THE RATIO BETWEEN THE UREA CONTENT OF THE URINE AND OF THE BLOOD AFTER THE ADMINISTRATION OF LARGE QUANTITIES OF UREA.

AN APPROXIMATE INDEX OF THE QUANTITY OF ACTIVELY FUNCTIONING KIDNEY TISSUE.

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The procedures which are at present regarded as the most accurate means to use in determining the function of the kidney have their origin in two fundamentally divergent views as to the mode of action of the normal kidney. Schlayer emphasizes the essential inconstancy in the rate of work of the kidney even under uniform conditions, while Ambard believes that variations in the rate of excretion of urinary constituents under any and all conditions are in reality manifestations of the constancy of kidney action, since they are exactly accounted for by alterations in the concentration of these constituents in the blood and in the urine, and do not result from inconstancy in the rate of work of the kidney itself.

The practical significance of these views is illustrated in the methods which have grown from them. Schlayer (1), believing that at any given time the kidney may be working either quickly or slowly in accordance with an unpredictable factor which he terms the "Reizzustand," draws the logical conclusion that no inferences as to the total functional capacity of the kidney can safely be drawn from observation of the rate of excretion of urinary constituents. The same kidney under the same conditions may at one time excrete much and at another time little. All that can be said is that in the one case it is in a state of hyperexcitation and that in the other the excitability is depressed. It naturally follows that all attempts to draw quantitative anatomical inferences from functional findings are illusory, and should be abandoned. It is true he finds that certain interrelationships between the rates of excretion of sodium chloride and water are characteristic of changes beyond the normal range of variation in the relative excitability of the "vascular" and tubular parts of the kidney, and that where the "vascular" apparatus is involved there is a decrease in the rate of excretion of lactose, and a decrease in KI excretion when the tubules are deficient, but he expressly states that at most only qualitative deductions can be drawn as to the presence or preponderance of one or the other type of lesion. It is not possible from such functional studies to determine how much of the kidney has been involved or destroyed by disease.

Ambard (2) on the other hand, holding that normally there is no variation in the rate of excretion apart from changes in the concentration existing on either side of the kidney cells, states that any departure from the rate of excretion which should according to his formula result from these determinable concentrations, is indicative of functional disorder. Although he does not draw exact quantitative anatomical inferences from the degree of change in his coefficient, there is no logical reason why this should not be done if the premises on which the formula is based are sound.

These views are so important and yet so divergent that some years ago we started a reinvestigation of the mode of action of the normal kidney.

Schlayer was considerably embarrassed in his work by the fact that the test-substances he chose—chlorides and water—are markedly subject to extra-renal influences. He admits that part of the variability in his twenty-four-hour rates of excretion may arise not from any difference in the excitability of the kidney cells, but from inequalities in the amounts of chlorides and water brought to these cells for excretion. As a matter of fact, we have knowledge of extra-renal factors which make it seem improbable that any considerable degree of uniformity in the rate of delivery of chlorides and water to the kidney is likely to be achieved even though the intake in the diet is constant. For neither chlorides nor water can be regarded as simply waste products which the economy of the body strives only to rid itself of. They both play an important part in physical and chemical metabolism and in particular are subject to regulation by the mechanism whereby osmotic equilibrium is maintained in the body. Furthermore, both of them have other sources of excretion; water through the lungs, intestines and skin; and chlorides into the stomach. And it must be remembered that though the ultimate discharge of water and chlorides from the gastro-intestinal tract is relatively small and uniform, the temporary excretions into the stomach and intestine are very large and not susceptible of measurement. Thus, though only 100 or 200 cc. of water are found in the stools it has been calculated that the volume excreted into the alimentary tract with secretion from the stomach, liver, pancreas, and intestine at various times during a twenty-four-hour period approximates 4000 cc. The total quantity of chlorides secreted into the stomach is also large, and the rate of secretion is variable at different periods throughout the twenty-four hours.

The objections we have mentioned to the use of water or of chlorides for the purpose of measuring the variability of kidney action do not apply to some other urinary constituents, such as uric acid or amino-acids, but on the other hand they have disadvantages of their own, for they are not true end-products. There is still a question as to whether uric acid may not in part be decomposed within the body and amino-acids may be retained for synthesis or may be deamidized.

The ideal test-substance would be a urinary constituent which was a true end-product in that it was incapable of chemical alteration within the body, one which subserved no physical function, so that its concentration in the blood would not be limited by any of its physical properties, and one whose only path of excretion was through the kidneys. Finally it should be possible at will to produce marked and uniform increases in the concentration of this substance in the blood supplied to the kidneys.

To a quite remarkable degree, urea fulfills these requirements.

There is no agency within the tissues which can either break it down or use if for synthesis.[1] It is present in all the tissues in concentrations which are substantially the same and which seem to depend only on the amount of urea solvents they contain (7).

Another very important property of urea from the point of view of its use as a substance for testing the work of the kidney, is the possibility of producing very marked increases in the urea concentration of the blood and tissues without disturbing any essential physical equilibrium of the body. Thus we have frequently induced in healthy individuals concentrations five or six times greater than the normal, a degree of increase which would be impossible with water or chlorides because of the disturbance of the osmotic balance which such concentrations would entail. Urea apparently does not give rise to any appreciable degree of osmotic pressure, because there are no barriers to its free diffusion through the whole organism. When urea enters the stomach, it begins to pass as once through the stomach wall and in a remarkably short time has become evenly distributed through all the tissues in accordance with their water content. This equality of concentration is confined not only to the tissues, but also to their secretions. The bile (7), and the milk (8), have a urea concentration similar to that of the blood. No observations, so far as we know, have yet been made on the urea content of the secretions of the stomcah or pancreas, but we have not any reason to believe that they are exceptions. Herter (9) has shown that during the intravenous injection of urea in dogs,

[1] Grafe (3) believes that during protein starvation administered urea may be used to a small extent within the body, but the work of Henriques and Andersen (4) has shown that these results may be ascribed to the retention of nitrogen of bacterial origin from the intestines, or to simple retention of unaltered urea. Abderhalden (5) has confirmed this and has further demonstrated that the administration of large quantities of urea has no effect on protein metabolism. Barnett and Addis (6) found an increase in the ammonia content of the blood after intravenous injection of large quantities of urea in rabbits in whom the circulation of blood through the alimentary tract had been occluded. These results are however susceptible of interpretation otherwise than by the splitting of urea within the body.

no urea enters the intestine until the blood concentration of urea has risen to about 0.2 per cent. Even then the concentration of urea found in the intestinal contents does not exceed 0.1 per cent and is usually much less. We therefore have some direct as well as indirect evidence that the kidney is the only path by which any active excretion of urea takes place.

Urea has a still further advantage over other substances which have been used to test the functional capacity of the kidneys, in the fact that we know exactly what part of the kidney is directly involved in concentrating the urea from the blood. Leschke's (10) micro-chemical studies, which have been confirmed by Oliver (11), leave no room for doubt that it is only within the cells of the proximal convoluted tubules that this concentration occurs.

There is thus a divergence in the physiological functions and physical properties of water and chlorides on the one hand and in urea on the other. Water plays a part in most of the chemical reactions occurring in the body, while urea once formed is chemically indifferent. Both water and chlorides are held within narrow limits of concentration by the mechanism which maintains a constant osmotic pressure, while urea can vary in concentration to an extent which is determined only by the balance between the rate of entry of urea into the body and the rate of its elimination from the body by the kidneys. Water and chlorides have other channels of temporary or permanent excretion than the kidneys, while urea is actively excreted by this path only.

These properties, or rather want of properties, of urea as opposed to other urinary constituents, are all such as to make it easier to attain that relative uniformity in rate of delivery to the kidney which is essential if its twenty-four-hour rate of excretion is to be used as a measure of the variability of kidney function.

Many of these special advantages of urea have been known for a long time, but they have not been taken advantage of because of the complexity of the methods required for the accurate determination of urea in the urine and blood. Neither the hypobromite method of urea estimation, nor the indirect method of total nitrogen estimations, can give sufficiently accurate results for the determination of the degree of variation in the rate of excretion of urea. It was not until the appearance of Marshall's application of the urease method to urea determinations in urine and blood, that it was feasible to carry out the large number of estimations which are necessary in order satisfactorily to determine such a question.

The quantities of urea excreted by a series of normal individuals on the same diet are not indentical. The differences presumably arise because in some protein catabolism exceeds anabolism, so that most of the amino-acids derived from the disintegration of food and tissue protein are deaminized with the consequent formation of relatively greater amounts of urea, while in others a greater proportion of these amino-acids are used in synthesis, so that smaller amounts of urea are formed. The variations in the rate of urea excretion arising from this cause were eliminated by dividing the experiments into two periods, a fore-period in which the average amount of urea formed from the constant quantity of protein in the diet and from the tissues of each subject was determined, and an experimental·period in which 20 or 40 grams of urea were ingested at the commencement of each day. The urea excreted during the foreperiod subtracted from the urea excreted after urea had been taken gave the rate at which the administered urea was eliminated.

This statement would be correct only if the amount of urea derived from food and tissue protein remained the same in each individual during both the fore-period and the experimental period. Any such assumption would be unwarranted. We know that there are not only differences in the level of protein catabolism in different individuals, there are also variations in the metabolism of the same individual from day to day. The differences in the rates of excretion of administered urea might then be due in part or altogether not to variations in kidney activity but to changes in individual metabolism. This cause of variation in rate of excretion was eliminated by comparing the degree of variability in two groups of individuals, one of whom took no urea and the other 20 or 40 grams of urea. The urea of the fore-period was subtracted from the urea of the experimental period, and the average deviation from the mean was determined for each group. If the variability thus measured should be as great in those who took no urea as in those who took urea, it is evident that the variability may be ascribed to the same cause in both groups—variation in metabolism in the same individual, from day to day—and that we could say that a high degree of uniformity in the rate of excretion of the administered urea must have been present since any differences which may actually have occurred, were not sufficient to increase appreciably the variability of the urea group. The average deviations for the average twenty-four hours of the experimental period were 1.41 grams urea in those who took no urea, 1.40 grams in those who took 20 grams of urea, and 1.43 grams in those who took 40 grams of urea. We therefore concluded that under these conditions there was no evidence of any inconstancy in the rate of work of the kidney. The reaction of the kidney to a constant stimulus is constant. Normal renal function measured over periods of twenty-four hours is not characterized by the intrinsic tendency towards variation described by Schlayer, but is uniform under uniform conditions (12).

This conclusion is identical with that at which Ambard arrived except that his observations extended over periods of about one hour instead of twenty-four. He excluded one important extrarenal cause of variation in rate of excretion—changes in the amount of the substance to be excreted brought to the kidney—by determining the concentration of this substance in the blood during the period over which the rate of excretion was measured. In the case of urea he found in individuals who happened to have the same concentration of urea in their urines, that the rates of excretion were proportional to the square of the bood urea concentrations, while in those in whom the blood concentrations were the same, the rates were inversely proportional to the square root of the concentration of urea in the urines. Uniting these mathematical expressions in one formula, he obtained a constant from which the rate of urea excretion could be predicted in any normal individual from the concentration of urea found in his blood and urine.

The laws of urea excretion on which Ambard's formula is based can only be verified after a considerable series of observations have been collected. For from this series only those instances can be taken in which either the blood or urine concentrations are alike. On reviewing our data, which had been collected over several years, we found 271 instances to which one or other of the two laws were applicable. Neither of them were verified, on the contrary there was very positive evidence not only that they were incorrect, but also that no mathematical formula could be constructed which would allow of even a rough prediction of the rate of urea excretion to be expected from any observed concentration of urea in the blood or urine (13). In the formulation of these laws, Ambard was undoubtedly misled by a chance agreement of the few observations on which he depended.

Although it was thus shown that the hourly rate of urea excretion by the normal kidney was not governed only by the urea concentration of the fluids on either side of the urea secreting cells, there remained the question of the degree to which it was influenced by these factors.

In order to determine the effect of changes in blood urea concentration, all the observations were plotted on a scale in which the abscissa represented blood urea concentrations and the ordinate hourly rates of urea excretion. It was found (14) that a curve could be drawn through these points which indicated that the blood urea concentration had a marked effect on the rate of urea excretion. When there was 20 mgm. urea per 100 cc. of bood the average hourly rate was 0.4 grams, with 40 mgm. 1.1 grams, with 80 mgm. 3.2 grams and with 120 mgm. 5.3 grams. But the observations showed a very considerable degree of scattering above and below this curve, so that at any given blood concentration there were wide differences in the recorded rates. For instance at a concentration of 40 mgm.

of urea per 100 cc. of blood the chart records rates ranging from 0.6 to 2.29 grams of urea per hour. It is evident therefore that the effect of changes in bood urea concentration only becomes clearly apparent when an average of a number of instances are taken. In any individual case the effect may be counterbalanced by other factors.

The conception that these variations in the rate of urea excretion occurring even when the blood urea concentration is constant, may be due to differences in the urea concentration of the urine, is one which from a purely theoretical point of view has much in its favor. For if the concentration of urea in the blood on one side of the kidney cell has, as we have shown, a pronounced effect on the rate, it sees likely that the concentration of urea on the other side of the cell, that is in the urine within the lumen of the tubules, should also have some effect. It might be expected that the diffusion of urea from the cell to the urine would be retarded when the urine concentration was high, and hastened when it was low. But this hypothesis is not supported by the facts (15). The rate of urea excretion is independent of the concentration of urea in the urine, and there is no evidence at all that any direct relation exists between them. If there had been, we should have been able to detect a general tendency towards high urine concentration in those cases in which the rate of excretion was less than the average found at any given blood concentration, and that a low concentration generally accompanied an unusually rapid rate of excretion. No such general tendency however was demonstrable. This after all is only what might have been expected if a broad view is taken of the function of the kidney in relation to the needs of the organism as a whole. For if the rate of excretion of urinary constituents were to rise and fall in accordance with the volume of water available for excretion, we should even under ordinary conditions of life be subject to a variation in kidney action which bore no necessary relation to the metabolic requirements of the body. It is not to be wondered at that kidney activity is not subject to the physical laws of diffusion or osmosis nor even in all probability of surface tension or adsorption. The phenomena of life are characterized by a continual annulment and overruling of the physical laws which inert material obeys. The increase in the rate of excretion of urea which accompanies an increase in blood urea concentration, although it is in general what might be expected on physical grounds, yet in detail cannot be even approximately so explained, while in the absence of a relation between the rate of excretion and concentration in the urine, we have an example of the manifestation of a force which acts in direct opposition to physical laws. Of the nature of this force we of course know nothing. All that we can say is that it acts for the good of the organism as a whole. It prevents any marked accumulation of urea in the body by increasing its rate of work when the blood urea concentration rises, and it does not allow variation in water excretion to interfere with this work.

Though we may speak of a regulation of the urea content of the tissues and of the blood by the kidneys, there is no such close regulation as is maintained in regard to other substances such as for instance the H ion concentration or even the concentration of chlorides. We found variations of from 24 to 60 mgm. of urea per 100 cc. in the blood of normal individuals even though the blood was taken in the morning before food (16). One individual on whom 50 estimations were made under these conditions showed variations of from 25 to 60 mgm. In a group of 28 subjects on a constant diet the blood urea content taken on the third day of the diet varied from 16 to 44 mgm. These changes were noted in subjects who had taken no urea.

It would seem then that within these limits the urea content of the blood is a matter of comparative indifference to the body. This no doubt arises from the fact that urea subserves no function and is foreign to the body. We have evidence that these variations in blood urea concentration parallel changes in the rate of protein catabolism, rising and falling with them. But this is certainly not their only cause. They may also result from changes in the activity of the kidney. During sleep the kidney is less active as regards urea excretion and the blood concentration tends to rise. There are also states of kidney inactivity which may be induced by the absence of food and water. These variations in activity are of course not intrinsic in origin, but arise from the action of other factors than the urea concentration of the blood. The marked effect of these other factors is illustrated in the wide variation in the rates of urea excretion which were noted in the same individual when the blood urea concentration was constant.

The facts determined by this study were, then, that the rate of urea excretion was independent of the concentration of urea in the urine, and that a relation existed between the rate of urea excretion and the blood urea concentration. This however was only a general relationship within which a wide variability was found. It should be stated that this variability was not confined to experiments in which the conditions as regards food and water intake, time of day, etc. were different. We found a marked variability in those subjects who were on a constant diet, and in whom there was no demonstrable inconstancy in the twenty-four hour's rate at which they excreted administered urea. The same kidneys were at the same time both variable and constant in their mode of work.

This apparent contradiction arises from the difference in the length of time of the periods during which the rate of excretion was measured. Over twenty-four-hour periods the output of the kidney is found to be constant. But when the output for each hour of the twenty-four is measured, considerable variability is found. There are retarding and accelerating factors which alter the rate over short time periods, but leave it unaffected over longer periods because they counterbalance one another. If during one hour the rate is unusually slow, it will be more than ordinarily rapid during a later hour, so that the total twenty-four hours excretion will remain the same. The variation in the hourly rate of excretion in individuals who have the same blood urea concentration are due to the action of these temporary and balancing phases of excitation and of depression in kidney acitvity.

These observations have a direct bearing on the question of what methods are best adapted to measure the functional capacity of the kidney. The failure to find any variability in the twenty-four-hours rate of excretion of administered urea in individuals free from kidney disease is significant since it raises the hope that variation from the normal rate of excretion may be a measure of the degree of functional and anatomical abnormality. But the conditions under which this normal constancy of function were observed are of still greater significance. It was seen in connection with the twenty-four hour rate of excretion of a substance which is essentially foreign to the body. It was observed in subjects who had all taken the same amounts of protein, salts and water. It was obtained under conditions involving an unusual strain on the capacity of the kidneys. Reasons for the special importance of the last point will be given later in the paper, but it may be said now that under such conditions, where the kidney is wakened to full activity under the influence of strain,[2] and where dietary factors are the same, the blood urea concentration tends to be constant except for such variations as arise from differences in protein metabolism. The effect of these variations on the amounts of urea excreted are measured during the fore period and in the main excluded by subtracting the average of the fore-period from the urea excreted in the experimental period. In effect therefore the result may be regarded as a measurement of the ratio between the urea content of the urine and of the blood, under conditions in which the blood concentration remains the same.

We have data on the mode of reaction of individuals suffering from disease of the kidneys under the above conditions, which we hope later to report in detail. There is one observation in this connection which may be cited now, since it illustrates a

[2] The more work the kidney is called on to perform, the less subject does it become to temporary fluctuations in rate of work. It should be noted, and this is a point we did not appreciate at the time the work was done, that this fact makes it impossible to conclude that any absolute constancy in the rate of excretion of administered urea was present in our experiments. For the urea group were under strain and might be expected to show somewhat less variability than the non-urea group. There may therefore have been some variability in the rate of excretion of the added urea, though the figures show that if present it could only have been of slight degree.

fact which is applicable to all methods of testing kidney function. We cannot by any strain within the bounds of practicability attain to a measure of the absolute maximum of the rate of excretion of any urinary constituent. All we can do is to determine the maximum rate in relation to a given concentration of the substance in question in the blood. If the concentration in the blood is increased still further, the rate of excretion will also increase, until the highest concentration compatible with life is attained. This was demonstrated by Herter when he showed that the rate of urea excretion in dogs increased up to the point where the animals died in convulsions because of the enormous quantities of urea injected. But it is not so evident that this would be the case in diseased kidneys. We might suppose that damaged kidneys would grow tired so that they would not longer respond by increased work to an increased load. But our experience shows that what is true of normal kidneys is true also of those which are diseased. As an example we may cite a case of subacute diffuse glomerular nephritis. The average normal twenty-four hours rate of excretion of administered urea following three doses of 20 grams given on consecutive days is 16.6, 18.7, and 18.9 grams. This patient however excreted only 6 grams after the first dose of urea thus retaining 14 grams, so that when 20 grams was taken again at the beginning of the second day, his kidneys were called on to excrete 34 grams. He responded to the call for increased work and eliminated 14.9 grams. On the third day his rate of excretion rose still higher to 18.9 grams. Thus the apparently paradoxical circumstance may be met with in which a patient with severely damaged kidneys is excreting greater quantities of urea than is an normal individual. The characteristic of the diseased kidney is not its incapacity to excrete large amounts of urea, but its incapacity to excrete as much urea as the normal kidney does in relation to the urea content of the blood. The diseased kidney will only excrete as much urea as the normal after it has failed to eliminate the urea as quickly as the normal, and has thus increased the amount of work which it is called on to perform through its own incapacity. In the particular test we are discussing, the essential point is the time which the kidney takes to respond to the extra load thrown on it by the ingested urea. A low rate of excretion during the first few hours after urea administration is the special characteristic of decreased functional capacity.

Any method of testing functional capacity which involves the necessity for a constancy in diet has only a limited applicability in clinical work. The constant diet however is necessary in order that variations in blood concentration due to differences in rate of protein metabolism may be eliminated. The method used by Ambard of determining the blood concentration during the period over which the rate is measured is a more direct and accurate method of accomplishing this end. But these periods must be short, otherwise the observed blood concentration will not be representative of the average concentration throughout the whole period. And as we have shown when these short periods are taken, we may have marked fluctuations in the rate due to the action of other factors than blood concentration. If however, conditions were found under which these other factors remained constant, the method would be an accurate and simple means of measuring kidney function. This problem resolves itself into a study of those conditions other than blood urea concentration which may influence the rate of urea excretion. The blood concentration has a marked influence, but it is one which can be measured and eliminated. This may be most simply done by dividing the hourly rate by the amount of urea found in 100 cc. of blood.

This ratio is not a mathematical abstraction. It gives the number of times by which the urea in one hour's urine exceeds the urea content of 100 cc. of the blood supplied to the kidney. It expresses the relation between the amount of work accomplished by the kidney and the most important measure of the amount of work the kidney was called on to perform. The question then is what are the factors which may influence this ratio.

On theoretical grounds it might be supposed that the ratio would vary with the amount of blood passing through the kidneys. Two kidneys might be supplied with blood which contained the same amount of urea per 100 cc., but if 20,000 cc. of blood passed through one kidney in the hour and only 10,000 cc. through the other, the total amount of urea which might have been excreted would be twice as great in the one case as in the other, and one ratio might be double the other. We have attempted to estimate the effect on the ratio of changes in the rate or flow of blood through the kidney and though for various reasons we have not succeeded in obtaining generally applicable results, we have evidence which favors the view that variations in the amount of blood passing through the kidney when that amount exceeds a certain minimum, have little effect on the ratio. If the kidney removed all the urea from the blood brought to it, the ratio would of course vary directly with the rate of flow. But we found on comparing the urea content of the renal vein and artery, that the decrease in the vein was only slight (17). We never found a greater difference than 12 mgm. per 100 cc., and in most cases the decrease represented only a small percentage of the urea present. The kidney is supplied with much more urea than it excretes and therefore it does not follow that a further increase in the supply will be followed by any increase in the output. On the other hand circumstances certainly arise in which the rate of blood flow has a very marked effect on the ratio. We have repeatedly noted that any handling of the renal artery is apt to be followed by a visible constriction of the vessel and that at the same time the secretion of urine stops, and the ratio falls to zero. This effect may however be interpreted as indirect. In order to carry out the enormous amount of work entailed in the separation of the urinary constitutents from the blood, a very large supply of oxygen and fuel is required. When this supply becomes defective, secretion automatically ceases. But here again variations in the supply of oxygen so long as it is above a certain minimum, do not appear to have any appreciable effect on the ratio. Thus we have found when the haemoglobin content of the blood is experimentally reduced by repeated haemorrhage, that a definite effect on the ratio is only produced when the degree of reduction is very marked. We think it probable therefore that variations in the amount of blood supplied to the kidneys do not under physiological conditions markedly influence the ratio. Instead of the blood supply ruling the work of the kidney, the evidence rather goes to show that the work of the kidney is largely independent of variations in blood supply. Such variations in kidney blood supply as may passively follow from alterations of the distribution of blood to other parts of the body would therefore be possible without any interference with the work of the kidney. If this view is correct, it is another instance of the comparative freedom of the kidney from passive subjection to mechanical and physical factors.

The differences in the rates of urea excretion which are found to exist in spite of constancy in blood concentration represent of course variations in the ratio we have defined. These variations cannot be explained by the differences in the urine concentration, and there is the evidence we have just given against attributing them to differences in the rate of blood flow through the kidneys. If we had found that certain individuals always gave low and others high ratios, there would be good reason to believe that the variation arose from permanent individual peculiarities, such as might arise from anatomical differences. This however was not the case. In a single individual 110 ratios were determined and a range of variation found which was comparable to that shown by a group of individuals. It would thus appear that the cause of variation cannot lie in differences between the kidneys of different individuals.

Certain facts in regard to the average ratio and to the unexplained variations from the average in the ratio become apparent when each ratio is charted according to the level of the blood urea concentration at which it was observed.

The average ratios represented by the line in figure 1 increase with increase in the blood urea concentration. The more the kidney has to do, the more efficiently does it work. It responds to a call for more work by an increase in output which is greater than the increase in demand.

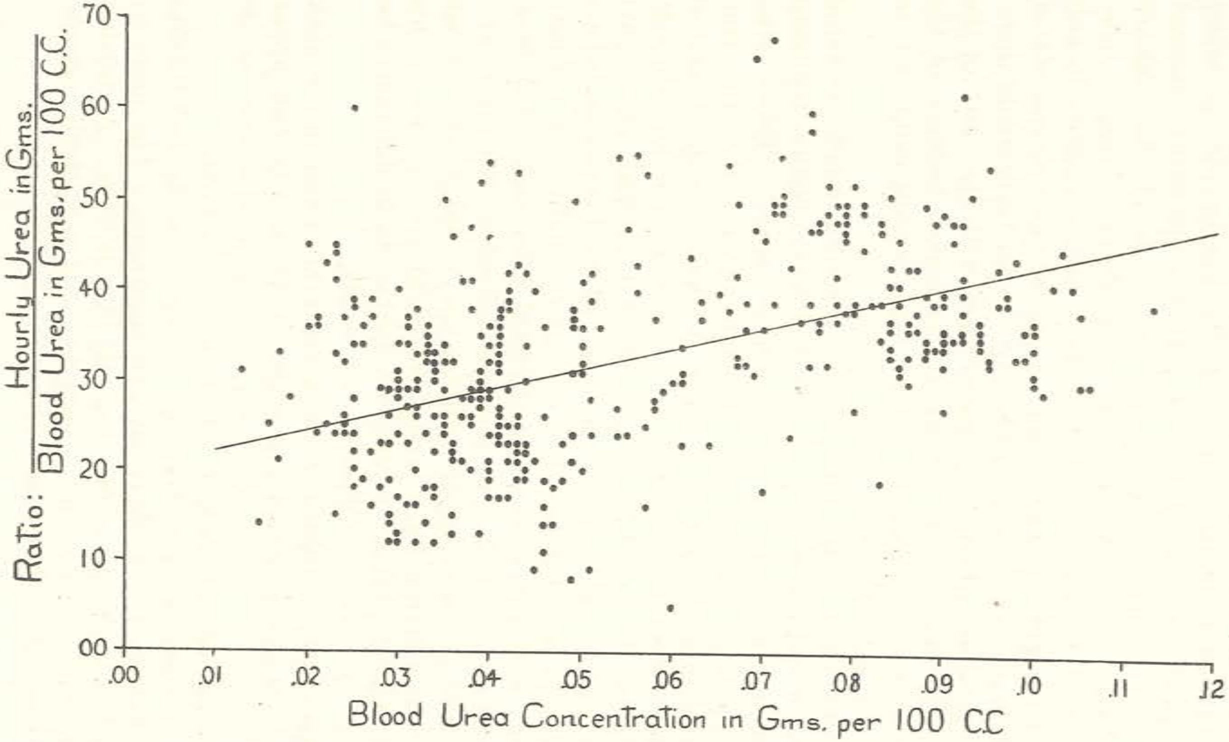

FIG. 1. THE INCREASES IN THE RATIO WITH INCREASE IN BLOOD UREA CONCENTRATION.

The variability of the ratio is represented in figure 1 by the scattering of the observations above and below the curve. The variability thus measured is the absolute range of variation. But it is the relative and not this absolute variability which is the true guide to the degree of variation in the activity of the kidney. Thus ratios varying from 10 to 20 have no greater absolute range of variation than ratios of from 50 to 60, but the relative variability is much greater. There is 67 per cent of variation from the average in the first instance, and only 18 per cent in the second. We have therefore determined the me-

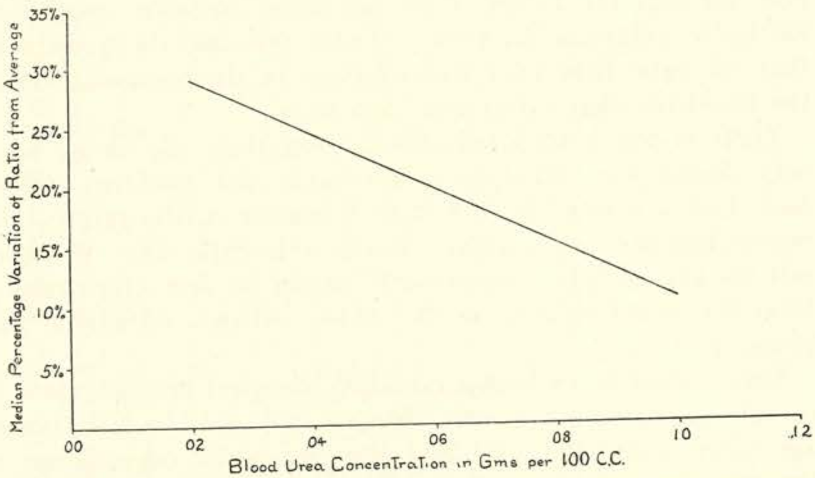

FIG. 2. DECREASE IN THE VARIABILITY OF THE RATIO WITH INCREASE IN THE BLOOD UREA CONCENTRATION

dian percentage variation from the average ratio as given by the curve in figure 1 at different levels of blood urea concentration (fig. 2).

The percentage variability which is represented in figure 2 decreases with increase in blood urea concentration. The more the kidney has to do the more uniformly does it work.

There is then no one average ratio which may be taken as a standard of normal kidney function, but a different average ratio for every blood urea concentration. There is no one normal range of variation, but a series of normal ranges which decrease with rise in the urea content of the blood.

Even at the highest blood concentrations there is a considerable percentage variation which prejudices the value of the ratio over short time intervals as a guide to the functional capacity of the kidneys. If the causes of this variability were known[3] conditions might be found under which it might be lessened. We know that changes in the concentration of urea in the urine and anatomical differences in the kidneys of the subjects of these experiments can be excluded as being to any appreciable extent factors in its production. There is also, as we have shown, reason to believe that variation in the rate of blood flow through the kidney does not under ordinary conditions markedly influence the ratio. There remains the possibility that the ratio may vary with changes in the concentration in the blood of other substances than urea.

There is here a large field for investigation. So far we have only found two substances—adrenalin and pituitrin—which have had a marked and definite influence on the ratio. Adrenalin increases and pituitrin decreases the ratio (18). What we call the normal ratio may possibly simply be that which results from the usual balance in the blood between adrenalin and pituitrin.

This finding has a considerable physiological interest, since it reveals a means whereby the organism frees itself from the bondage which would have resulted from any strict dependance of the rate of excretion on the concentration in the blood of the substance to be excreted. It is another example of the independence of the kidney from the rule of purely physical law, and its regulation by forces working in accordance with the requirements of the body as a whole.

The antagonistic effects of adrenalin and pituitrin may also be of importance in connection with the measurement of kidney function. If the temporary variations in the ratio are due in part to changes in the adrenalin-pituitrin balance in the blood, it will be necessary to find what are the experimental conditions

[3] Part of the variability shown in the great scattering of the observations in figure 1 arises from a constant deviation from the average ratio manifested by the normal kidney at certain time intervals following the ingestion of urea.

under which the balance tends to be most constant. We have shown that the ratio is most variable when the kidney has little to do. This might be explained by supposing that when there was no accumulation of catabolites in the blood, the balance between adrenalin and pituitrin might fluctuate from one side to the other in accordance with the needs of the body for adrenalin or pituitrin for other than excretory purposes. The result would be a wide variability in kidney action. But when a pressing need arose for the rapid excretion of accumulated end-products the balance would swing only in one direction—towards an increase in adrenalin—and the kidney would become more constant in its rate of work. Again we have shown that the normal kidney meets progressive increases in the amount of work it is called on to perform by augmentations in the rate of excretion, which with every increase in load become progressively greater than that required to simply maintain an equality between work required and work done (fig. 1). This capacity might be attained through a reciprocal relation between the adrenalin content of the blood and the degree of strain on the kidney of such a nature that every increase in strain was met by a still greater increase in adrenalin. Further and more direct data will however be required before such hypotheses can be accepted.

The subtitle of this paper expresses the view that the ratio after the administration of urea may be taken as an approximate index to the amount of actively functionating kidney tissue. If this direct relationship exists, the ratio obtained in animals with small kidneys should be proportionately smaller than the ratio in animals with larger kidneys. We have made several hundred observations of the ratio in rabbits, and have found on an average 2.03 times more urea in one hour's urine than was present in 100 cc. of blood when the urea content had been raised to 225 mgm. per 100 cc. At this level of blood urea we should expect from figure 1 a ratio of 66 in man, that is a ratio about 33 times as great. We do not know the relative kidney weights in the rabbit and in man, but these weights will have a relation to their respective body weights. The average weights of our rabbits was about 2 kgm. and an average weight for man is about 70 kgm. or thirty-five times greater than the weight of a rabbit. It would thus appear that the ratio varies in nearly direct proportion to the weight of the kidneys.

Evidence of the above nature only becomes of value when the average of large numbers of observations can be compared. We hope later to be able to extend it by averages for the rat and possibly for the cat also. The insufficient data we have at present tends to support the hypothesis of a direct relation between the magnitude of the ratio and weight of the kidneys.

The question has been more directly approached through only on a very small scale, by the comparison of the ratios following urea administration before and after the removal of one kidney. In three rabbits an average ratio of 1.29 was obtained when both kidneys were functioning, and a ratio of 0.54, or less than half, when only one kidney remained. (19)

It is of course not contended that in individual cases it is possible to demonstrate a constant and absolute relation between the ratio and the kidney weight. There were doubtless differences between the kidney weights of the normal individuals on whom we determined ratios, but such differences were too small to lead to any appreciable effect. They were obscured by the variability of kidney action. In any single case it is only gross differences in the size of the kidneys which can be detected.

We have been dealing hitherto with normal kidneys. But in the diseased kidney the weight or the size cannot be taken as a measure of capacity, for part of the renal tissue may be functionally inactive. What is needed here is a measure of the amount of renal tissue which remains capable of active work. An anatomical estimate of this sort will only be reasonably correct under certain favorable conditions. In many acute pathological states the methods at present used in histological work give little or no idea of the amount of tissue which has ceased to function, and on the other hand, some conditions associated with strikingly abnormal anatomical pictures are not necessarily combined with great functional deficiency. But this is not true of all anatomical lesions. Varying doses of uranium produce varying degrees of degeneration or necrosis in the terminal portion of the proximal convoluted tubule—the site of urea excretion—and it is possible to make a roughly quantitative classification in such cases in accordance with the amount of secreting tissue involved.

Classifications of cases of uranium nephritis according to the extent of the anatomical change and to the degree in which the ratio was depressed were found to agree (20). This may be considered as evidence of the dependence of the ratio on the size of the kidney, if the word "size" is considered as applying only to actively functionating renal tissue.

So far then as our present knowledge reaches it would appear that there are two main causes determining the magnitude of the ratio, one, a constant, the amount of normal kidney structure, and the other, a variable, the state of activity of the kidney cells, which there is some reason to suppose may vary with the balance between adrenalin and pituitrin in the blood.

The problem resolves itself into the determination of the conditions under which this variable factor becomes constant or relatively constant. The ratio might then be taken as a measure of the amount of active kidney tissue present not only in groups of individuals but in single cases. This would give us what we most need in clinical work—an anatomical foundation for early diagnosis, prognosis and treatment. For functional studies have in the last resort no fundamental significance unless they are of such a nature that structural inferences may be drawn from them.

One essential factor in the conditions necessary before the ratio can be regarded as indicating the size of the kidney has already been made clear. The ratio was not found to be decreased after the removal of one kidney except when the remaining kidney was subjected to a marked strain on its excretory function. The ratio itself then is no measure of kidney size, but only the ratio after the administration of a large quantity of urea. This is a principle so obvious that it does not require elaboration. We could as little expect to estimate the muscular strength of two individuals without imposing a task which called for all their energy, as we can hope to measure the functional capacity of their kidneys apart from conditions requiring the maximum activity of all their renal tissue.

SUMMARY

1. The ratio between the urea content of the urine and of the blood expresses the number of times by which the urea excreted in the urine during a certain period of time exceeds the amount of urea present in 100 cc. of the blood supplied to the kidney during this time. It is the relation between the amount of work accomplished by the kidney, and the most important measure of the amount of work the kidney is called on to perform.

2. Ratios measured over periods of twenty-four hours are constant in normal individuals who have the same blood urea concentration. The normal kidney is therefore not characterised by any intrinsic tendency towards variability of function. Variations in kidney function arise from differences either in the environment or in the anatomical structure of the kidney.

3. Ratios measured over short periods of time vary widely even though the blood concentration be the same. This variability must be due to short lived alterations in environment which counterbalance one another over long but not over short time intervals, for it can be shown that such anatomical differences as may exist between the kidneys of young healthy adults do not play any appreciable part in its production.

4. Differences in the concentration of urea in the urine are not the cause of this variability in the ratio over short periods of time.

5. Evidence is given against the supposition that this variability arises from such alterations in the amounts of urea or of oxygen brought to the kidney as would be produced by differences in the rate of flow of blood through the kidney. Reduction of kidney blood supply below a certain minimum has a marked effect on the ratio, but it does not follow that alter-

ations above that critical amount would have much if any effect.

6. Since it is possible to increase the ratio by the subcutaneous administration of adrenalin and to decrease it by pituitrin, the hypothesis is advanced that part of the variability of the ratio for one hour periods at the same blood urea concentration, may be due to alterations in the adrenalin pituitrin balance in the blood.

7. It is shown that the magnitude of the ratio increases with increase in the blood urea concentration. In other words the kidney responds to a call for more work by an increase in output which is greater than the increase in demand.

It is further shown that the relative variability of the ratio at different levels of blood urea concentration decreases the higher that level rises. In other words the greater the demand for work, the more constant does the rate of work of the kidney become.

Both of these phenomena may be brought into relation with the hypothesis of a regulation of kidney activity by means of the balance between adrenalin and pituitrin in the blood.

8. There is evidence that a direct relationship exists between the magnitude of the ratio and the size of the kidneys. This has been shown by comparing the average ratios obtained from species possessing kidneys which differ widely in size. The removal of one kidney leads to a depression of the ratio. In kidneys whose effective size has been reduced by necrosis or degeneration of varying extent, there is a relation between the degree of depression in the ratio and the amount of tissue which has been rendered functionless.

9. This direct relation between the magnitude of the ratio and the amount of actively functionating kidney tissue is only demonstrable under conditions in which the kidney is called on for the maximal activity of all its secreting elements and is subject to the least degree of variation in rate of work. The ratio can be taken as an approximate indication of the size of the kidney only when it is determined during the strain induced by the administration of a large quantity of urea.

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