insignificant part in their formation. The further development of the thrombi resulted from the disintegration of the plaques. A granular or stroma-fibrin (Landois), and a fibrillar or plasma-fibrin, must be recognised. The former, which was identical with the peculiar metamorphosis of cells to which Weigert applied the term coagulation-necrosis, was the process which occurred in the white thrombi; their chief mass was made up of a granular matrix, in which the outlines of the plaques had ceased to be visible. The central softening of a white thrombus was a consequence of the disintegration and liquefaction of the plaques.

The whole question required to be studied again in the light of these new observations on the connection of the blood-plaques with thrombi, particularly the relation of the white and mixed thrombi, and the mode of formation of the clot in aneurysms. Dr. Osler felt assured of the truth of the statements here made regarding the connection of the plaques with thrombosis, from careful observation on the structure of the white thrombi (1) on atheromatous ulcers, (2) on the valves of the heart, (3) in aneurysms, and (4) in thrombi of the veins. Though he had not lately had an opportunity of examining a "globular vegetation" of an auricle or ventricle, he ventured to assert that they were composed originally of similar structures.

A LECTURE

ON

A SOURCE OF UREA TOO LITTLE RECOGNISED.

Delivered at the College of Medicine, Newcastle-on-Tyne.

By THOMAS OLIVER, M.D., M.R.C.P. Lond.,

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IN our last lecture, we dealt with the subject of the acidity of urine, and its causes. We saw that, while the reaction of urine was normally acid, there were yet certain periods of the day during which it would be found alkaline. During the digestion of a meal—more particularly towards the termination of that process—it is the rule to find the urine alkaline, a reaction which I sought to explain, not so much by the removal from the blood of elements necessary to form the gastric juice, which is acid, as by the entrance into the blood of a wave of alkaline material—the absorbed products of gastro-duodenal digestion; and, in support of this latter view, is the fact that the urine gradually increases in alkalinity for the first three hours after meals, and when the tide again turns in favour of acidity. In such a case, the alkaline reaction depends upon the presence of fixed alkalies, such as potash and soda, and is entirely different from the alkalescence of putrescent urine, due to the existence of volatile ammonia. And I also drew your attention to this fact, that, while admitting that the large and highly organised cells in the upper portion of the convoluted tubules assisted in the removal of urea circulating preformed in the blood of the branches of the renal artery—for the knowledge of which we are indebted to the experiments of Heidenhain—yet, as urea is a very soluble agent, passing fairly readily, without pressure, through the various chambers of a dialyser, I am inclined to believe that the greater part of it is squeezed through the walls of the glomeruli of Malpighi, along with the water of the urine, and such soluble salts as chlorides. Urea requires, in my opinion, no specially organised cell to remove it from the blood, as is shown by its presence in the serous effusions of pleurisy and in ascites, and by the presence of urea, in the form of crystalline scales, on the skin of the feet and legs in certain cases of Bright's disease. The function which these cells in the convoluted tubules perform is, in my opinion, this. Surrounding these tubules are the capillaries, formed by the breaking up of the efferent vessels of the glomeruli. We have, on the one side of these cells, alkaline blood circulating, which, in its passage through the glomeruli, has lost water, urea, and certain soluble salts. We know that the fluid which comes from the glomeruli is alkaline, for it is simply a filtrate from the blood, and yet, no sooner does this fluid begin to pass down the centre of the tubuli uninfused than it becomes acid. Clearly, therefore, the seat of the formation of that which causes the acid reaction of urine is the protoplasm of the cells lining the convoluted tubules. The acidity of the urine, however, depends, not upon the

presence of a free acid, but upon that of the acid phosphate of soda. The blood is alkaline, owing to the disodic phosphate which it contains. According to Flint, phosphates exist in the fluids of the body in three different conditions. There is, first, the basic phosphate of soda. It possesses three atoms of the base, and has an alkaline reaction. In contact with carbonic acid, the salt loses one atom of the base, forming sodium carbonate and neutral phosphate, which is feebly alkaline. This neutral phosphate, in contact with uric acid, loses one atom of the base, becoming urate of soda and the acid phosphate of soda. It is in these cells that uric acid unites with the neutral phosphate of soda, forming the acid phosphate. This escapes from the cells into the interior of the tubules, where it is washed downwards by the fluid which has been pressed through the glomeruli, and, intimately mingling with it, changes its reaction from alkaline to acid.

While urea is thus, in my opinion, very easily removed by the kidneys from the blood, our task is more difficult when we come to inquire into its source or sources. Urea is no longer regarded as a special product of the kidney; it does not stand related to the kidney as bile does to the liver; it is not formed in, but simply removed by, the kidneys. The chemistry of urea is so complex, and its source in the body so recondite, that we cannot speak dogmatically upon the subject; and yet I must confess that the sources of urea described in the text-books have never seemed to me sufficient. Physiologists are agreed upon this point, that the amount of urea increases when the amount of proteid matter taken in the food increases. Generally speaking, this is true. Regarded as the end-product of the decomposition of proteids in the body, urea may have many antecedents. Considering that the muscular system constitutes a very large part of the animal economy, and knowing, as we do, how active are the changes going on in muscle, it seems fair to presume that the kreatin of muscle may, when it has passed into the blood, be transformed into urea by some of the tissues or organs. Kreatin, however, is eliminated by the kidney in the form of kreatinin; so that, unless this nitrogenous product be transformed into urea in some other organ, the kidney itself does very little to bring about that change. Experiments on man and animals have shown that muscular exertion has been followed by a slight increase in the amount of urea excreted. After all, it should be remembered that this increase is very slight. The experiments of Fick and Wislicenus, conducted upon themselves during their ascent and descent of the Faulhorn, showed that, when no albuminous food was taken, the amount of urea in the urine was really decreased. A food-source of urea having been, in this way, eliminated, it looks as though muscular exertion caused little, if any, perceptible disintegration of proper muscular-tissue; or, at any rate, that kreatin, a product of muscular metabolism, was not a source of urea. Power, in his *Elements of Physiology*, p. 164, says that it is an error to assume that muscular tissue, if wasted at all, should cause an immediate increase in the quantity of urea in the urine; for, on the ground of the possibility of the decomposition of the muscle into urea, the change may not be immediate. I take it, that the evidence of experiments, carried out for several days, for such a time, at least, as would suffice for the conversion of midway nitrogenous products into urea, would go far towards a settlement of this question. Professor Haughton found that, with a daily walk of five miles for five consecutive days, the quantity of urea eliminated was 501.28 grains (500 grains is considered the normal); while, with a daily walk of twenty miles, other conditions remaining the same, the amount of urea discharged was 501.16 grains, a trifle less than before. In this case, there was no increase in the amount of urea after muscular exertion carried on for five days. It is true that, in Pavy's experiments on Weston, the pedestrian, there was an excess of nitrogen eliminated over that which was taken in the food; but, as it is admitted that the nitrogenous waste, during the walking period, insufficiently accounted for the mechanical work done, I am inclined to think that, as Weston broke down, on the morning of the fourth day, from utter exhaustion, there must have been some other cause for exhaustion on the one hand, and increased amount of urea on the other, than muscular exertion.

The close relationship which exists between the products of pancreatico-duodenal digestion and urea, and also between it and other nitrogenous products absorbed into the blood, such as uric acid, alloxan, and hypoxanthin (for, if these latter be injected into the blood, they appear in the urine as urea), compels us to acknowledge nitrogenous food as a source of urea, and these other substances as its all probability antecedents of urea. For some months past, I have been carrying out a series of experiments on urine—partly clinical and partly physiological—and I have been struck by two things; the first is that, while admitting that the specific gravity of urine is a gauge of

the urea present in it, the higher the specific gravity, within limits, the greater the amount of urea, yet this is not absolutely correct; and the second is that, while the digestion of nitrogenous food is a great source of urea, it is not always so; and particularly is this noticeable where the liver is at fault. In one of my cases of splenic and hepatic disease, watched for several months, a greater amount of urea was thrown off by the kidneys when the patient was upon milk than meat diet. In fact, time after time, the substitution of animal food for milk was always followed by a diminution in the amount of urea, and by increased gastro-intestinal disturbance on the part of the patient. In health, however, it may be said that increase of nitrogen in the food is always followed by a corresponding rise in the urea excreted. Another thing which struck me is this, that the colour of urine is a better indication of the amount of urea present than the specific gravity. A deep amber-coloured urine I have always found to contain a large amount of urea, a lighter amber-coloured urine less, and a straw-coloured urine less urea still; and, knowing that the colouring matter of urine—urobilin—is a derivative of the biliary colouring matter bilirubin, and this again a derivative of hæmoglobin, I am in a position to show you that the blood itself, or rather its hæmoglobin, is one of the sources of urea. Besides forming bile and glycogen, the liver, in some way or other, causes a disintegration of red blood-cells; it is, in this sense, their grave. Bile-pigment, as already mentioned, is formed from hæmoglobin. The hepatic vein contains fewer red corpuscles than the blood of the portal vein. Well, since red blood-corpuscles are broken up in the liver, and the hæmoglobin goes to form bile-colouring matter; and that, again, urobilin—the colouring matter of the urine—what becomes of the rest of the protoplasm of the blood-cells so acted upon by the liver? I am strongly convinced that it is converted into urea to a very large extent. A healthy man eliminates about 500 grains of urea daily. The urine of such a man will be found of a pretty deep amber colour, and it will have a specific gravity ranging from 1015 to 1025. That the specific gravity of itself may be shown to have nothing to do with the amount of urea present, is shown by comparing the urine of a diabetic patient with that of a person in health. The average percentage of urea in healthy urine is 2.5 to 3.5; but, in diabetes, though the specific gravity may be 1060, I have not noticed more than .5 per cent. of urea in the urine. This, of course, is based upon the amount of urine passed in diabetes, which is excessive, so that, when the quantities passed in health and diabetes are compared, there is no diminution, but an excess, of urea. The simple percentage, however, is diminished. In diabetes, you have a pale greenish urine, containing a deficiency of colouring matter, and with that a deficiency of urea per cent. Or take a case of anæmia; here you have pale-coloured urine, with, it is true, a lower specific gravity than in health. In such, urea is deficient. It appears to me that the deficiency of urea is, supposing the kidneys to be sound and able to throw it off, always traceable either to a permanent diminution in the number of red blood-cells, as in anæmia and cachexia, or that it depends upon some imperfect transforming power on the part of the hepatic cells. It is from this latter point that I would supplement the opinion expressed by Sir Andrew Clark, in the interesting and valuable lecture which he gave on Renal Inadequacy, three years ago (BRITISH MEDICAL JOURNAL, February, 1883). Patients, the subjects of this affection, pass habitually, we are told, urine of low specific gravity, deficient in urea. You may give these people any amount of rich nitrogenous food you please, only to find that you tend to produce a still further diminution in the quantity of urine, and a further aggravation of the illness. The fault here is as much in the liver as the kidneys; the latter simply throw off, so far as water and urea are concerned, regulated by variations of pressure, what is brought to them. And in support of the fact that the kidneys are, in all probability, healthy, we are told by Sir Andrew Clark that the amount of uric acid is normal. This, as a very insoluble constituent of the urine, requires a special mode of elimination by the renal cells, and is not filtered off, as I believe, urea to a great extent is.

Landois states (and the opinion is pretty general in the profession) that the amount of urea is increased by a rapid breaking up of the nitrogenous tissues of the body, that this breaking up is increased by a diminution of oxygen, and that, in fever, generally there is an increased elimination of urea. My observations do not support this *in toto*. I know of no disease which causes such a rapid diminution of the body-weight, no illness in which emaciation is so quickly progressive, nor one in which a high temperature is so constantly present, as phthisis pulmonalis; and yet, while you have rapid emaciation and a high temperature going on week after week—the very conditions favourable, as Landois would tell us—there is really no increase, but a most notable decrease, in the amount of urea eliminated. This de-

fective elimination of urea lasts for a longer or a shorter period—months frequently—with, it is true, the appetite greatly diminished, a point which enables us to deal more exclusively, therefore, with the waste-tissue theory; and it will only be just as the terminal stage of the illness is reached, that the urine will be found not necessarily diminished in quantity or increased in specific gravity (in fact, I have frequently noticed a reduction in the specific gravity), and yet, with this, there will be noticed a fairly rapid rise in the amount of urea excreted.

I have noticed, time after time, during the course of phthisis pulmonalis, attended by high temperature and rapid emaciation, and with a complete absence of diarrhoea to complicate the investigation or the existence of any other source whereby urea might be vicariously eliminated save the sputum, that, for a period, the percentage of urea has been low, and that, when an increase took place, the colour of the urine correspondingly deepened; that the patient became, in addition to the loss of flesh, markedly paler day by day; and that a fatal termination was approaching. A patient, we shall say, has been ill with phthisis for a few months; there has been a fairly high temperature, and emaciation has been taking place; you examine his blood, and you find there is about the normal number of blood-cells in a cubic millimetre (5,000,000). At this stage, urea is not increased in the urine; more probably, it is diminished. A few weeks or months later, you find that the urea is increased in the urine; but, at the same time, you notice that your patient has become distinctly paler, and, on examination of the blood, you notice a marked reduction in the number of red blood-cells, only 3,500,000, or thereabouts, being found in a cubic millimetre. In such cases, no urea was formed out of the products of tissue-disintegration, the opportunities for so doing were most favourable were this the source; but towards the end of the illness, when, from some cause or other, the blood-cells were being rapidly disintegrated in the liver, as was shown by the deepened tint of the urine, depending upon the presence of a greater amount of urobilin, the urea rose accordingly. Nor is it the rise of temperature which explains the increased elimination of urea in fevers. It is admitted that, before the thermometer registers a rise of temperature in the early stage of fever, an examination of the urine always shows a very marked and sudden increase in the amount of urea eliminated; may, more than this, that, during the height of the fever, the urea diminishes, to rise again during convalescence. This has sometimes led me to consider, whether the rigor and the period immediately preceding the rise of temperature in fever, may not be associated with a temporary increased disintegration of blood-cells; as if a wave of blood-cells had been suddenly engulfed, followed by disturbed hepatic function.

The amount of urea in urine is diminished when the blood has become permanently impoverished. I have, in another paper, drawn attention to the fact that, in lead-poisoning, no sooner is the peculiar anæmic condition developed in these cases, than the elimination of urea falls. In every case of anæmia, not only is the urine wanting in colouring-matter, but also in urea.

It is said that, in cancer, urea is increased. This applies to the early stage, when the cachexia is forming, and red blood-corpuscles are being rapidly disintegrated; for, in the fully developed cachectic condition, the urine becomes paler, and the amount of urea diminishes. There is one highly coloured condition of the urine which calls for some remark. I have frequently found a jaundiced urine to be one which did not contain an excess of urea. In many instances, it has contained less than the normal. And here I would say that this is the only kind of urine to which colour does not apply as a rough test of the amount of urea present; and the same may be said of urine accidentally coloured by medicines, etc.

In one of my cases of phosphorus-poisoning, the percentage of urea for the first five days was 1.99; but, when the patient became jaundiced, the amount of urine passed remaining about the same, the percentage of urea fell to 1.08; in a few days later still, the jaundice being very persistent, it even sank to 0.6 per cent., to increase again as the patient improved, and the urine ceased to give the reaction of bile. I have noticed a similar deficiency in the urine of patients suffering from jaundice, due to catarrh of the biliary ducts. In such cases, one can only suppose that, owing to the overfilling of the biliary canaliculi by bile (some of which is absorbed into the blood), the function of the hepatic cells has been, for the time being, disturbed; blood-cells have not been acted upon and transformed into urea.

I believe the liver to be the chief organ concerned in the formation of urea, and that, while urea may be formed within it out of leucin and tyrosin—the products of the pancreatic digestion of proteids—I am more than convinced that a great part of it is formed out of the red blood-corpuscles, the colouring matter of which goes to form bili-

rubin, and afterwards urobilin, and the greater part of the rest of the corpuscles to form urea.

Since delivering this lecture to my class at the College of Medicine, I have read, with very great interest and profit, the paper on urea by Dr. Noel Paton, which appeared in this JOURNAL during February. The clinical investigations, which I have made so fully, confirm the results arrived at by that gentleman, who, by experiments carried out in the larger and well equipped laboratories of the University of Edinburgh, has proved the close relationship which exists between urea and the secretion of bile.

Dr. Paton is, I believe, about to show experimentally how the blood-corpuscles and urea stand related to each other. It is in support of the same view, arrived at by clinical observation, that I have forwarded this paper to the BRITISH MEDICAL JOURNAL.

ONE HUNDRED AND THIRTY-NINE CONSECUTIVE OVARIOTOMIES PERFORMED BETWEEN JANUARY 1ST, 1884, AND DECEMBER 31ST, 1885, WITHOUT A DEATH.

Read before the Birmingham and Midland Counties Branch.

By LAWSON TAIT, F.R.C.S.,
President of the British Gynecological Society.

FROM our recent experience in ovariectomy, it would almost appear as if the time had arrived when we had the last word to say about it, and had now merely to refer to it occasionally in valedictory or inaugural addresses as one of the marvels of the nineteenth century. Certainly nothing more astonishing can be indicated than the advance during the last eight years, at the beginning of which period Sir Spencer Wells left ovariectomy with a mortality of 25 per cent., and the position it has now reached, having a mere fractional mortality, due to influences of a purely accidental kind. By accidental, I mean such influences as are not inherent to the operation itself, influences which may be avoidable, it is true, and ought to be avoided, but which may fairly be classed as outside risk. I do not see, for instance, how tetanus can be avoided; and, therefore, its occasional fatal influence in ovariectomy is sure to be felt. So also death, either directly or indirectly from the effects of the anæsthetic, will surely come occasionally forward as an unavoidable result. But all the truly intrinsic causes of death have been banished, and I wonder very much if this is true of any other grave operation in surgery.

We speak of the mortality of certain operations, but I doubt very much if we have arrived at any notion of what the mortality of any other operation really is; that is, the mortality due to the operation pure and simple, not to causes which are avoidable, as unsanitary surroundings, or bad surgery; not the mortality of this or that hospital, this or the other operator, but the lowest mortality which can be, and, therefore, that which ought to be, achieved.

This success in abdominal surgery has been the basis of a large number of lessons applicable within its own range, and not without benefit to other fields. It has, for instance, absolutely destroyed our fear of the peritoneum, and has justified our opening that sacred sac very much as we open our pockets. It has revolutionised our notions of pathology in some directions, and has confirmed them in others; and it, above all things, overwhelmed with confusion the utterances of therapeutic dogmatists. Baker Brown, after a series of disasters, uttered the truism, "It's the peritonitis that beats us." Now, we beat the peritonitis. On the slightest indication of peritonitis after an ovariectomy, we give a rapidly acting purgative, it matters not what; the patient's bowels are moved, and the peritonitis disappears. This practice I introduced in 1875, and it is now almost uniformly adopted. How different from the views we had drilled into us years ago, that opium was the sheet-anchor of the practitioner in all abdominal troubles, when I say now that all opiates are forbidden in my practice, unless they be required to ease a dying patient out of the world.

Peritonitis was formerly regarded as a bar to any abdominal operation, but, thanks to the courage of Keith and Wiltshire, it is now the most trenchant argument for immediately opening the abdomen. Let me briefly recite the subsequent history of one of the cases on that list (101), a young girl, only 14, from whom I removed a large cystoma of the left ovary on July 18th, 1884.

On March 4th of this year, I received a letter from Dr. Pearson, of Kingswinford, who placed her under my care, to say that he feared something had gone wrong with the other ovary. I telegraphed to him to bring her over at once, and, when I admitted her to my private hospital, there was abundant evidence to prove that Dr. Pearson was right. The pelvis was occupied by a firm doughy swelling pushing the uterus forward and upwards, and this mass could be felt above the pelvis. To the right side, another similar mass could be felt running up and over the right kidney. It was not clear whether these masses were or were not connected, and they both felt to me like soft cancer, an idea justified by the patient's age. What history could be obtained from the friends was not clear, and, therefore, I recommended that the abdomen should be at once reopened. After some demur, this was agreed to by the parents, and it is fortunate for the child that they gave their consent. I operated on March 5th, and found two large encysted peritoneal abscesses, containing about three pints of the most stinking pus I ever encountered. Neither of the cavities communicated, so far as I could discover, with the general sac of the peritoneum, nor did they communicate with one another, and I could detect no other fluid or mass in the abdomen. But, in a few days, it became evident that I had encountered and had overcome only half the difficulty. Whether from the lower cavities the rest of the peritoneum became infected, or whether the suppuration of the whole of the sac was the original scheme, I cannot tell, but the whole of the rest of the sac did suppurate, and I drained out of it about seven pints (eleven pints in all) of horrible stuff; and the child is now practically well.

The conclusion is now completely established in my own mind, and receives confirmation every month: "When in doubt, open the abdomen;" the doubt being one that my patient will not recover if left alone. In the case I have just narrated—and it might be supplemented by many other cases just as striking and quite as successful—I might have concluded that the second growth was a mass of soft cancer, and have sent the poor child home to die from my mistake. If it had proved to be cancer on exploration, the chances are infinitely small that I should have done any harm; and now, as the matter stands, I have achieved a brilliant success.

This is the doctrine which I want to preach, for the support of which I have recently had the powerful aid of Dr. Wade; and not all the foolish outcries about the laparotomy epidemic, raised either at Liverpool or elsewhere, or any other kind of opposition, is in the least likely to hinder its propagation. I have not spoken to Dr. Wade precisely on the subject, but I strongly suspect that a powerful and moving influence in his mind, towards the adoption of this view, is a case which was, to me, a revelation and a lesson of the most terrible kind. It was, I think I may say, the initiation of this new course of practice; for I have never since allowed a case of peritonitis to die without at least proposing abdominal section as the proper course.

Many years ago, a lady of high social rank, who honoured me by her friendship, and to whom I was deeply attached, had performed on her by me a trifling uterine operation, which had been done without ill effect many times before. It was the insertion of a sulphate of zinc pellet into the uterus, for the arrest of extreme menorrhagia due to a myoma. She died about fourteen days after, suffering from many symptoms which suggested peritonitis, save that her pulse and temperature always contraindicated this conclusion. Dr. Wade saw her just before the end of her illness. At the *post mortem* examination, we found a large quantity of pus, all of which could have been cleared out by an abdominal section and drainage.

Three great lessons were taught me by this case: first, that tinkering with the inside of a uterus occupied by a myoma is not satisfactory, and more dangerous than removing the appendages; second, that fatal peritonitis may occur with a low pulse and a low temperature—a fact I did not know before that; third, that suppurative peritonitis might be treated like any other abscess. And from all these lessons I have most abundantly profited.

The absolute want of fear of the peritoneum, which has grown out of our success as a matter of necessity, has brought about many other startling changes. We are now dignified by the name of the "Birmingham School of Gynecology," and our views are treated with respect; but it is not many years since language of a totally different kind was levelled against my colleague, Dr. Savage, and myself, and many blows had to be received, and not a few were given back. But the incredulity which was so freely expressed in this country by people who would not come to see for themselves, was speedily overcome by the evidence of those who came in large numbers from America, and finally by a missionary tour which I undertook in the States, demonstrating on material freely supplied to me there, and to audiences neither stupid nor prejudiced, many of the most important facts