The Goulstonian lectures : observations on the pathology of the kidneys : delivered before the Royal College of Physicians of London, on March 15th, 17th, and 22nd, 1898 / by John Rose Bradford.

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The Goulstonian Lectures:

OBSERVATIONS ON THE PATHOLOGY OF THE KIDNEYS.

LECTURE I.[1]

Mr President and Fellows,—In bringing before you the following observations on the pathology of the kidney I shall necessarily only touch the fringe of a large subject. The pathology of the kidney may be considered to include the study of at least three more or less separate classes of phenomena: (1) the mode of production of renal diseases; (2) the changes produced in the kidney by renal diseases; and (3) the remote effects produced on other organs or tissues by diseases of the kidney. I propose to deal mainly with the last of these questions and to a certain but very limited extent with the second, but not at all with the first, important as it is.

Diseases of the kidney may affect the general economy in one or more of the following ways: (1) the excretory activity of the kidney may be affected so that, on the one hand, the composition of the urine is more or less altered, and, on the other hand, the blood and tissues may possibly become contaminated with excessive quantities of substances normally excreted; (2) the production of dropsy; (3) the production of cardio-vascular changes; (4) diseases of the kidney are associated with profound changes in the nutrition and in the general metabolic processes of the body; and (5) the tendency to so-called secondary inflammations.

I propose to consider in these lectures a series of observations, experimental and clinical, dealing mainly with the questions associated with the excretory activity of the kidney (Section I.) and the influence of this organ on metabolism (Section IV.); a few observations dealing with Section III. will be detailed, but I have no observations to describe to you on either the causation of renal dropsy or

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with reference to the diminished resistance to microbic invasion that is so frequently seen in certain varieties of kidney disease.

As an introduction to the pathological side of the question it will be necessary to consider in some detail the physiology of the kidney.

The Physiology of the Kidney.

The modern physiologist discusses the physiology of glands under the headings of external and internal secretions and according to this view the kidney would be placed in the former series, although some years ago Brown-Séquard hazarded the view that this gland also possessed an internal secretion. The kidney, however, is peculiar amongst glands, not only owing to the peculiarity of the arrangement of the circulation in it, but also owing to the extreme vascularity of the organ, so that quite apart from its functions as a gland the kidney has afforded a means of investigating various problems connected with the circulation and more especially with the vaso-motor mechanism. I think the very intimate relationship of the kidney to the vaso-motor mechanism is a factor that is sometimes overlooked by the more mechanical school of pathologists.

The physiological considerations that are of more immediate interest from a pathological point of view may be classified somewhat as follows: (1) circulation in the kidney; (2) the excretory activity of the kidney; (3) the synthetic activity of the kidney; and (4) the metabolic activity of the kidney.

I. Circulation in the kidney.—The circulation of the blood, as is well known, is carried on by the blood-pressure, but in different organs it is actually effected by very different means. In the case of the kidney there is what may be called a high-pressure circulation; the difference of pressure between the blood in the renal artery and that in the renal vein is brought about by the pressure in the artery being very high. This is due, in the first place, to the immense number of small arteries in the kidney, and, secondly, to the very abundant innervation that these receive from the vaso-constrictor nerve fibres. In the case of the liver there is a low-pressure circulation, the difference of pressure being effected, not by a high pressure in the portal vein, but by the blood being more or less sucked out of the organ by the low negative pressure in the right auricle and vena cava. In the lungs, where the vaso-motor supply is also comparatively slight, the circulation is very largely effected passively by the movements of respiration varying not only the amounts of air in the lungs but also the amounts of blood. Finally, in the spleen there is yet another means of effecting the desired object, as here the intermittent contractions

and expansions of the organ must exercise a very powerful influence on the circulation through this organ. To return to the kidney, the blood-vessels are very abundantly supplied with vaso-constrictor nerves and these, like the vaso-constrictors distributed to other organs, are derived mainly from the dorsal region of the spinal cord. Vaso-constrictor fibres destined for all such vessels as are supplied by them leave the cord throughout the dorsal region and most abundantly through the lower half of the dorsal series of nerves. There are a few vaso-constrictor fibres derived from the upper dorsal region from the first to the fourth dorsal, and it is only when the sixth and eighth dorsal nerves are reached that the outflow of these vaso-constrictor fibres is at all abundant. The upper three lumbar nerves also contain such fibres distributed to the kidney amongst other organs.

All the above remarks apply to the dog, where there are twenty dorso-lumbar nerves, of which thirteen are usually reckoned as dorsal and seven as lumbar. It is remarkable that the kidney receives its vaso-constrictor fibres from such a very extended series of nerve roots extending as it does from the sixth dorsal above to the third lumbar below and there is no break in the series. Other parts of the body may receive their nerves from a fairly long series but not so long as that supplying the kidney; thus the fore limb is supplied from the third dorsal to the tenth dorsal and the hind limb from the tenth dorsal to the third lumbar. The kidney, however, is a "long" organ from a morphological point of view and this may account for the fact that it receives these vaso-constrictor fibres from some eleven spinal segments in the dog. The kidney not only receives its vaso-constrictor nerves from such an extended series, but each individual nerve root produces very marked effects on the renal circulation. It is not possible to diminish the volume of a limb (by excitation of the vaso-constrictor nerve supplying its blood-vessels) to anything like the same extent that the volume of the kidney can be diminished; doubtless this is in part due to the greater vascularity of the kidney, but it is also due to the very abundant nerve supply distributed to the renal vessels. The vaso-constrictor fibres pass down from the vaso-motor centre, probably in the lateral columns of the spinal cord, and it is of some interest that hemisection of the spinal cord above the level at which the renal nerves come off has no effect on the volume of the kidney. A number of experiments were made on the effect of hemisection of the cord at the level of the fifth dorsal, inasmuch as there is no appreciable outflow of renal vaso-constrictors until the sixth dorsal root is reached. Hemisection of the cord at this level fails to cause any dilatation of the renal vessels, but it also does not materially interfere with the conduction of impulses downwards from the vaso-motor centre to the kidney. Excitation of the vaso-motor centre

causes, of course, constriction of the renal vessels, but if a hemisection be made at the level of the fifth dorsal the kidney on that side contracts on excitation of the vaso-motor centre, as far as my observations go, just as well as it did previously to the hemisection. Hemisection of the cord, however, causes dilatation of the limb-vessels although it fails to cause dilatation of the kidney of the same side. One half of the spinal cord, therefore, can maintain the tone of the vessels of both kidneys and can convey impulses freely from the vaso-motor centre. The fact that there is what may be called unilaterality with reference to the spinal vaso-constrictor supply for the limbs—and there is no such differentiation in the case of the fibres distributed to such a symmetrical organ as the kidney—is a point of some interest from an evolutionary standpoint.

Vaso-dilator fibres.—Although the vaso-constrictor fibres spring from such an extended area of the cord the great bulk of these fibres is found in the lower dorsal and upper lumbar roots and here also by appropriate methods of excitation renal vaso-dilators can be demonstrated. Their action, however, is very slight when compared to that of the constrictors.

Reflex effects.—It is well known that the excitation of the central end of an afferent nerve causes reflexly constriction of the arteries of the body and especially of the blood-vessels of the abdominal viscera such as those of the intestines, spleen, and kidneys. This constriction does not normally cause any long-continued rise of blood-pressure owing to the fact that coincidently with it the heart is inhibited, partly directly by the action of the afferent stimulus on the vagus centre, partly indirectly by the heightened blood-pressure stimulating the ends of the vagi distributed to the endocardium. That, after all, is the great function of the vagus and as long as this mechanism is intact it is practically impossible to materially raise the general blood-pressure for any length of time. This is a factor probably of some importance in regard to the production of high tension in disease, as from a physiological point of view one would be inclined to say that no mechanical means could produce high tension as long as the nervous mechanism of inhibition and the relation between the vaso-motor system and the cardio-inhibitory mechanism were intact. The excitation of the central end of a posterior root causes (provided the vagi are cut) a rise of blood-pressure just as the excitation of any ordinary nerve does, but there are two differences of considerable interest. If a posterior root below the third lumbar nerve be excited the rise of blood-pressure is similar to that seen on excitation of the great sciatic; if, however, the central end of one of the upper lumbar or lower dorsal posterior roots be excited the rise of blood-pressure is far greater in amount and more sudden in its onset; in fact, the effect is quite different to that seen with the lower roots.

The anterior roots of these nerves contain, as we have seen, the vaso-constrictor fibres distributed to the vessels of the viscera and these observations tend to show that these posterior roots also contain special afferent fibres capable of affecting the vaso-motor system to a far greater extent than the ordinary afferent fibres seen in sensory nerves. In other words, this great and sudden effect on the blood-pressure would tend to show that some posterior roots contain afferent fibres derived probably from the viscera and from the kidney amongst other viscera. The fact that there are such nerves distributed to the kidney and that the excitation of their central ends is capable of causing a very great effect on the vessels of the body generally is also a fact that may have some bearing on the production of high tension in certain renal diseases. The other point of interest about these afferent visceral fibres is that although their excitation causes a rise of blood-pressure with general constriction there is local dilatation of the kidney—in fact, this is the only method by which experimentally any very considerable dilatation of the renal blood-vessels can be produced.

It is a common belief that there is some intimate relationship between the state of the kidney vessels and those of the skin. It is possible that such is the case, but numerous experiments directed to this end have failed to demonstrate any such relationship. I would sum up the relationship existing between the renal and the general circulation by saying that the kidney vessels take part in almost all effects produced by reflex excitation of the vaso-motor centre and that the general blood-pressure can be profoundly affected by reflex stimuli reaching the central nervous system through the renal nerves, but that alterations in the calibre of the kidney vessels only are not capable of causing anything like so profound an effect.

II. The excretory activity of the kidney.—The most obvious function of the kidney is, of course, the removal of various substances from the blood stream and as is well known in performing this the kidney manifests marvellous selective affinity as shown by the fact, amongst others, that although there is some five times as much sugar in the blood as there is urea, yet the urine contains mere traces of the former and 2 per cent. of the latter. The elimination of water by the kidney is usually held to be determined ultimately by the rate of blood-flow through the organ and most diuretic substances causing an increased excretion of urinary water bring this result about by causing an increased rate of blood flow through the kidney. This is sometimes effected by dilating the renal vessels, the general blood-pressure remaining unaffected; at other times the same result is brought about by constricting the renal vessels and at the same time raising the blood-pressure. It is not essential for the action of a diuretic that the diuretic substance should cause

dilatation of the renal vessels although the most potent and useful diuretics do this. Observations published by me in the Proceedings of the Royal Society, 1892, showed that the quantity of water excreted by the kidneys could be affected by excising portions of the kidneys. These results may be shortly summarised as follows. Excision of a portion of one kidney is followed by a slight increase in the amount of urinary water sometimes transient, in others more permanent in its duration, but unaccompanied by any permanent increased excretion of urea or by any deterioration in general health. The excision of portions of both kidneys is followed by a very great increase in the amount of urinary water; thus it may be trebled or even quadrupled in amount, and this increase is permanent and in some of my experiments has been observed as long as eighteen months after the operation. This hydruria is not accompanied by any other ill effects, the animal remains in good health and does not excrete any increased quantity of urea. Simple incision of the kidney with subsequent suture of the damaged organ or division of the renal plexus is not followed by any of these effects. The excision of a portion of one kidney and the subsequent removal of the whole of the other also causes this extreme hydruria and provided that at least one-third of the original total kidney weight is left such an animal will remain in good health for prolonged periods—e.g., eighteen months. There is no marked wasting and no increased excretion of urea takes place. Such an animal, however, is unable to excrete a concentrated urine and if very large amounts of nitrogenous foods are given the urea formed is readily excreted, but only thanks to a still further increase in the amount of urine. Such an animal resembles a case of diabetes insipidus or of contracted kidney, but the urine is not albuminous. The cause of the increased excretion of urinary water when the amount of available kidney is thus reduced is by no means clear; it is, however, not associated as far as my observations have gone with any very great increase of the general blood-pressure. It is similar to the increase seen in many renal diseases where the quantity of kidney substance is often greatly diminished in amount. Some physiologists have urged that the kidney not only excretes water, but also that it re-absorbs water, and it may be that if the quantity of kidney tissue is diminished the excretion may continue and the re-absorption fail; but, as said above, I am not prepared to explain the fact that when the kidney is thus reduced in amount by the experimental procedures mentioned above the urine passed is a copious dilute one. Normally an animal such as a dog, if it requires to excrete a large amount of urea, can do so in two ways, either increasing the percentage of urea or by increasing the amount of urine. In my experience the former is the more common, but these animals after the above partial nephrectomies are only able to effect the latter. There is a slight increase in the percentage of urea in the blood after this operation and it is

possible that this may be the cause of the hydruria and, if so, there is still greater resemblance between this experimental hydruria and that seen in renal cirrhosis, since, as will be seen later, the blood in this malady may contain a notable excess of urea. This hydruria is also seen when the amount of kidney left is very small. Thus in one case approximately one-tenth of the original kidney weight was all the available kidney tissue left after the removal of a large amount of one kidney and the ligature of the opposite ureter, yet this animal excreted three times as much urinary water with one-tenth of the original kidney weight than it did with intact kidneys. This experiment shows well the extreme facility with which small fragments of healthy kidney will excrete the urinary water.

The excretion of urea.—The excretion of urea, like the excretion of water, is readily effected by these small fragments of kidney, but there is this difference that whereas all partial nephrectomies, single or double, slight or extensive, increase the amount of urinary water, to different degrees, it is true, the amount of urea is not increased by either single partial nephrectomy, or by double partial nephrectomy, or yet by the removal of one kidney and a portion of the other, provided always that at least one-third of the original total kidney weight is left to the animal. If, however, this limit be exceeded and only one-quarter of the original total of the kidney weight be left then the quantity of urea excreted is increased. This increase in the urea excretion is not so great as the increase in the urinary water, but it is considerable. Thus the amount of urea excreted may increase by half of its previous amount without any increase in diet, and more commonly, notwithstanding a diminution in the amount of food, owing to failure of appetite. The increased excretion of urea sets in from one to three days later than the increased excretion of water, so that the animals in which three-quarters of the total kidney weight has been removed present for the period of one or two days a condition of simple hydruria before the polyuria sets in. This polyuria is persistent and accompanied as it necessarily is with great emaciation it leads to death in periods varying from one to six weeks. These small fragments of kidney excrete urea abundantly and even as when in the case quoted above the amount of kidney is reduced to so small an amount as one-tenth of the original weight there is no evidence that the fragment is unable to excrete urea. In the cases where three-fourths or more of the total kidney weight had been removed the polyuria was marked and persistent and invariably led to death; where, however, two-thirds of the total kidney weight had been removed there was quite exceptionally a slight increase in the urea excretion accompanied by slight wasting, but this was never marked in amount or fatal in its course. This fact shows, however, that there is not an absolute line to be drawn between the two-

third and the three-quarter cases and the main point of interest is that a very small difference in the amount of kidney substance will turn the scale from the condition of simple hydruria which is compatible with good health for prolonged periods to a condition of polyuria accompanied by great wasting and leading rapidly to death. In these fatal cases the body temperature falls, but there are no other signs of uræmia; vomiting, coma, convulsions, and dyspnœa are conspicuous by their absence, the only marked symptoms being progressive weakness, emaciation, and subnormal temperature.

Amongst the salts excreted in the urine the aromatic sulphates are of interest as showing that substances elaborated in the alimentary canal may be absorbed and excreted by the urine instead of being voided by the rectum and thus it is possible that when the excretory functions of the kidneys are impaired auto-infection from the alimentary canal may ensue.

III. Synthetic activity of the kidney.—The kidney is known to effect at least one synthesis—namely, the formation of hippuric acid from benzoic, and the view has been advanced that this organ also makes uric acid possibly from urea; that, however, is a question that from the physiological standpoint requires a great deal more investigation before it can be definitely accepted.

IV. Metabolic activity of the kidneys.—I have advanced the view that in addition to the well-known functions of the kidney enumerated above this organ has a further function of in some way influencing the metabolism of the tissues so that when the quantity of kidney substance present is greatly reduced the proteid tissues, and more especially the muscles, break down and liberate urea. This view is based on the following experimental facts: (1) when the quantity of kidney is reduced to one quarter of the original total kidney weight the quantity of urea excreted in the urine is increased; (2) the amount of urea in the blood is greatly increased at a time when this increased excretion of urea is going on; (3) there is great emaciation even if the appetite is maintained and the emaciation cannot be arrested by the most abundant diet; and (4) if the appetite be completely lost and no food be taken the amount of urea in the urine may remain at a level as high as that at which it stood when the normal animal was eating freely and maintaining its body weight.

I think it is clear from a consideration of these facts that after such operations the production of urea is increased, and in the light of the great emaciation and the muscular weakness that ensues it is at any rate probable that the urea is derived from the muscles. The increased production of urea is determined by the quantity of

kidney removed, or, to be more accurate, by the quantity of kidney remaining. It is not brought about by any reflex effect produced on the nervous system by the operation. This is seen to be the case from the consideration of two facts: first, the removal of portions of both kidneys does not lead to this increased production, although under these circumstances the maximum mutilation is inflicted, and therefore if it were a reflex effect or indeed if it were due to any disturbance of the nervous system the increased production of urea ought to occur in these favourable conditions; and, secondly, the occurrence or not of polyuria depends entirely on the size of the fragment of kidney found post mortem and very often a greater mutilation and a more severe operation may result in the removal of quite a small wedge, whereas in another case a large wedge may be readily and easily removed. There is, however, no exception to the statement that whatever the mutilation or severity of the operation the question of the occurrence of the polyuria is entirely a question of the weight of kidney substance found post mortem. In this respect these kidney experiments present a remarkable resemblance to the experiments on the pancreas with reference to diabetes and to those on the thyroid with reference to myxœdema. In all these cases the results are entirely dependent upon the quantity of gland left. In the case of the thyroid there is definite evidence that the phenomena following its removal are at any rate largely due to the cessation of the action of an internal secretion; in the case of the pancreas this is also probable. Although it is quite possible that this is so with the kidney also there is no conclusive evidence to this effect, since for this to be the case it would be necessary to show that the ill effects seen after removal of the larger amounts of kidney can be arrested or at any rate benefited by the injection of the kidney extract, but such experiments have not as yet been carried out. Brown-Séquard considered that the so-called uræmia produced by the experimental removal of the kidneys could be benefited by the administration of kidney extract, but beyond this fact there is not, I believe, any clear evidence in favour of the view of the existence of an internal renal secretion, probable as such an hypothesis is for some reasons.

If the views advanced above are correct, that the kidney controls in some way the metabolism of the proteid tissues of the body, it is difficult to see how this can be effected except by the agency of an internal secretion, since the effect is not one produced through the nervous system, as division of the renal plexus not only does not produce any analogous effect but division of the renal plexus in no way modifies the effects of partial nephrectomy.

Another point of interest in the physiology of the kidney as bearing on the pathology is the amount of kidney substance necessary in order for life to be maintained. This can be deduced from a comparison of the two series of experiments—the fatal one where three-quarters of the total

kidney weight had been removed and the other the non-fatal series where but two-thirds had been excised and where life was maintained for an indefinite period in good health. The comparison of these two series shows that when the animal possesses some 2 grammes or more of kidney per kilo of body weight life can be maintained in good health but when the amount of kidney substance is less than 2 grammes per kilo the typical disturbance of nutrition described above sets in and the animal dies. The normal amount of kidney in dogs such as those used in the above experiments is approximately some 6·7 grammes per kilo. The comparison of the kidney weight with the body weight gives practically the same result as the direct estimation of the kidney weight, that is to say that as soon as there is less than one-third of the original quantity of kidney the danger limit is reached and a very small amount of renal tissue will turn the scale. Prolonged life with much less than 2 grammes of kidney per kilo is impossible, but some experiments suggest that the duration of life even in the fatal series is influenced by the amount of kidney—thus the longest duration of life was fifty days and the amount of kidney was 2·1 grammes per kilo. In another case the duration of life was six days and the amount of kidney was 0·9 gramme per kilo.

Although the effects on metabolism are so marked when three-quarters of the total kidney weight have been removed and are so slight when two-thirds have been removed, yet the transition from the fatal to the non-fatal series is probably a gradual one. A careful analysis of the non-fatal series with the larger amount of kidney left shows that this series contains some animals where there was slight emaciation and some increase in the urea excretion, so that it is quite possible that these animals if they had been kept for a more prolonged period might have succumbed to a more chronic form of the disorder. When the quantities of kidney substance removed are still greater than three-quarters of the total kidney weight—e.g., four-sixths, five-sixths, or even nine-tenths, the small fragments left excrete urea freely and I have quite failed by partial nephrectomy in producing a kidney fragment that was unable to excrete urea freely. For this reason, in addition to those mentioned above, I think it is evident that the disordered metabolism induced by the operation can in no way be related to any impediment in the excretion of urea, but that it must be dependent upon a disordered production, as mentioned above.

These operations, even when fatal, have not caused the development of any typical uræmic symptoms except a fall in body temperature; coma, convulsions, dyspnœa, and vomiting have been absent; diarrhœa has sometimes been present and in a few cases where the marasmus was of rapid development considerable quantities of indican have been found in the urine. Indicanuria is a phenomenon frequently associated with the breaking down of proteid material in the

body either in the tissues or in the alimentary canal. In some observations it was present where no food was eaten and was thus similar to the increased excretion of indican seen in starvation.

The blood in the fatal series contains a great excess of nitrogenous extractives and more especially urea; the increase of urea in the blood in the fatal series may amount to as much as twenty times the normal. This increase in the blood is present at a time when the increased excretion in the urine is in full swing. The increase in nitrogenous extractives, however, is not confined to the blood, but it is also seen in the tissues such as the muscles, the liver, and the brain, and it is more especially marked in the muscles. The percentage amount of nitrogenous extractives is much higher in the muscles than in the liver and approximates to that found in the blood. Although in the case of blood the increase in the extractive matters is practically confined to an increase in the amount of urea this is not so in the muscles; here there is not only a great increase in the amount of urea—i.e., nitrogenous extractive soluble in absolute alcohol—but there is also a great increase in the nitrogenous extractives insoluble in absolute alcohol but soluble in rectified alcohol. Hence the increase in the total amount of nitrogenous extractive matter in the muscles is still greater than it appears at first sight when compared to those present in the blood. It is a little remarkable that the increase in the liver should be less than in the muscles, but this was always observed. Great as the increase in the blood is, yet owing to the fact that the muscles form the bulk of the body the great bulk of the increase in these nitrogenous extractives is in the muscles and not in the blood. As the increase in these nitrogenous extractives was so marked in the muscles, this suggested that these bodies were formed there directly from the muscle proteids as a result of the deficient amount of kidney. In order to check this observations were made on the distribution of nitrogenous extractives and of urea after (1) double nephrectomy and (2) injection of urea into the circulation after preliminary ligature of the ureters.

1. *Double nephrectomy.*—After complete double nephrectomy the distribution of the nitrogenous extractives in the body is very similar to that seen after partial nephrectomies described above. There is a great increase in the blood, a great increase in the muscles, and a smaller increase in the liver. The percentage increase in the muscles may equal that found in the blood as regards the amount of nitrogenous extractive matter soluble in absolute alcohol, but the increase in those insoluble in absolute but soluble in rectified alcohol is very great in the muscles and small or absent in the blood. Speaking broadly, in the blood the great increase is confined to bodies of the urea type, whereas in the muscles there is not only a great increase in this but also in bodies of the creatin class.

2. *The injection of urea.*—After the injection of urea the greatest increase is found in the blood, the next greatest in the muscles, and the least in the liver, so that here again there is a similarity of distribution, but there are at least two striking differences. In the first place the increase in the blood, muscles, &c. is confined to material soluble in absolute alcohol, and there is therefore no marked increase in the nitrogenous extractives soluble in rectified alcohol. In the second place, and of much more importance, is the fact that although the percentage in the muscles is greater than that in the liver it does not approximately equal that in the blood as is so frequently the case after double and after partial nephrectomy—in other words, after complete double or after partial nephrectomy there is a more uniform distribution of the increase of these extractives in the blood and muscles, but after the intravenous injection of urea the only great increase is in the blood. This, however, is not the case if the animal is allowed to survive the injection for some hours—then there is a more uniform distribution of the injected urea in the blood and muscles.

These facts are of considerable importance in estimating the significance of the increased amount of nitrogenous extractives found in the blood and tissues after double and after partial nephrectomy. The injection of 20 grammes of urea may cause a percentage increase in the blood equal to that seen perhaps in a case of double nephrectomy, so that it might be supposed that but 20 grammes of urea were retained in the latter case, whereas a comparison of the muscle extractives in the two cases shows that in the partial nephrectomy case the actual amount of urea in the body must be far and away greater than in the case of the injection of urea, although perhaps the percentage amounts in the blood of the two cases may be fairly equal. I insist on this great increase in the nitrogenous extractives in the muscles after partial nephrectomy, and at a time when the urea excretion is increased, as I think it is a fundamental point in estimating the significance of these experiments. It is only in the cases where three-quarters of the total kidney weight have been removed that this greatly increased amount of nitrogenous extractives is present in the blood and tissues. In the cases where two-thirds of the kidney weight have been removed and where life has been maintained and hydruria only produced a slight increase in the urea excretion was sometimes seen, and in these cases there was a slight increase in the amount of urea in the blood, nothing, however, comparable to that seen in the fatal series, but still an increase. Normally, in the dog 0·015 to 0·02 would be a fair average for the amount of urea per cent. in the blood. In the fatal series this may rise to 0·3 per cent., but the highest percentage seen in the non-fatal series was 0·06 per cent. This is another fact showing that no hard-and-fast line can be drawn between the non-fatal and the fatal cases and is, I think, further evidence that the kidney

in some way controls the production of urea as well as its excretion. Inasmuch as in the three-quarter cases it is quite impossible to hold the view that the kidney fragment is unable to excrete urea and that the increased amounts in the tissues are due simply to retention, in the two-third non-fatal cases this view becomes still more untenable.

The general blood-pressure remains high both in the cases where two-thirds and where three-fourths of the total kidney weight have been removed, notwithstanding the marasmus and the cachectic condition of the animals in the latter series. In this respect the blood-pressure in these cases is in striking contrast to the general blood-pressure seen after double nephrectomy, as here it falls rapidly and greatly. The blood-pressure in the carotid after removal of three-quarters of the total kidney weight varied from 94 to 100 mm. of mercury. This height of blood-pressure is fairly comparable to that seen in the normal dog and it cannot be said to be increased absolutely, but seeing the wasted and feeble condition of the animal it has certainly increased relatively. I have, however, failed to produce experimentally by this operation any permanent increase in the blood-pressure at all comparable to the well-known increase seen in many renal diseases, and even in cases that survived and are still surviving the operation of removal of some two-thirds of the total kidney weight performed some eighteen months ago the highest blood-pressure observed in the femoral artery, as estimated by Mr. Leonard Hill's instrument, was but 130 mm. I have also been unable to satisfy myself that any cardiac hypertrophy was present after these operations; but that is a very difficult matter to settle in dogs owing to the great variations in the size of the heart normally, and hence the height of the blood pressure is really a better measure of the absence of greatly increased arterial tension than observations on the size and weight of the heart. These observations would tend to confirm the view that although heightened arterial tension is a familiar phenomenon in certain renal diseases and although often associated with renal disease in which there is a great diminution in the amount of kidney substance, yet it is not entirely dependent upon that diminution.

LECTURE II.[1]

MR. PRESIDENT AND FELLOWS,—In my last lecture I detailed at some length the results following partial nephrectomies (of varying degrees of severity) both on the composition of the urine and on the general metabolism of the body, and I trust that I showed that whereas all partial nephrectomies increased the flow of urinary water only the more severe ones increased the excretion and production of urea. We will now consider some of the results following complete double nephrectomy.

Experimentally the phenomena following the cessation of the renal functions may be studied by three different methods of procedure: (1) ligature of the renal arteries; (2) complete removal of the kidneys; and (3) the ligature of the ureters. The first method is on the whole unsuitable, since there is always a certain amount of doubt as to the extent of the collateral blood supply, and therefore in all my observations either both kidneys were removed or both ureters ligatured. When the kidneys were removed this was done in two operations in order to minimise the effect of shock, &c., and this was more especially done in order that an accurate comparison might be made between the effects of double nephrectomy on the one hand, and the effect of double ligature of the ureters on the other. The ligature of both ureters from an operative point of view is a trivial procedure, especially if they are both ligatured through an incision near the pubes. On the other hand, the removal of both kidneys at once, whether through one incision or by two lumbar incisions, is a very severe operation and thus it is misleading to compare the immediate effects of the two proceedings. The removal of one kidney in the dog is an operation which does not cause much shock and with due care hæmorrhage may be avoided. Even when the second nephrectomy is performed and the only kidney present is removed it is astonishing to see the small amount of shock that is produced. The animal is in no way collapsed and immediately after recovery from the anæsthetic may run about and behave very much like a normal animal, so that, provided the kidneys be removed like this, in two stages, there is no objection to contrasting the effects following the operation with those seen after ligature of both ureters.

In all the experiments on this question care was taken that full antiseptic precautions were used and in but one

[1] Delivered on March 17th.

case was there any peritonitis either local or general. This is a point of very great importance and it is not improbable that many of the symptoms described formerly as following complete nephrectomy were really dependent upon the presence of septic peritonitis and not upon the absence of the kidneys.

The duration of life in dogs after complete nephrectomy carried out, as above described, in two stages is usually from three to five days, the animals in no case living beyond the fifth day and more usually dying on the fourth day. During the first two days very little amiss is to be noted about the animal except that the appetite is poor and that after the first day all food is liable to be refused. Muscular weakness begins to show itself on the second day, is well marked on the third day, and progresses steadily, but the nephrectomised animal is usually able to run about even on the third and perhaps on the fourth day. Thirst is sometimes present, but not as a rule to a marked extent. Wasting is very marked and progressive; for instance, one dog weighing six kilogrammes lost three-quarters of a kilogramme in from three to five days. The most characteristic feature apart from the weakness and wasting is, however, the course of the body temperature. At the time of the operation the rectal temperature is probably between 101° F. and 102° F. Within twenty-four hours of the operation it falls to 100°, on the second day after the operation the temperature had probably fallen to 99°, and on the third day to 98° or even to 97°. The fall is a continuous and progressive one and the animal remains active and lively until the temperature reaches from 98° to 97°. When the temperature falls to 96° the animal is really in a moribund condition although it may reach 95° before death actually occurs. The course of the temperature chart is the best indication of the probable duration of life. These are the most prominent symptoms seen after double nephrectomy and it is most important to bear in mind that certainly for three days and sometimes for longer the animal not only remains conscious but is active and lively and able to run about. As death approaches the weakness increases and there may be slight drowsiness, but this is never a prominent symptom, and personally I have never seen in nephrectomised dogs anything approaching to coma. Vomiting is also not a conspicuous symptom and in this my experience is contrary to that of the older observers and I cannot help thinking that the vomiting observed and made so much of by Bernard and others was really due to septic complications such as peritonitis. Vomiting, as just mentioned, is not a conspicuous symptom, and sometimes it is completely absent. In others it is present towards the end after the third day. Convulsions I have never seen, and that very constant uræmic symptom, dyspnœa, is also not conspicuous. Slight diarrhœa may be present. It will be seen from the above sketch of the symptoms following complete double nephrectomy that they only very distantly resemble the clinical picture

of acute uræmia or at any rate of the acute uræmia seen in Bright's disease.

The results following the ligature of both ureters are very similar if not identical with those seen after complete nephrectomy, and I have been quite unable as yet to differentiate in any way between the symptoms produced by those two procedures. The duration of life after ligature of both ureters was if anything rather shorter than after complete nephrectomy, but this may have been due, although improbably, to both ureters having been tied at once. The animals usually died in from three to four, instead of from three to five, days, otherwise the symptoms were practically identical. Vomiting was observed in one case especially after drinking, and in this case some local peritonitis was found, the ureters having been ligatured by two separate incisions in the lumbar region. The vomited fluid yielded no gas by the hypobromite method, and I think it most probable that the vomiting arose from the peritonitis, as this was the only instance in the series where this symptom was at all marked.

The fact that whether the renal functions be abrogated by the complete removal of the kidneys or by ligature of both ureters the resulting symptoms are practically identical is, I think, a factor of some importance with regard to the nature of uræmia. Ligature of the ureter experimentally invariably leads to the production of hydronephrosis, and in no case was the obstruction of the ureter followed by that complete suppression that has been observed in man after complete obstruction of the ureter. Inasmuch as the ligature of the ureter is always followed by hydronephrosis it might be argued that the results following this operation ought not to be similar to those seen after complete double nephrectomy. That this is so, however, can be shown not only by the facts already detailed but also by the fact that after the removal of a large portion of one kidney the disturbance of nutrition and the alteration in the urine described in my last lecture are seen to follow equally well whether (*a*) the opposite kidney be excised or (*b*) whether the ureter of this kidney be tied. Not only are the same effects produced but the duration of life with the fragment of one kidney is in no way prolonged by the fact that the ureter of the opposite kidney is tied instead of that kidney being removed. A further and perhaps even more conclusive proof of the same fact is the following: ligature of the ureter causes hydronephrosis, if after the production of this the ureter be cut down upon and opened and the hydronephrosis drained the kidney returns to its former shape but not to its former size. It is to the eye apparently a normal but small kidney. On microscopic examination such a kidney shows that the epithelium of the tubules has undergone a peculiar change, the cells shrinking and losing their granules and becoming glass-like in appearance; the nuclei, however, stain, although the protoplasm of the cells is quite clear. These appearances

suggest that these are resting cells not capable of performing their usual functions. Such a kidney secretes a clear acid fluid containing little if any urea. Although it secretes such a fluid comparatively freely, such a kidney is, however, quite useless to the economy, and if the opposite healthy kidney be removed, all the phenomena characteristic of double complete nephrectomy are seen. This experiment shows two things—in the first place that ligature of the ureter permanently damages the epithelial cell structures of the kidney, for these are more affected than the glomeruli (and there is no overgrowth of fibrous tissue), and in the second place it affords another demonstration that the essential portion of the kidney is the epithelium lining the convoluted tubules. This experiment is in striking contrast to those described in the first lecture, where a small fragment of normal kidney was shown to be capable of maintaining the renal functions for an indefinite period. An entire kidney that has been exposed for even a short time—i.e., fourteen to twenty one days—to the effects of the complete obstruction of the ureter with consequent hydronephrosis is unable when that obstruction is removed by draining the distended ureter to perform renal functions that are of any avail in prolonging life. Such a kidney is practically useless to the animal, although, as mentioned above, it is able to secrete an acid, clear liquid. It is probable that this is a glomerular secretion, modified it may be by the amount of damage that has been inflicted on the glomerulus by the increased pressure that has been produced in the glomerular chamber by the ligature of the ureter. At any rate, the ligature of the ureter leads to much more pronounced and permanent lesions in the epithelium of the tubules than it does in the glomeruli, and it seems to me that by this method of tying the ureter and subsequently draining the hydronephrosis so produced we may be able to differentiate in the mammal the functions of the glomerular chamber from those of the convoluted tubules. I have with this object in view some observations in progress at the present time. As ligature of the ureter causes these changes in the epithelial structures of the kidney very rapidly it is not very surprising that ligatures of the ureters and removal of both kidneys should produce practically identical effects. This fact is an argument against the existence of an internal renal secretion, since in other cases where glands have an external and an internal secretion the ligature of the excretory duct does not produce the effect seen after the removal of the gland. This is undoubtedly the case with the pancreas and also with the liver, since in the latter case it is fair to look upon the glycogenic function of the liver as an internal secretion of a kind, and the ligature of the bile duct does not materially interfere as far as is known with the other and metabolic functions of the liver. Although it may be argued that the ligature of the ureter very soon destroys the activity of the cells of the

convoluted tubules, yet the production of the hydronephrosis and the fairly free secretion that continues after draining the distended ureter show that the secretory activity of the glomeruli at any rate persists, so that it cannot be said that ligature of the ureters is theoretically equivalent to the removal of the kidney. Some of the views held on the nature of the different forms of uræmia have been based on the idea that the results following complete nephrectomy and those following ligature of the ureters were different, and this, I think, is untenable from an experimental point of view, and I hope to adduce evidence later that it is equally untenable in the human subject.

After ligature of both ureters and after double nephrectomy there is of necessity a great accumulation of nitrogenous extractive matters in the blood and tissues and, as mentioned above, the increase in the muscles is not only very great but, unlike that in the blood, it is not confined to the nitrogenous extractives, such as urea, that are soluble in absolute alcohol, but those like creatin (insoluble in absolute alcohol) are also increased. The increase of urea in the blood after double nephrectomy or after ligature of both ureters may amount to some twenty times the normal 0·3 per cent., and even more is by no means exceptional. This same great increase is seen in the muscles, where normally there is no urea, the small quantities detected by ordinary procedures being in all probability dependent upon contamination with blood. The amount of other extractives in muscles after nephrectomy may be nearly trebled, and seeing that normally there is as much as 0·2 per cent. of creatin this means that very large quantities of creatin and such like substances accumulate in the muscles after double nephrectomy. Similar large quantities of these extractives accumulate in the liver and brain. I have not been able to satisfy myself that there is any essential difference in these results whether the kidneys have been removed or the ureters tied.

The quantities of extractives in the blood are so large that the question naturally presents itself, and more especially in the light of the experiments on partial nephrectomy detailed in my first lecture, whether these quantities can be accounted for on the hypothesis that they are simply the products that cannot be excreted of a normal metabolism. If the views advanced in the first lecture are correct it is clear that after complete nephrectomy as after partial nephrectomy there should be increased disintegration of proteid material leading to the production of nitrogenous extractives in excessive amount. In order to test this theory experiments were performed to determine the distribution of urea in the blood and tissues after its intravenous injections in large quantities, the ureters being ligatured a few minutes before the urea was injected into the jugular vein. The animals were anæsthetised with chloroform and morphia and killed by bleeding at periods varying from a few minutes to an hour and a half after the injection. The distribution

of urea in the blood and tissues was very similar to that seen after partial or double nephrectomy—that is to say, the muscles contained a greater percentage than the liver—but the very large quantities seen in the muscles after double nephrectomy were not seen after the injection of urea unless huge quantities were injected. Further, as the amount of urea normally excreted by the dogs before nephrectomy could be readily determined and the duration of life after the complete nephrectomy was known it was quite possible to calculate how much urea the nephrectomised dog should have produced but was unable to excrete owing to the absence of the kidneys. This quantity of urea was then injected into a dog of the same weight as the nephrectomised animal and the results of the analysis of the tissues were compared in the two cases. In all the cases, four in number, where this was done the amounts of urea, &c., as determined in the nephrectomised animal were greater than in the control animal which had received the amount of urea that theoretically should have been found in the nephrectomised animal. In these observations the other extractives were neglected but, as pointed out above, after nephrectomy these are also increased, so that I think there is clear evidence that after complete double nephrectomy the amounts of nitrogenous extractives in the blood and tissues are greater than can be accounted for on any hypothesis of simple retention. I think that the results following double nephrectomy are quite in accordance with those described above as seen after severe partial nephrectomy (removals of three-quarters of the total kidney weight) and that we must admit that whether the kidney be entirely removed or greatly diminished in amount in both cases there is a sudden and great disintegration of the proteid tissues of the body leading to the production of this large excess of nitrogenous extractives. After double nephrectomy practically no food is eaten and there is rapid and great wasting, so that these extractives have a tissue origin and, as insisted on above, the same is the case after the more severe partial nephrectomies.

I have described at some length the results obtained by experimentally investigating the effects following the operations of nephrectomy partial and complete. Now I propose to consider shortly some results obtained clinically by the investigation of cases of chronic renal disease, more especially with reference to the influence of this disease on the formation and the excretion of urea. Speaking broadly, the tendency of chronic renal disease is to cause a diminution in the excretion of urea, or at least this is the common teaching on the subject, and no doubt it is to a great extent true, but when this diminished excretion of urea is referred entirely to a supposed incapacity of the damaged kidney to excrete such bodies the basis of this view is not so sound. It is irrational to expect a patient suffering from chronic renal disease to excrete quantities of urea comparable to the normal for the following reasons: the appetite

is poor and frequently a considerable amount of what food is taken is rejected by vomiting, diarrhœa is also frequently present, and all these factors will seriously diminish the amount of proteid available for disintegration into urea. Albuminuria is often present and frequently is excessive in amount, and perhaps this loss is greatest where it is not always suspected—namely, in persons with chronic renal disease passing a considerable quantity of urine with a moderate or even a low percentage, such as a third or a quarter, of albumin. The greatest losses of albumin do not occur in cases where the percentage amount of albumin is highest, since in such cases the quantity of urine passed is usually greatly diminished A daily loss of 20 grammes of dry proteid is by no means exceptional in renal disease and in some cases the amount rises to as much as 40 grammes. Lastly, in dropsical patients a considerable quantity of urea and other extractives is retained in the dropsical effusions. All these causes operate in tending to diminish the amount of urea that can be excreted by the kidneys, and it is most misleading to compare the urea excretion of such a patient with the normal text-book amount of 30 grammes per diem excreted by a healthy person on a diet sufficient to maintain the body weight and to argue that an excretion of 20 grammes per diem or less is dependent entirely and directly upon the renal lesion. In many cases of chronic renal disease quantities of urea not greatly below the normal amount may be excreted even at a time when the patient is very seriously ill and even in a very dangerous condition, and this remark applies more especially to the cases where dropsy is absent. It is more especially true in the cases of what is called the "contracted white kidney," a grave form of Bright's disease in which the quantity of urine is considerably increased and contains 1 or even 2 per cent. of albumin. No doubt in the cases of chronic Bright's disease associated with dropsy and also where cardiac lesions such as mitral disease are present the urea excretion undergoes a great diminution. Personally I consider that a better notion of the state of the kidney lesion can be formed by observing the quantity and specific gravity of the urine than by observations on the amount of urea. The latter are often misleading for the reasons mentioned above. The quantity of water excreted, particularly if it is controlled by other observations, gives most reliable and valuable information ; copious dilute urine, if not due to the presence of waxy disease (by no means so common now), is a matter of grave significance not only as indicative of the probable presence of what is ordinarily spoken of as the granular kidney but also as indicating the existence of other destructive diseases of the renal tissue such as the so-called contracted white kidney, cystic kidneys, &c. It is customary to consider that the excretion of this dilute urine is dependent upon the heightened blood-pressure that is so often seen in these kidney diseases, but the character of the urine approximates very closely with that described above as

occurring after partial and more especially after double partial nephrectomy. If this comparison be fair the quantity of dilute urine excreted may afford an idea of the extent of the destruction of renal tissue in disease, just as it does in the nephrectomy experiments, the greater the hydruria the less the available kidney substance. The comparison instituted between the experimental results and the results of disease is, however, fallacious ni one respect. Whereas in both the quantity of kidney is diminished in the experimental case what renal tissue remains is healthy, whereas this is not so in most diseased conditions even when the incidence of the disease is not absolutely uniform. In cystic disease of the kidneys, however, for a time at any rate, the remaining kidney tissue is practically normal, and there is, I think, a fairly close parallel here between the results of disease and the phenomena of the laboratory. In both a dilute urine is excreted, in both the renal tissue is greatly diminished, and in neither do cardio-vascular changes necessarily ensue. If the amount of water excreted can be correlated to the amount of kidney tissue left and so the experimental facts and the clinical facts be brought into harmony this cannot be done with regard to the urea excretion. Although it is a very familiar fact that patients with renal disease, and more especially perhaps patients with the more insidious and chronic forms of renal disease, such as contracted white kidney, granular kidney, &c., suffer from great weakness and wasting and the body temperature is low, yet the one striking difference between the two sets of results clinically and experimentally lies undoubtedly in the fact that whereas the urea excretion is increased in the latter it is apparently not in the former. I believe this discrepancy is due to the fact that in renal diseases the epithelium of the tubules is diseased and unable to excrete urea freely and in this respect it resembles the kind of epithelium described above as produced by ligature of the ureter. It will be remembered that the atrophied kidney that has been produced by ligature of the ureter is quite unable to excrete urea and that the epithelium of the tubules of such a kidney is glass-like and devoid of all the granules and striations that are so characteristic of renal epithelium. The other most striking difference between the effects of disease and the results of experiment is that whereas complete suppression is quite a common clinical occurrence as a result of obstruction of an ureter, yet it is not possible to produce this condition in the laboratory.

Extractives in the blood and tissues in renal diseases.—I have examined the blood and tissues in a considerable number of cases of chronic renal disease fatal from uræmia and in addition to this I have made a few analyses of the blood and of the dropsical exudations in cases that were not uræmic at the time the analysis was made. In a few instances subsequent analyses were made in the same cases

when death had occurred from uræmia. In addition there is a series of analyses in cases where complete and fatal suppression resulted from a variety of causes. In all cases the blood was received into an excess of absolute alcohol, this was evaporated, the residue dissolved in absolute alcohol, again evaporated, and extracted with water. The filtered watery extract was divided into two portions; in the one the amount of nitrogen liberated by the Dupré process (hypobromide of soda) was measured and in the other half the total nitrogen present was determined by the Kjeldhal process. In this way a control on the Dupré estimate was obtained. The blood was obtained usually within twelve hours of death; in some cases where venesection had been employed in the treatment of uræmia the blood was received fresh.

Five cases of complete suppression were examined. In three of these the suppression arose as the result of calculous obstruction. The first case was a remarkable one of double calculous anuria; in the other two the ureter of the only efficient kidney was blocked by a stone. The other two cases were patients in whom suppression resulted, in the one case apparently reflexly as the result of latent peritonitis set up by the perforation of a duodenal ulcer, and the fifth case was a very remarkable if not an unique one where endarteritis and thrombosis of all the small arteries of the kidney led to complete necrosis of the cortex of both kidneys and caused complete suppression of urine.[2]

All these patients presented clinically the phenomena described by Sir William Roberts as characteristic of calculous suppression—that is to say, that until shortly before death there were none of the most typical and characteristic phenomena of uræmia, such as coma, convulsions, dyspnœa, &c. The following conclusions can be drawn from these cases. There is an enormous increase in the amount of urea in the blood and far greater than is usually supposed: thus 0·015 per cent. may probably be taken as a fair average for the amount of urea normally present. In Case 5, living nine days, there is approximately thirty times the normal amount present. Secondly, the increase is fairly proportionate to the duration of life; thirdly, patients at the time of death have very different amounts of urea in the blood, thus confirming the old views that in all probability death cannot be attributed to the mere excess of urea, although when the percentage in the blood and tissues reaches the higher amounts mentioned above there may be as much as eight or ten ounces of urea in the body.

I have only one analysis of a fatal case of acute Bright's disease with suppression and without dropsy and there the

[2] Published in detail in the forthcoming number of the Journal of Pathology.

percentage of urea in the blood was 0·35, which is comparable in amount with the quantities seen in complete suppression. In another case of Bright's disease fatal from pneumonia and where uræmic fits were present there was 0·12 per cent. of urea. In another case acute Bright's disease was seen as a complication of diabetes mellitus and this is rather remarkable and a few details will be necessary. This was a case of a diabetic of some duration and acute Bright's disease supervened. The urine was loaded with albumin and blood and deposited that peculiar grumous sediment so characteristic of acute Bright's disease. Although the urine presented all these characteristics of acute Bright's disease and also in addition abundant casts, yet the quantity passed was considerable—e g., 100 oz. I think this case peculiar and interesting in the fact that notwithstanding the very acute and fatal nephritis the presence of diabetes caused the excretion of a copious urine. The blood in this case contained 0·072 per cent. of urea—that is to say, a compara

Table showing some Results observed in Five Cases of Complete Suppression of Urine.

No.	Percentage of urea in the blood.	Duration of life.	Cause of anuria.
1	0·15	Two days	Reflex from perforative peritonitis.
2	0·277	Five days	Calculous suppression.
3	0·324	Six days	Calculous suppression.
4	0·36	Seven days	Endarteritis and thrombosis of renal arteries.
5	0·44	Nine days	Calculous suppression.

tively small increase; there was no dropsy. The amount is comparable to that found in another case of diabetes fatal from coma and where the kidneys were not seriously diseased and where some 0·096 per cent. of urea was present. In a third case of diabetes also fatal from coma the amount of urea in the blood was 0·06 per cent

In chronic Bright's disease the amounts of urea found in the blood vary within wide limits even at the time of death and more especially according as to whether the dropsy was present or not and whether death resulted from uræmia or from some other complication. The blood, however, may contain an excess of urea at the time when the patient is apparently in good health. Thus a certain patient presented a mitral systolic murmur and a trace of albumin in the urine. The general health was quite good and she was up and about and attending to household duties. Fatal syncope occurred suddenly whilst at a meal and post mortem it was found that the cardiac lesion was secondary to unsuspected renal

disease and the blood of this patient contained 0·08 per cent. of urea.

The amount of urea in ascitic and pleuritic fluids will also give a fair indication of the amount present in the blood. It is not exact, as for that purpose a comparison should be made between the ascitic and pleuritic fluids on the one hand and the blood plasma on the other. But for all practical purposes the analysis of the dropsical effusion of renal disease gives an approximate indication of the amount of urea in the blood, erring on the side of making the amount greater than it really is.

In a case of chronic Bright's disease fatal with general dropsy the ascitic fluid contained 0·039 per cent. of urea one month before death and 0·046 per cent. three weeks before death; at death the blood contained 0·1 per cent. In another case six weeks before death the pleuritic fluid contained 0·15 per cent. at the time when the patient was excreting 20 grammes of urea per diem on a diet of 2000 c.c. of milk. This patient, however, died from uræmia and the percentage in the blood at death was 0·44 per cent. Two other cases of chronic Bright's disease, fatal and accompanied with general dropsy, showed that the blood at the time of death contained 0·16 per cent. and 0·07 per cent. of urea respectively. All these observations and others that I need not quote show that with chronic Bright's disease, with and without general dropsy, there is an increase of urea in the blood even when the patient is fairly well and that this increases at death, as would be expected, but the increase is not so great as that seen in suppression unless uræmia occurs.

It is, however, in uræmia that the greatest increase is found and the following statements are based on the analysis of the blood in twenty-five cases of fatal uræmia unaccompanied with dropsy. The highest percentage of urea in the blood was 0·5 per cent. This was observed twice. In one case the amount was 0·46 per cent., in nine other cases the amounts varied between 0·3 per cent. and 0·4 per cent., so that in half the cases investigated the percentage of urea in the blood was between 0·3 and 0·5. In all the other cases the quantity varied between 0·2 per cent. and 0·3 per cent. and in no case of chronic Bright's disease, fatal from uræmia and unaccompanied by dropsy or some inflammatory complication, did the percentage sink below 0·2 and, in fact, this smaller amount was only seen in two cases. The quantities of urea found in the cases of Bright's disease, fatal from uræmia, are comparable with the quantities found in the cases of complete suppression that lived approximately one week from the time of the onset of the suppression. There are, however, at least two points of difference between the two series of cases. In the suppression series there was always complete suppression of urine and this in my experience is uncommon in the acute anæmia complicating chronic renal disease unassociated with dropsy. In the second place, the dura-

tion of life after complete suppression was at least six days when the percentage of urea reached 0·3, whereas in acute uræmia life was not prolonged for more than from two to three days from the onset of acute symptoms in most cases. One case was exceptional and presented acute uræmic symptoms for more than a week and it is of sufficient interest to quote in detail. The patient was bled with great relief on account of the onset of uræmic symptoms on Feb. 25th and the average of three determinations of the amount of urea in the blood yielded 0·13 per cent. The venesection was followed by considerable improvement, but the next day the patient again became comatose and a second venesection was performed with very beneficial results. This second specimen of blood yielded 0·24 per cent. of urea. During these two days the urine was passed unconsciously and could not be collected. From Feb. 28th to March 3rd it could be collected in part and the daily average for these days was at least twelve grammes and certainly much more was passed as the patient passed a considerable quantity unconsciously and also some with the stools. The benefit of the venesection was temporary, the uræmic symptoms returned, and the patient died on March 3rd, and the blood contained 0·3 per cent. of urea. This case illustrates several points, and more especially shows the onset of uræmic symptoms when the percentage of urea in the blood was still low, and the further point that a very great increase in the amount of the extractives in the blood may take place whilst there is still a considerable excretion of urea, since it must be borne in mind that, in the first place, all the urea was not recovered, and, in the second place, that little or no food was taken, and hence it will be seen that the urea excretion in this case was by no means so small as it appears to be at first sight. This case was investigated more thoroughly than any other, but in another case where there was 0·38 per cent. of urea in the blood some 8 grammes of urea were recovered from the urine in the preceding twenty-four hours notwithstanding the loss of some urine and the presence of severe diarrhœa and persistent vomiting.

All these observations tend to the same conclusion, that in uræmia there is a very great excess of urea in the blood, even greater than in most cases of complete suppression, and there is not only not necessarily complete suppression of urine, but quantities of urea may be passed in the urine that are not very inadequate considering the condition of the patient.

We have as yet only considered the presence of extractives in the blood, but there is a similar, and in fact a greater, increase in the tissues, and as in he experimental cases, this increase is especially marked in the muscles. In the muscles there is not only an increase of urea approximately equal in percentage amount to that seen in the blood, but in addition there is a corresponding or even greater increase in the other extractives belonging to what may be called the creatin group. These are not present to any great extent in the

blood even in uræmia, but the excess in the muscles is very notable. I have been able to examine the blood in two cases of eclampsia and here the percentage of urea in one case was 0·06 per cent. and in the other 0·036 per cent., confirming former observations that in this malady there is a striking difference between the state of the blood and that found in uræmia. In one of the fatal cases of eclampsia it is of some interest that the urine was highly albuminous and contained considerable quantities of blood; in point of fact there was nephritis, but notwithstanding this the percentage of urea was but 0·036. Thus the greatest excess seen in eclampsia was only four times the normal.

The conclusions drawn from the examination of the blood and tissues in renal disease may be shortly summarised as follows: (1) in suppression there is a great increase in the nitrogenous extractives in the blood and tissues; (2) in acute uræmia without dropsy there may a be still greater increase; (3) in chronic renal disease fatal from other causes there is some increase, but not comparable with the above; (4) in renal disease even in apparent good health there is a certain small excess; and (5) in eclampsia the excess is trivial in amount.

LECTURE III.[1]

URÆMIA.

MR. PRESIDENT AND FELLOWS,—Having discussed in the last lecture the results of nephrectomy in animals (dogs) I propose to deal to-day with some of the phenomena of uræmia as seen clinically in renal diseases. Uræmia may perhaps be defined as a toxæmia which is apt to supervene either during the course of, or as a terminal phenomenon in, renal diseases or disorders. Although it may occur in any form of renal disease it is, as is well known, most frequently seen in the young and more especially, perhaps, in those forms of chronic renal disease, such as certain varieties of contracted kidney, where the quantity of kidney substance is very greatly reduced in amount. Although uræmia is sometimes seen in what may be called the ordinary granular kidney (the raspberry kidney) associated with general arterial degeneration, yet it is not the natural termination of this malady. The more characteristic mode of death is either from cerebral hæmorrhage or else from secondary cardiac disease, the heart failing as a result of the long-continued increased pressure to which it has been subjected. Although uræmia may occur in cases of granular kidney associated with extreme arterial disease in the middle-aged or elderly, uræmia, and more especially acute uræmia, is peculiarly associated, in my opinion, with the contracted white kidney, which may probably arise either as an independent renal affection or secondarily as the sequel of some other form of nephritis, acute or chronic, such as, for instance, the so-called large white kidney. It is probable that several forms of renal disease are included under the terms "small white," or "contracted white," kidney, and certainly different specimens of this form of kidney differ greatly in their microscopic if not in their macroscopic appearances. In all forms of this disease, however, the amount of kidney tissue, and more especially of cortical tissue, is very greatly diminished and, speaking broadly, there is frequently a greater reduction in the amount of kidney tissue in this form of renal disease than in most if not in all cases of the true granular kidney. Such kidneys are small, weighing together probably less than seven ounces, sometimes as little as five or even three ounces. The capsule is thickened and on stripping tears the kidney substance but little, and leaves an exceedingly granular surface, the granulations being large and prominent. The cortex is greatly diminished in width and is of a pale-yellow colour or

[1] Delivered on March 22nd.

may be mottled; this appearance is seen both on section and externally. The medulla varies but is usually red and congested. The fat in the renal sinus is prominent. The condition of the vessels varies; sometimes there is extensive endarteritis, at other times this is not so conspicuous. Such a kidney is familiar to all pathologists. It is remarkable that although the appearances just described are fairly constant yet the state of the cardio-vascular system in these cases varies; usually there is cardiac hypertrophy and the other well-known vascular lesions associated with high tension, but cases are seen where although the kidneys conform in all respects to the description just given, yet neither during life nor after death are there any marked and obvious signs of the usual accompanying cardiac and arterial changes. I have seen cases where the kidneys were quite small, weighing together but from five to six ounces, and where post mortem cardiac hypertrophy was either absent or very ill-marked. Usually, however, it is a marked phenomenon The type of kidney just outlined can probably be recognised during life owing to both the clinical course and the composition of the urine being peculiar and distinctive. The urine is dilute, the specific gravity is low, and the quantity is either about the normal or it is increased. It is in my experience exceptional for it to be seriously diminished and it is most usually distinctly above the normal. These urines contain a considerable quantity of albumin, thus from one-sixth to one-third would probably be a fair estimate for the majority of cases. Clinically, I would say, such cases are characterised by the rarity of the occurrence of dropsy and the frequency of the presence of albuminuric retinitis, and most important of all by the fact that the patients die from uræmia, and usually from acute uræmia. I believe it is exceptional for cases presenting this clinical picture and characterised anatomically by the kidney lesion described above to terminate by the other complications of Bright's disease, such as dropsy, secondary inflammations, cerebral hæmorrhage, &c. These cases not only usually succumb to uræmia, but they tend to be associated with a particular variety of uræmia—namely, acute uræmia or even so-called fulminating uræmia, the *urémie foudroyante* of the French. Although this form of Bright's disease is, in my opinion, peculiarly associated with uræmia, yet acute uræmia occurs under other circumstances and more especially occasionally in acute Bright's disease and after the surgical exploration of the kidneys where these organs are diseased, as, for instance, where pyelitis is complicated by chronic Bright's disease or by waxy degeneration. Exploratory nephrotomy may, and not uncommonly does, under such circumstances lead to fatal uræmia.

Eclampsia is a variety of acute uræmia, but in some ways this affection is quite different from the uræmia seen in renal cases and need not be further considered here.

Chronic or subacute uræmia or gastro-intestinal uræmia,

as it is sometimes called, is probably more especially associated with that form of chronic Bright's disease which is accompanied by dropsy and where the kidneys are not only not greatly diminished in bulk but where these organs are larger than natural and come under the general description of large white kidneys. Chronic uræmia is also seen in other chronic destructive renal diseases, as, for instance, in cystic kidneys, and more especially perhaps in the so-called "consecutive nephritis" of the surgeon where the kidneys may be riddled with abscesses.

The form of uræmia described by Sir William Roberts as occurring in cases of obstructive suppression is so well known that little need be said as to its main features. It is undoubtedly very characteristic of cases of calculous suppression, but it is not, I believe, limited to these or even to cases of obstructive suppression, as I hope to show. The phenomenon seen in these cases of obstructive suppression may perhaps be termed "latent uræmia," as all the most obvious symptoms of uræmia are conspicuous by their absence, as pointed out by Sir William Roberts. Latent uræmia—that is to say, a condition where the patient remains for many days quite conscious, with no coma, convulsions, or dyspnœa, but where myosis, fall of temperature, occasional vomiting, and towards the end slight and rare twitchings of the voluntary muscles and perhaps slight drowsiness, may be present—has occurred in my experience in the following variety of cases: (1) calculous anuria and other varieties of obstructive suppression; (2) in the case already alluded to in Lecture II. and published in detail in the *Journal of Pathology*, where owing to endarteritis and thrombosis of the renal arterioles the entire cortex of both kidneys was necrotic; and (3) in a case where as the result of inflammation of a sacculus of the urinary bladder suppression ensued, and this notwithstanding the fact that the kidneys were not greatly diseased. It was most remarkable to see that in all these three different conditions the clinical symptoms were precisely similar and they were all regarded during life as typical examples of obstructive suppression. In the calculous cases this was the case but in the others the conditions were very different. In the one the patient practically had no kidneys, as, owing to the vascular lesion, thrombosis of the arterioles, the circulation must have been completely arrested, and in Case 3, although the kidneys were present and were apparently healthy and there was no obstruction to the ureters, yet there was complete suppression. is unnecessary to describe the symptoms seen in the cases of calculous anuria as they are now so well known, and it will suffice to state that the longest duration of life was nine days and the shortest five. It will be, however, necessary to describe shortly the other two cases where the symptoms during life were characteristic of calculous anuria but where the post-mortem examination showed no such condition.

A woman, aged thirty-six years, was admitted into University College Hospital on March 3rd, 1896, owing to inability to pass urine. The patient was quite well until Feb. 28th, on which day she was delivered of a dead full-term child. After her confinement she was sick once and she complained of headache and a feeling of slight drowsiness which had remained much the same till the day of admission. There had been no fits and no muscular twitchings, and the patient stated that she had passed no urine since her confinement with the exception of two drachms drawn off by catheter on March 2nd. She had had no previous illness, and there was no history of any swelling of the legs or any attack of lumbar pain. On admission the patient was perfectly conscious and rational and could answer all questions clearly and intelligently; she had no headache or sickness but she complained of thirst; her temperature was 98° F. and there was no œdema. On March 4th the patient remained in the same condition; the temperature fell to 97·8° and no urine was passed. On the 5th she was weaker but quite conscious and intelligent and the temperature reached 95·4°, and one and a half drachms of urine containing a trace of albumin were drawn off. On the 6th the patient was still quite conscious, there had been no convulsions, and no vomiting; she was decidedly weaker and the highest temperature was 96·4°. No urine could be obtained on catheterisation. On the 7th she was still quite conscious and rational and she died suddenly and apparently from failure of respiration. On post-mortem examination no urine was found in the bladder or in the pelvis of either kidney and there was no obstruction to the ureters. The two kidneys presented the same appearance and weighed 7½ oz. each, and it will be sufficient to say here that the entire cortex of both kidneys was of a bright buff colour and necrotic. The convoluted tubules throughout the cortical substance were found to be necrotic and this necrosis depended upon endarteritis of the renal arteries and thrombosis of the interlobular arterioles; the medulla was normal and there was no cirrhosis.[2]

I must apologise for quoting this case at length, but inasmuch as the lesion was such as to practically deprive the patient of both kidneys the case is a near parallel to the experimental removal of both kidneys and is therefore of very great interest and tends to the conclusion that the destruction of all the secreting tissues of both kidneys in the human subject does not necessarily produce uræmia in the ordinary sense of the word, notwithstanding the production of complete anuria. The second case, in which symptoms characteristic of obstructive suppression were seen and in which the post mortem examination showed no obstruction, is also of sufficient interest to be quoted in some detail.

[2] For full details see Endarteritis of the Renal Arteries Causing Necrosis of the Entire Cortex of Both Kidneys, Journal of Pathology, 1898.

A woman, aged thirty-eight years, was admitted to University College Hospital on Dec. 19th, 1897. The patient was a married woman, who was five months pregnant, and she said that she had had no previous illness except typhoid fever five years ago and that subsequently to this she had passed a gall-stone. She stated that she had been quite well until ten days before admission when she was seized with pain in the abdomen followed by vomiting and diarrhœa. The abdominal pain still persisted and there had been occasional vomiting. No urine had been passed since Dec. 18th, although she stated that up to that time she had had no difficulty and that she passed as far as she knew the usual quantity. She had never had any previous attack of abdominal pain or any similar difficulty with her urine. On admission on the evening of Dec 19th the temperature was 97° F., the pulse was 116, and the respirations were 12 per minute. She vomited several times during the night; no urine was passed and none was found in the bladder on passing a catheter, and there was very slight œdema all over the trunk and especially on the sternum (this has been noted as an occasional phenomenon by Sir William Roberts in cases of calculous anuria, and as in the case described by him so in this case the œdema, which was of the slightest description, disappeared before death). On palpation the abdomen was especially tender in the right lumbar region and the right kidney could be felt and seemed tender. On the 20th the vomiting was slightly less severe, the patient was conscious and rational, and the highest temperature was 97·8°. Two drachms of putrid urine were drawn off, containing a trace of albumin and showing numerous pear-shaped cells but no blood corpuscles and no casts. At 11 P.M. the catheter was again passed and five drachms of ammoniacal urine were drawn off. There was no muscular twitching and the temperature was 97 5°. On the 21st the temperature was still 97°, the pupils were small, the tongue was coated with brown fur, and in the twenty-four hours eight and a half ounces of urine were passed of specific gravity 1012; it was alkaline in reaction and contained one-twelfth albumin. Vomiting was still present, the œdema was less, but an erythematous rash had appeared on the left arm and hand. On the 22nd the bright-red rash had spread all over the body and also on to the face; the pupils were very small and the œdema had practically disappeared. Vomiting was still present and the patient was slightly drowsy and about five ounces of urine were passed. On the 23rd no urine was passed and none was obtained by catheter. The rash was fading, the temperature was 96, and the patient was slightly drowsy. She aborted at 3 P.M. The weakness and prostration gradually increased and she died at 10 P.M. Post mortem all the organs seemed healthy with the exception of the urinary bladder. The bladder was small and the mucous membrane was of a dark grey colour; about half an inch above the opening of the right ureter there was a small sacculus and the mucous membrane

of this was greyish black, swollen, and necrotic. There was a small patch of necrotic mucous membrane about one-third of an inch in diameter on the corresponding surface of the opposite side of the bladder. The kidneys were abnormal in shape and the lower half of the right kidney was partially separated from the upper part; and this kidney had two ureters which opened by separate orifices into the urinary bladder a quarter of an inch apart. The ureters were not dilated and there was no obstruction at the orifice of the ureters on either side. Microscopic examination of the kidney showed no signs of any gross disease; in fact the kidney seemed healthy. This case is also a remarkable one, and it would seem that the suppression must have arisen reflexly from the cystitis in the vesical sacculus. The patient lived nearly six days and secreted in that time some fourteen ounces of urine, so that the suppression was not quite complete, but it is quite comparable to what is seen in calculous anuria, as it is not at all uncommon for small quantities of dilute urine to be passed even in fatal cases. This patient, like the patient in the other case quoted above, did not present the usual clinical picture of ordinary uræmia, although vomiting was a slightly more prominent symptom than in many cases of calculous anuria, still it is not uncommon for severe vomiting to occur in some forms of calculous suppression and even for this symptom to be the most prominent and severe one.

I have quoted these two cases at length as showing what I think is a very important fact—that whether the functions of the kidney be arrested by blocking of the ureter or by destruction of the entire cortex or reflexly (even when the kidneys are apparently healthy) the resulting phenomena are those which we have been familiar with in calculous anuria or obstructive suppression and not those of acute uræmia seen in renal disease, although from the suddenness and the gravity of the lesions acute uræmia might well be expected to ensue in such cases. We may thus conclude that the train of symptoms which has been called above latent uræmia ensues not only when the ureters of more or less healthy kidneys are suddenly blocked but also when these kidneys are suddenly prevented from secreting by vascular or nervous disturbance. The results of clinical experience are thus in complete harmony with the experimental facts detailed in my last lecture and the train of symptoms produced experimentally and by disease are really precisely similar and in neither case are they the symptoms of acute uræmia. In disease we apparently meet with three rather than two forms of suppression of urine—that is, with obstructive suppression and two varieties of non-obstructive. One, as in the cases above described, where the activity of more or less healthy kidneys is suddenly completely abolished, and the other where suppression occurs during the course of acute or chronic renal disease and more especially perhaps in Bright's disease. It would seem as if it were not so much

a question of the symptoms of suppression being different according as the suppression was obstructive or non-obstructive but rather according as the suppression occurred as a complication of acute and chronic renal disease on the one hand, or on the other hand whether it occurred with fairly healthy kidneys. This is a matter not only of theoretical importance with regard to the nature of acute uræmia and its relationship to lesions of the kidney but also of practical importance in our treatment of such cases. In cases of calculous anuria there can be but little doubt that operative interference should be resorted to very early, but if the typical clinical picture seen in this condition is also seen where the suppression arises independently of any obstruction, as in the cases described above, and where surgery can be of no avail, it introduces a very serious and difficult question of differential diagnosis in such cases. From the theoretical point of view I think we must conclude that complete suppression of sudden origin and dependent either upon the obstruction of the ureters or upon certain acute lesions of the kidney causing entire cessation of the renal activities (such as the cases described above) does not produce acute uræmia. Having thus described at some length the conclusions I have arrived at in reference to so-called latent uræmia and its relationship to sudden and complete cessation of the renal functions experimentally and clinically we will now consider shortly some observations on acute uræmia.

True acute uræmia has only been observed clinically. I have not as yet been able to reproduce it in the laboratory and I have only made observations on the acute uræmia seen as a complication or termination of chronic and insidious renal diseases, and more especially, as already mentioned, on the uræmia that occurs in a form of contracted kidney seen in young subjects and usually described as a variety of contracted white kidney. It may seem far-fetched to associate acute uræmia more especially with one form of kidney lesion, but all I can say is that I have not as yet seen a case of this form of renal disease fatal from any cause except acute uræmia, and I have watched for such cases for the last eight years. Acute uræmia is, of course, also seen as a terminal effect in several other forms of renal disease, acute and chronic, but for some reasons it is more convenient to study it when it supervenes on a chronic disorder than when it complicates such a malady as acute Bright's disease. Acute uræmia resembles diabetic coma in the rapidity with which it is apt to supervene in these cases of contracted kidney unaccompanied with dropsy.

Urine in Acute Uræmia.

In some cases the onset of acute uræmia in cases of chronic renal disease is heralded by a great and sudden diminution in the amount of urine excreted; but, speaking

generally, complete suppression is rare and certainly acute, and rapidly fatal uræmia may occur in this form of Bright's disease whilst the patient is passing quite considerable quantities of urine and urea, as in the case quoted in my last lecture where a patient passed more than thirty-two ounces of urine containing more than twelve grammes of urea during the last twenty-four hours of life. This amount was recovered and an unknown amount of urine was passed unconsciously in the bed in addition. In this patient, at any rate, fatal acute uræmia occurred with little and perhaps with no suppression, and she had marked uræmic phenomena, such as twitchings and epileptiform seizures, at a time when the daily urine contained at least seventeen grammes of urea. Very little food was taken and some of this was rejected by vomiting Post mortem the total amount of kidney present was less than four ounces. Such a case stands in great contrast to what is seen in the cases of suppression described above and demonstrates how fatal acute uræmia may occur without any obvious suppression, and, in fact, such a case is really the converse of the suppression series. In other cases quantities of urea up to ten grammes were recovered during the last twenty-four hours of life, but exact determinations could not be made owing to the great difficulties experienced in collecting the urine. It is often said that although such uræmic patients may pass quantities of urine not very much less than the normal, yet owing to its dilute character such urine must contain but little solid matter. This is, of course, true and is made much of by those who consider that uræmia is dependent upon the retention of the saline constituents of the urine. This view is, in my opinion, untenable in the light of the facts obtained from the consideration of the cases of complete suppression, where of course all urinary constituents were retained and yet ordinary uræmia did not ensue. It is sufficient, then, for our present purpose to admit that although a certain diminution in the amount of urine and of urea excreted is common in acute uræmia, yet this condition may supervene and be fatal without there being any great diminution in the urinary excretion. The urine of uræmia is almost invariably dilute, pale, and of low specific gravity, and I have met with only one exception to this statement. In a case of chronic Bright's disease without dropsy fatal uræmia occurred at a time when the patient was passing a dense, highly coloured urine, with a specific gravity of 1025, and here a serious error in diagnosis resulted, as it was thought that with such a urine the symptoms—e g., the vomiting, &c.—were of gastric rather than of renal origin. Another important question is the relation of albuminuria to uræmia and I have notes of three cases where albuminuria was said to be absent at the time of the onset of uræmic symptoms. The absence of albumin from the urine has often been asserted to be an occasional occurrence in cases of ordinary granular kidney, but in none of the three cases alluded to here was the kidney lesion of this

type. In two cases the kidney was of the contracted white variety, and in this particular specimen the urine was only examined once, in the other cases repeated examinations were made. In one of the cases alluded to above, where the specific gravity was 1025, there may have been a minute trace of albumin, but even this is doubtful, and in this case the patient had uræmic vomiting for many days, then muscular twitchings developed and finally coma. Post mortem the kidneys were rather large, the cortex was diminished in thickness and microscopically showed signs of considerable disease; the absence of albumin and the high specific gravity led to quite an erroneous diagnosis. The third case was one of a young man admitted for urgent dyspnœa and dry pericarditis. The dyspnœa was uræmic and was followed by other uræmic symptoms. Post mortem the kidneys were found to be very small, somewhat granular, and the urine, though dilute, was stated to be free from albumin.

The toxicity of the urine in uræmia is a subject that has attracted more attention abroad than here. I unfortunately have only made a very few observations on this point; one of these observations is of sufficient interest to quote here, as it was an experiment to compare the toxicity of the urine secreted by the uræmic patient and the toxicity of the blood serum in the same case. The urine and the blood were obtained on the same day, the patient having had venesection performed for the relief of uræmic coma 20 c.c. of the urine filtered through porcelain and injected rapidly into the jugular vein killed a rabbit of 1·75 kilos., the pupils becoming contracted and the respiration ceasing. 22 c.c. injected very slowly killed another rabbit of 1 kilo. with convulsions. Thus this urine was certainly highly toxic, as 11 c c. of urine per kilo. killed the animal when injected rapidly and 22 c.c. when injected slowly. 77 c.c. of blood serum from the same patient killed in a few minutes a rabbit of 1·15 kilos. causing coma and cessation of respiration. In another case of uræmia where venesection was also used 150 c.c. of serum injected into a dog weighing 5 kilos. caused arrest of respiration; the heart, however, continued to beat; after 100 c.c. had been injected the respiration became very irregular. Such observations would require to be greatly extended, but they tend to show that even in uræmia the urine is still toxic and that the blood serum is also highly toxic.

Although convulsions have not been seen experimentally after ligature of the ureters, nephrectomy, &c., yet the cerebral cortex is very excitable, as is shown by such experiments as the following. After the administration of ether the ureters were ligatured in a dog, and forty-eight hours afterwards the cortex cerebri was exposed again under ether and stimulated. Under these circumstances very weak electrical excitation of the motor area is liable to be followed by well-marked clonic spasms of the limbs.

The most striking post-mortem appearance of acute uræmia apart from the frequency of the presence of the small contracted white kidney is the occurrence of well-marked œdema of the lungs quite apart from the presence of general œdema and serous effusions. In the particular class of cases investigated dropsy and serous effusions were conspicuous by their absence. This pulmonary œdema is a well-known accompaniment of uræmic dyspnœa and is perhaps its cause, as it cannot very well be its result, since other varieties of dyspnœa are not accompanied by the well-marked œdema so common in uræmia. The so-called cerebral œdema is a very variable occurrence, but there can be no doubt that sometimes there is a very notable excess of cerebral spinal fluid, and a similar excess was noted in many cases of experimental partial nephrectomy.

Theory of Uræmia.

All pathologists would probably admit that uræmia is a toxæmia and that it is not brought about by either cerebral anæmia or cerebral œdema. The old objections to a toxic source for this condition were mainly two-fold: first, that it was difficult to conceive of a poison circulating in the general blood-stream and producing more or less localised effects, since localised fits and even localised paralyses are not uncommon in uræmia; secondly, the manifestations of uræmia are so varied that it was thought difficult to conceive of a poison producing such diverse effects. Both of these propositions are probably untenable since such a poison as lead or arsenic can not only produce local effects but can even produce a palsy of a symmetrical function on only one side of the body, although both these metals more often produce symmetrical lesions, yet arsenic may produce unilateral herpes. Further lead may cause psychical disturbance or epileptiform seizures or degeneration of the spinal cord or more usually a palsy of peripheral origin. Thus one and the same metallic poison may produce the most varied effects, and therefore the argument against the toxic nature of uræmia, resting on the basis of the statement that it is impossible for the same poison to produce the varied effects seen, falls to the ground. At the same time it is, of course, possible that the poisons of uræmia are varied. Supposing that uræmia is dependent upon the circulation in the blood and tissues of a poison or poisons the next question that presents itself is whether these are substances formed by normal metabolism that ought to be excreted and are only toxic because they are retained and therefore present in increased amount, or whether these poisons are the products of an abnormal metabolism. Is uræmia dependent on the retention of some body? or is the condition due to the formation of a toxic substance or substances by the disordered metabolism? I think the consideration of the facts, experimental

and clinical, that have been adduced will show that uræmia cannot be explained on the hypothesis of the retention of either one or many or all of the urinary constituents, products derived from a normal metabolism. The sudden and complete suppression of the functions of kidneys up to that time healthy produces a train of symptoms similar to those seen in obstructive suppression and, as already insisted on several times, a group of symptoms only resembling very distantly those of acute uræmia. If acute uræmia were dependent on the retention of some normal urine constituent or constituents this condition ought certainly to occur when the functions of the healthy kidney are suddenly suppressed, although it may perhaps be open to argument whether they ought to ensue when the suppression of urine is dependent merely on obstruction to the ureters. Formerly it was thought that obstructive suppression was in some way quite different in nature and produced different results to those seen in non-obstructive suppression and that although obstructive suppression was not followed by uræmia non-obstructive suppression certainly caused uræmia. The main conclusion that I hope I have established to your satisfaction is that both in the laboratory and in disease suppression of the activity of the kidneys up to that time healthy fails to produce acute uræmia whether the suppression be caused by obstruction or by vascular or nervous mechanism. In other words, the uræmia of the laboratory is the latent uræmia of the clinician. If the facts brought before you afford evidence against the view that uræmia is dependent on the mere retention of normal urinary constituents they also equally militate against the view that uræmia is dependent upon, or associated with, the arrest of a hypothetical internal renal secretion. As long as latent uræmia—i.e., the symptoms of obstructive suppression—was only known to occur in the condition of obstructive suppression the contrast between these effects and the acute uræmia of Bright's disease was so great as to suggest the view that uræmia might in some way be associated with the cessation of the action of an internal secretion. According to this view in obstructive suppression there was retention of urinary products, but the supposed internal secretion went on, whereas in Bright's disease and other renal diseases the internal secretion was arrested in addition to the occurrence of accumulation of the urinary products. If latent uræmia occurs equally well when the circulation through the kidneys is completely arrested and therefore when the kidney is practically absent this view in my opinion falls to the ground.

Although these are the principal reasons for not accepting the view that uræmia is dependent upon the retention of one or more normal urinary constituents there are certain subsidiary facts also pointing to the same conclusion. Death in acute uræmia usually supervenes much sooner than in cases of suppression even when this is complete, and further in the acute uræmia seen at any rate in chronic renal disease without dropsy complete suppression is rare, and this, after

all, is the most frequent condition in which acute uræmia is seen. Further cases of acute uræmia are seen, as in a case quoted in these lectures where considerable quantities of urine not falling far short of those seen in health were passed. In addition there is the well-known fact that no observers are agreed as to which elements in the urine are to be considered the toxic ones. This, however, owing to chemical difficulties, is not an argument of much value. The analyses of the blood quoted in the last lecture showed that the blood in uræmia contains very large quantities of such urinary constituents as urea, and although in some cases the quantities were as great as, or greater than, those seen in cases of complete suppression, yet it will be remembered that in the great bulk of the uræmic cases the percentage of the urea in the blood was not so high as in the cases of complete suppression. This is, I think, a point of some importance, as it might be argued that the symptoms in the uræmic and suppression series were different owing to the fact that the accumulation of urinary products might have been more or less gradual in the former case and more sudden in the latter. Poisons, as is well known, often produce different effects according as to whether they are administered in gradual doses or suddenly ; the fact that the majority of the cases of uræmia died with a lower percentage of urea in the blood than was found in the cases of complete suppression is, of course, only to be expected seeing that quantities of urine were passed during the last days of life in these cases, but it is surely another fact against the pure retention theory of uræmia inasmuch as almost all the cases of uræmia analysed were those in which this event terminated a chronic insidious disease. The argument would be fallacious if it applied to the analysis of the blood in such a condition as the uræmia accompanying the suppression of scarlatinal nephritis, where the conditions are more complicated than in the terminal acute uræmia of such a disease as contracted white kidney, where owing to the long duration of the illness one would imagine that the patient would if anything tolerate a larger accumulation of urinary products than in cases of complete suppression supervening during comparative or even complete good health. For all these reasons the retention theory of uræmia is, I venture to think, inadequate. If the uræmic poison is not a retained normal urinary constituent it is probable that it is an abnormal product of a disordered metabolism and there are a number of facts in favour of this view. The experimental facts brought before you in my first two lectures point strongly to the conclusion that the kidneys in some way control the metabolism of the tissues of the body and that when the kidney substance was greatly diminished in amount or entirely removed the blood not only contained a great excess of urea but the tissues, and especially the muscles, contained large quantities of urea and other nitrogenous bodies of the creatin class. I also adduced experimental evidence to show

that both after partial and after complete nephrectomy this increase of nitrogenous extractives could not be explained on the hypothesis of simple retention and that there was clear evidence of the increased production of these bodies. In uræmia the extractives of muscles are enormously increased, but here one can only surmise, with great probability, it is true, that they accumulate as the result of increased production, since the condition of the patient has prevented me as yet from obtaining the exact information as to the amount of nitrogen ingested and excreted that can be obtained with comparative ease in the laboratory. The really very great quantities of extractives present in the muscles make it more than probable that these quantities are too great to be explained by retention. This conclusion is in harmony with the observations of Oppler, Perls, Schottin, and others, who held that in uræmia there was accumulation of creatin-like bodies. If we assume that in acute uræmia the toxic substances are derived from the products of a disordered tissue metabolism some of the many difficulties of the subject disappear; but still I must confess it is difficult to see why removal of the kidney does not produce acute uræmia unless it be that under these circumstances life is not maintained for a sufficient length of time for the disordered tissue metabolism to be in full swing.

There is a further possibility that as a result of the renal lesions the disordered tissue metabolism produces toxic substances, but that the kidney is able to excrete these products, and that then, as a result either of retention or of greater increased production, they again accumulate and destroy the patient. This may be thought rather fanciful, more especially as I have no observation to detail to you as regards the actual nature of the uræmic poison, but my purpose is really to emphasise two points: (1) that uræmia cannot be held to be due to simple retention and (2) that in kidney disease and after experimental lesions of the kidney there is evidence of great tissue disintegration and that it is more than probable that uræmia is dependent upon this directly or indirectly. It might be thought that the tissue disintegration was itself dependent perhaps upon the retention of urinary products, but the experimental facts negative this, as in the cases of experimental partial nephrectomy there was never any evidence of the retention of urea, and, as already detailed, there was much evidence of the increased excretion of urea. It is to be hoped that further observations will throw much more and greatly needed light on the real nature of the toxic substance or substances found in uræmia.

It remains for me to express my best thanks to my colleagues at University College Hospital for the courtesy they have always shown to me in allowing me to make all use of their material, as without their constant aid I never could have observed the considerable number of cases of acute uræmia from which the above conclusions have been drawn.

I have also to thank you, Sir, and the College most heartily for the honour you have done me in selecting me to deliver these Goulstonian Lectures, and although I fear I have by no means fulfilled literally the intentions of the founder, who laid down that the College "would annually appoint one of their four youngest doctors to read this lecture between Michaelmas and Easter, on three days together, both forenoon and afternoon, on some dead body if possibly it can be procured, which shall then and there be dissected for the diseases treated of and shall afterwards be buried," yet I hope I have not entirely missed the purpose of his action.

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