobilin was in traces ; one of these latter had casts also. In eight cases of plague with albumen in urine, seven showed copious urobilin. Ten cases of pneumonia with albumen in the urine showed copious urobilin also. Two cases of acute metritis showed both albumen and urobilin in large amount. Out of four cases of heart disease with renal complication, copious urobilin was found in three samples.

In diabetes, urobilin was not found much increased as a rule ; however, in two cases both albumen and urobilin were in excess. In three cases of septic infection the same has been found true.

In a case of sunstroke, albumen was three parts per 1,000, casts were also present ; however, free urobilin was present in moderate amount, *i.e.*, a fairly well-marked band was present. A case of filariasis had copious urobilin in conjunction with albumen during the acute attack of orchitis and lymphangitis. Finally, in a case of malignant disease of the liver both albumen and copious urobilin were found to be present.

In fevers red blood corpuscles suffer most destruction, as in malaria (eighteen cases), relapsing fever (six cases), and plague (nine cases) urobilin was considerably increased—in fourteen, five and six cases respectively. In a case of kala-azar, and another of cerebro-spinal meningitis, urobilin was found in traces only. Both these cases had copious indican and uric acid. On the other hand hepatic affection did not show any increased urobilin as a rule. Thus, out of thirty-seven cases of hepatitis only thirteen had increased urobilin. Again, out of these, twenty-five cases had jaundice. Eleven of these cases had copious urobilin ; however, two had tubercle, so the increased urobilin may

be attributed to that complication. In most of the cases when the faeces was examined for the presence of urobilin (mercury perchloride), it was found to be absent when urobilin was absent in the urine also ; however, in one case although no urobilin could be detected in the faeces it was found to be excessive in the urine. Surely in this case the source of the urobilin in the urinary secretion was not the alimentary canal. Both bile-pigments and salts were found in moderate amount in the urine of this case. In one case of jaundice the urine had only traces of urobilin during the commencement of the illness, when there was a good deal of bile-pigments and salts, while at a later period as the patient was getting better urobilin was found to be copious and at the same time bile salts and pigment were in traces only. Now at this stage the patient's skin and conjunctivae were still deeply jaundiced. What is the significance of this ? Was this a case of simple jaundice to begin with and that it became one of urobilin jaundice at a later period, or that the bile-pigment in the tissues was gradually eliminated as urobilin without the help of the liver ? The latter supposition is much more likely. It is stated by von Noorden (4) that urobilin as such is not present in the blood but as bile-pigment, and that it gets excreted in the urine as urobilin. If this be so, why is it that bile-pigment is excreted as such in most cases of jaundice ? It may be suggested that as long as the bile ducts are blocked up, the bile-pigment in the tissues gets excreted as bile-pigment in the urine ; but when the ducts become patent, the liver being relieved of the pent-up bile is able to re-absorb the bile from the tissues, whence it reaches the alimentary canal where it is converted into urobilin. This is the usual explanation ; but is very roundabout, and presupposes the existence of urobilin in blood, which has not been found to be the case. Serum obtained from the blood of such cases is deep yellow coloured but does not show the spectrum of urobilin, although the urine may be full of it.

Again, in case of digestive trouble where indican is increased, and also in uric acid diathesis where the liver is generally at fault, urobilin has not been found to be increased generally, so it is much more probable that the bile-pigment in the blood gets changed into

urobilin somewhere else, perhaps in the kidneys (von Noorden (4), von Jaksch (5)).

Out of four cases of hepatic abscess (tropical) urobilin was found to be increased in one case only, and this was a case where the abscess had burst into the lung producing secondary pneumonia at the same time.

Out of eight cases of cirrhosis of the liver only two cases showed much urobilin. One of these cases had severe scurvy also, so one can attribute the presence of urobilin to the scorbutic condition rather than to the cirrhotic liver. Thus, at least in pathological conditions of the liver, this organ does not seem able to produce urobilinuria, while in the case of hepatic abscess with secondary pneumonia, and in cirrhosis of the liver complicated with scurvy, urobilin was in excess. Pneumonia and scurvy are diseases which have invariably shown the presence of copious urobilin in the urine.

In cases of malignant tumours of abdominal organs, urobilin was increased in five out of eleven cases. Seven of these cases had cancer of the liver and four of these had copious urobilin (von Noorden (6)).

In a case of malignant disease of the larynx, and another of the jaw, urobilin was not increased.

As regards nervous diseases it may be stated that in five cases of chronic myelitis, urobilin was found to be copious; while in three cases of peripheral neuritis it was in traces. Out of two cases of beri-beri, one showed excess of urobilin. In a case of hemiplegia due to haemorrhage urobilin was not increased even a few days after the attack. Probably the haemorrhage was not excessive. This case was interesting on account of the fact that both indican and uric acid were copious. A case of neuromata did not show any excess of urobilin. In the cases of chronic myelitis the onset was accompanied with severe fever, so the inflammation of the spinal cord must have been due to some specific infection. A case of pseudo-hypertrophic paralysis did not show any excess of urobilin.

In cases of septic infections it was not always that urobilin was found increased. Out of fourteen cases seven showed an excess.

Out of five cases of filariasis only one showed excess, and that was at a time when there was high fever with orchitis.

In some of the diseases mentioned above the observations have been made in such a small number of cases that it is not possible to try to generalise about the relation of urobilinuria to such conditions; however, these show that the liver and the intestinal putrefaction do not play any important part in the production of excess of urobilin, at least in diseased conditions.

Those diseases which produce the destruction of red blood cells seem to be much more prone to show urobilin in urine. It may be stated here that in three cases of pernicious anaemia urobilin was copious, an observation which agrees with that of others. Thus malaria, relapsing fever, plague, scurvy, and tuberculosis show increased urobilinuria, as compared with cases of uric acid diathesis, hepatic diseases, dysentery, sprue, and diabetes. All these conditions are often accompanied by digestive disturbance, and increased intestinal putrefaction, as is shown by the increased excretion of indican in such states.

As regards the question whether the increase of urobilin in urine helps the diagnosis of disease, it seems that although this condition is not pathognomonic of any one disease, it can help one at differential diagnosis of some conditions. Thus one often meets with cases of remittent fevers which clinically appear to belong to the group of the enteric type, but Widal test is not obtained with some of the typho-coli group of bacilli which are generally available in a laboratory on the one hand, while malarial parasites are absent on the other.

Thus in one of the cases mentioned above where the typho-coli bacilli did not give the reaction, it was afterwards found that a bacillus of this group isolated from the urine of the patient gave Widal test quite readily. Urobilin was found in traces on every occasion that the urine was tested in this case.

In such cases the diagnosis generally lies between malaria, enteric, and tuberculosis.

Ehrlich's diazo reaction if present in such a case will exclude malaria, especially so if the hyaline large mononuclear leucocytes

are not in large number. In regard to tuberculosis, Calmette's reaction and the opsonic index are supposed to be of no value in such a condition, as the ophthalmic reaction has been found in genuine cases of typhoid and, again, the opsonic index has been lowered for tubercle bacillus in similar cases.

In such a case an excessive amount of urobilin will increase the probability of tubercular infection being present.

As regards the question whether urobilin and indican excretion in urine show any relationship which warrants one in assuming that the originating cause of the former in diseased states is intestinal putrefaction, it would seem that it must be answered in the negative.

Again, these observations seem to indicate haemoglobin destruction to be the principal cause of urobilinuria, in diseased conditions at least, rather than derangement of hepatic functions.

In conclusion it may be stated that nearly 500 samples of urine were examined to determine the various facts mentioned in this paper.

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