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THE DARKENING IN COLOUR OF CERTAIN URINES ON EXPOSURE TO THE AIR.

Read in the Section of Physiology and Pathology.

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MANY urines in perfectly normal conditions show a slight deepening of tint when exposed to the air, but so slight as to be hardly perceptible. The presence of certain bodies in the urine may, however, develop this phenomenon to an extraordinary degree. One instance is a matter of common observation. All urines contain a quantity of indican, and if the urine be allowed to stand until putrefied, a blue film is formed on the surface, from the oxidation of the indican to indigo-blue; if the indican be present in excess, a greater development of the colour may take place, and the blue tint may be diffused throughout the whole of the urine. The result of the oxidation may often be seen in testing the urine for albumen by the nitric acid method, when a dark rim is frequently observed at the junction of the acid and the urine.

I wish more particularly to call attention to certain cases where a brown or black pigment is developed in the urine after standing for a short time. Most if not all the substances which cause this appearance belong to the aromatic group of compounds. Starting with the hydrocarbon benzol, C_6H_6 , we may substitute other radicles for the different atoms of hydrogen, and obtain a series of bodies whose relations to each other are sufficiently shown by their formulæ. Thus:

It is seen that, by substituting for two atoms of hydrogen in the benzol, two molecules of the radicle hydroxyl (OH), we have three bodies produced; hydroquinone, pyrocatechin, and resorcin, which have the same chemical composition, but merely differ from each other as to the position which the molecules of the hydroxyl occupy in the benzol radicle.

Two, at least, of these substances, hydroquinone and pyrocatechin, if present in the urine, may spontaneously cause the phenomenon in question, when oxidation occurs. The first substance, hydroquinone, is now of common occurrence in the urine of surgical patients whose wounds are dressed by the antiseptic method.

Hydroquinone.—It is well known that the dark urine of carbolic acid poisoning grows still darker on exposure to the air. It does not, however, appear to be so generally known that such an urine may show no abnormality of colour when first passed, and may only develop the dark pigment after standing for perhaps twenty-four hours. Such was the case in the urine of a boy, who was a patient in the Manchester Royal Infirmary under the care of Mr. Hardie, and on whom excision of the hip had been performed; the resulting wound being dressed and syringed out with carbolic acid solutions. An attack of convulsions suddenly occurred, which at first seemed to point to a gross cerebral lesion, but was afterwards found to be due to carbolic acid poisoning. An account of the clinical features of the case has already appeared in the *Lancet*. The urine at this time, when drawn by a catheter or passed voluntarily, was of a bright yellow colour, but in twenty-four hours assumed a dark-brown tint, and finally deposited a brown sediment. It is obvious that the light colour of urine might easily mislead a surgeon as to the cause of the symptoms; for, as ordinarily observed in the hospital ward, such urine would not have time to develop its characteristic colour to any remarkable extent.

¹ I have preferred to use the more popular, rather than the correct chemical names.

The explanation of the phenomenon is found in the researches of Baumann and Preusse,² who have shown that the carbolic acid absorbed is excreted for the greater part, not as such, but as hydroquinone. The hydroquinone appears in the urine as a sulphate, which is very unstable, and by breaking up liberates the free hydroquinone. This then undergoes oxidation, forming the brown pigment, the composition of which is, however, not ascertained. The chemical process, as it occurs in the body, is very interesting. Thus, it has been shown that if benzol (C_6H_6) be given internally, it is excreted as carbolic acid, $C_6H_5(OH)$; so, too, carbolic acid in its passage through the body takes up another atom of oxygen, and is excreted as hydroquinone $C_6H_4(OH)_2$. The phenomenon may be seen, not only after the use of carbolic acid externally, but in cases of poisoning by its internal administration. Thus, in a case of carbolic acid poisoning, admitted into the Manchester Royal Infirmary under Dr. Leech, the urine, when passed naturally, was already somewhat dark, but, as usual, deepened in colour on standing. When drawn by the catheter, however, a short time after micturition, it was found to be of a very pale colour, such, indeed, as is shown by the specimen I now present to the meeting. This specimen of urine was received into a test-tube, and protected from the air by a layer of oil on its surface. It has, as you see, preserved its light colour; but a similar specimen exposed to the air for twenty-four hours possessed the well known deep brown, almost black, colour. This would tend to show that the dark pigment is a product of oxidation.

Pyrocatechin.—This substance is of common occurrence in the urine of the horse, and is said by Baumann to occur in small quantities in normal human urine. It has the property of absorbing oxygen when in alkaline solutions, and forming a dark-brown pigment. This is well seen in the urine of the horse after standing for some time. In certain rare cases, pyrocatechin is present in human urine in such amounts, as to show this darkening in colour to a remarkable extent. Ebstein and Müller³ have reported the case of a child, aged four months, whose urine was almost colourless when first passed, but, on exposure to the air, assumed a dark brown tint. The urine was afterwards found to contain pyrocatechin. Previously to this observation, however, an urine was described by Hödecker,⁴ which when treated with alkalis absorbed oxygen, and assumed a brown colour. He hence called the substance which caused this change of colour, alkapton (alkali, *κατάρειν*). Three similar cases have been described, one by Fürbringer,⁵ and two by Fleischer,⁶ one of the latter having occurred after the administration of salicylic acid. It is probable that, in all these cases, there was present either pyrocatechin or protocatechuic acid, which will be presently discussed. It is important to notice that such urines have shown a considerable reducing action on Fehling's solution. The other reactions of pyrocatechin may, however, be more conveniently discussed under another heading.

Resorcin.—This substance, corresponding in composition with hydroquinone and pyrocatechin, does not, so far as I am aware, occur in the urine spontaneously. If, however, the urine of a patient who is taking resorcin as a therapeutic agent be alkalisied with liquor potassæ, and then exposed to the air, it assumes a dark green tint, which is at once removed by the addition of acetic acid. The reaction is much slower than in the case of the two preceding substances, and does not take place at all if the urine be acid. I have not met with any case in which a urine containing resorcin changed colour on exposure without artificial alkalisiation.

Protocatechuic Acid.—If, in addition to substituting hydroxyl (OH) for the hydrogen of the benzol radicle, we also replace an atom of hydrogen by the acid radicle, carboxyl (COOH), we obtain a series of compounds, of which the first is salicylic acid, corresponding to phenol, where one molecule of hydroxyl is present; when two molecules of hydroxyl are introduced together with the acid radicle, we obtain a compound $C_6H_3(OH)_2COOH$, which is known as protocatechuic acid. The phenomena produced by the presence of this body in the urine may be illustrated by the account of a case which recently came under my notice.

The subject of the observation was a lady, aged 27, who was under the care of Dr. Gray, of Armagh, and had been seen in consultation with him by Dr. Whitla, of Belfast. To the courtesy of these gentlemen I am indebted for an opportunity of examining the urine, and recording the clinical features of the case. In the summer of 1882, the patient began to suffer from symptoms of gastric ulcer, such as pain in the epigastrium, disturbances of digestion, vomiting of mucus, and occasionally of blood. About last Christmas, there occurred appa-

² *Zeitschr. für Phys. Chemie*, Band III, p. 156.

³ *Virchow's Archiv*, Band XLII, p. 554.

⁴ *Annalen der Chemie*, Band cxvii.

⁵ *Berlin. Klin. Wochenschr.*, 1875, Nos. 23 and 24.

⁶ *Ideen*, No. 33 and 40.

rently a perforation of the stomach, with an attack of localised peritonitis, which was controlled, however, by opium. In January of this year, there was first noticed a remarkable condition of the urine. Although perfectly clear and of a pale yellow colour when first passed, after a short period of exposure to the air it assumed a dark brown, almost black tint, and finally deposited a brown precipitate. The condition continued with intermissions up to April of this year, when Dr. Gray kindly sent me a specimen of the urine for examination.

The urine, as I received it, that is, after being corked up for some little time, was of a dark brown colour, and was alkaline from fixed alkali. Its specific gravity was 1032, and it contained no albumen. It showed a very slight reducing action on Fehling's solution, but an ammoniacal solution of nitrate of silver was at once reduced in the cold to the metallic state. There was neither blood nor bile present. Heat produced no effect. Acetic acid rendered the colour lighter, while liquor potassæ had the opposite effect, and made it much darker. Nitric acid showed merely a dark rim at the point of junction of the fluids, this being probably due to indican. The addition of an equal volume of hydrochloric acid developed a pinkish colour, due, again, to indican. On standing, a white sediment formed, consisting of triple and stellar phosphates. If the urine were exposed to the air, it became still darker in colour, while, if corked up tightly, the dark colour was, to a great extent, lost. If, then, the cork were removed, so as to admit air to the bottle, the urine could be seen to grow dark from above downwards. This conclusively proves that the pigment was a product of oxidation. It has been stated that the urine, at intervals, remained of the normal colour on standing. It was found, however, that in these intervals the urine was acid, and not alkaline, as when the dark colour appeared. Dr. Gray also sent me a specimen of the urine during these intervals. To one portion of the urine, liquor potassæ was added, and to another, a little acetic acid. The two specimens were then exposed to the air, and, in a short time, the alkalinised urine became dark brown from above downwards, while the acid urine retained its light colour. Thus, we may conclude that alkali as well as oxygen was necessary to develop the dark colour, and that the reason why the urine, at intervals, did not show the phenomenon was that it then had an acid reaction. From the above reactions, it would not be certain whether we had present pyrocatechin or protocatechuic acid; and, indeed, in the earlier observations of such urines, it is probable that the distinction was not made.

The following reactions of the urine in question would, however, show that we had to deal with protocatechuic acid, and not with pyrocatechin. To a portion of the dark urine a weak neutral solution of ferric chloride was added, when a bluish green colour was produced. The addition of ammonia to this caused a change of colour to a darkish red. If pyrocatechin had been present, the ammonia should have produced a violet colour. The dark urine, when alkalinised, did not give up its colour on shaking with ether, neither did the colouring matter nor the colour-producing matter distil over on heating, as should have been the case if pyrocatechin had been present. Pyrocatechin shows a marked reducing action on Fehling's solution, while protocatechuic acid has no such reducing action. Now, the urines described by Ebstein and Müller, Bodecker, etc., mentioned above, reduced Fehling's solution markedly, while the urine I have described only showed a slight reducing action on the copper, no more than, I think, would be accounted for by the uric acid present. We may hence conclude that the urine contained protocatechuic acid. As far as I can ascertain, the only other case on record in which this body was discovered was reported by Dr. Smith in the *Dublin Medical Journal* for 1832. Dr. Smith described an urine, possessing reactions and peculiarities closely corresponding to those I have mentioned; and he showed that it contained protocatechuic acid.

We may now inquire what was the source of this substance in the case I have reported. The patient was not taking any drug which could cause the peculiarity of the urine. It is necessary to mention particularly that, although tannic acid had been prescribed for the hæmatemesis from which she had suffered, it had not been administered for some time before the urine showed its peculiar behaviour. The patient was hysterical, but every precaution was taken to prevent simulation. Pyrocatechin and protocatechuic acid are contained in certain plants, but this source was also excluded in the case of Dr. Gray's patient. The phenomenon could not, therefore, be referred to anything exterior to the body, and must be entirely pathological. We know, however, that compounds of the aromatic group result from pancreatic digestion. The most abundant of these is indol, from which probably the indican of the urine is derived. Phenol and its derivatives are also formed thus; and I should be inclined to think that we had here the source of the protocatechuic acid in the urine I have described. Possibly adhesions from the attack of peritonitis

may have delayed the passage of the intestinal contents, and so favoured the absorption of the by-products of digestion.

I have entered into some detail concerning this case, because, apart from its pathological and chemical interest, it also possesses a certain amount of clinical importance. Such a condition of the urine would naturally cause considerable alarm to the patient, and possibly some perplexity to the medical attendant. To both, however, it would be reassuring to know that the appearance was due to an entirely functional disorder.

The other substances I have to mention, which colour the urine in this manner, require only a very short notice.

Pyrogallol and Gallic Acids.—These are similar compounds to those mentioned, and are produced, as their formulæ given above will show, by substituting, in the benzol group, three molecules of hydroxyl for a similar number of hydrogen atoms. When used medicinally, these bodies are excreted by the kidneys; and then the urine, on the addition of caustic potash, absorbs oxygen, and becomes of a dark brown colour. These substances do not occur naturally in the body, and hence are not of so much interest as some mentioned above.

Melanin.—Patients suffering from melanotic tumours, especially when such tumours affect the liver or the skin, occasionally pass a urine loaded with a dark pigment called melanin. The fact was first pointed out in 1820 by Norris. In 1826, also, a full account of melanosis, with the condition of the urine, was published by Fawcington, a Manchester surgeon. In some such cases, however, the urine, although pale when passed, contains a body, melanogen, which on oxidation, either by exposure to the air, or by the addition of a mixture of sulphuric and chromic acids, yields melanin. I have not met with a very typical example of such a urine. A patient in the Manchester Royal Infirmary, a short time ago, under Mr. Jones, had a melanotic tumour of the foot, for which amputation was performed; subsequently, a group of glands in the groin, melanotic in character, was also removed. The urine of this patient showed some darkening of colour when a mixture of sulphuric and chromic acids was added to it, but the change was only slight. The patient has now left the hospital, and I have not had an opportunity of watching the progress of the case.

A most interesting case has recently been reported by Zeller,⁷ which throws considerable light on the origin of the pigment in these cases. In Zeller's case, the melanin varied in amount in inverse proportion to the amount of urobilin present in the urine. Since the urobilin is probably derived from the liver, a similar origin is claimed for the melanin.

NOTES OF A CASE OF EXTIRPATION OF THE LARYNX.

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THE operation of extirpation of the larynx is still on its trial. It has been, if I mistake not, rarely performed in England, certainly in London, and its justifiability is still a matter of dispute. All cases, therefore, should, I think, for the present at least, be recorded.

The patient, H. V., a man aged 63, was admitted on May 16th, 1884. He had been in perfect health up to Christmas. Then he began to complain a little of sore-throat, and deafness in the left ear. Soon afterwards, the neck became stiff, and he was conscious of a swelling on the left side. For the past six weeks, he had had difficulty in swallowing and breathing. Solids seemed to stick about the level of the cricoid cartilage, and sometimes to come up into his mouth again. Lately, he had had a very troublesome choking cough, with frothy blood-stained expectoration. He had no fits of dyspnoea, but his breathing was becoming more difficult. For the last month, his voice had been very hoarse; he had found it very difficult to talk long, and had been forced to live on fluids. He had been getting weak and losing flesh.

On admission, he seemed tolerably well nourished. His complexion was dusky, and his voice hoarse and indistinct; respiration was noisy and laboured, and cough was frequent. The thyroid cartilage was expanded and bulged, especially on the left side. Above the larynx, there was considerable fulness on this side, reaching up to the jaw, and extending in an irregular manner up the neck. The new growth here seemed firmly attached to the structures around, but the trachea was quite free. The larynx was examined by Dr. Whipham, who reported that the growth involved the epiglottis chiefly, but also, probably, the arytenoids. A portion of the epiglottis had been destroyed

⁷ *Archiv für Klinische Chirurgie*, Band xxix, p. 245.