THE RATE OF UREA EXCRETION.

III. THE EFFECT OF CHANGES IN BLOOD UREA CONCENTRATION ON THE RATE OF UREA EXCRETION.

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On one side of the urea-secreting cells of the kidney there is blood and on the other side there is urine. The rate of urea excretion is the rate at which these cells transfer urea from blood to urine. Under these circumstances it seems probable that changes in the concentration of urea in the blood will have an effect on the rate of urea excretion.

If the concentration of urea in the blood were the only factor governing the rate of excretion, it would be possible to obtain a direct measure of its effect by determinations of the rate at different levels of blood concentration. But we have already shown\(^1\) that the rate may vary when the blood concentration remains constant, and that there may be considerable differences in the rate, even when the concentration of urea in the urine as well as in the blood is constant. It is therefore certain that other factors besides the urea concentration of the fluids on either side of the kidney cells exercise a determining influence on the rate of excretion. And unless these other factors can be kept constant, any observed rate of excretion may be higher or lower than that which would have resulted had the blood concentration been the only operative factor.

We have not succeeded in framing experimental conditions under which we could be sure that this necessary constancy was attained. This of course was to be expected, since some factors which seem likely to influence the rate of work of the kidney

\(^1\) Addis, T., and Watanabe, C. K., \textit{J. Biol. Chem.}, 1916, xxiv, 203.

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cells, as, for instance, the rate of flow of blood, could not be directly controlled in our experiments. But we have found that under certain conditions these unknown and uncontrolled factors tend to increase the rate of urea excretion above that usually found at the observed blood concentration, while under other conditions the rate tends to be decreased. Since these factors alter the rate in both directions, an average of a number of observations at different levels of blood concentration will give an approximation to the effect of blood concentration alone. The accuracy of this approximation will depend on the degree to which these observations represent an equal distribution between instances where the rate has been increased under the influence of other factors than blood concentration, and those in which it has been decreased.

The general method we have followed was to estimate the average blood urea concentration for intervals of 15 to 120 minutes during which the urine was collected. The rates of urea excretion were expressed as gm. of urea per hour. Points were plotted on a scale, so that the ordinates were equal to these rates, and the abscissae to the corresponding measures of blood urea concentration. The curve drawn through these points will measure the effect of changes in blood urea concentration on the rate of urea excretion more or less accurately according as the above condition has been fulfilled.

The subjects were adults, at or below 35 years of age, who were free from any sign of kidney disease.

The higher levels of blood urea concentration were obtained by the administration of urea in doses of 20, 30, or 40 gm. of urea, the intermediate by observations taken before or after the concentration had reached its maximum following urea ingestion, while a considerable variety of lower concentrations was found in subjects who had taken no urea.

The conditions as regards food and water intake were very variable. In some experiments no food was taken for as long as 20 hours, in others considerable quantities of urea-forming food had been consumed. The water intake varied from no water for 12 hours or more before an experiment to quantities of 1,500 cc. before, and large quantities during the period of observation. No experiments in which drugs were given are included.
Collections of urine were made over periods which were made as short as was compatible with accuracy, and the average blood urea concentration for each of these periods was calculated. The error in the actual estimation of urea in the blood is small in comparison with the possible error which might arise in calculating an average concentration over a period of time from the concentration found during a few moments of that time. For the blood urea concentration is constantly changing, and it does not follow that the concentration found at the middle of a half hour period accurately represents the average concentration throughout the whole of that time. As a rule, however, changes in urea concentration rise or fall fairly evenly over periods of hours. The majority of our observations were made in consecutive series extending over 3 to 12 hours, and the blood urea was determined every hour or every half hour. In this way a curve of urea concentration was obtained and from this the average concentration for each period was calculated. This was particularly useful in those experiments in which urea was administered, for there the concentration rose and fell from a maximum. Where there was a smooth curve of this sort there was probably little error in the calculation of the average concentration for each period, except for that period in which the maximum was attained.

There is still another possible source of error in connection with the determination of the blood urea concentration. In experiments of the type we are concerned with, it seems to have been tacitly assumed that the concentration of urea found in blood removed from an arm vein is the same as the concentration which exists in the blood reaching the urea-secreting cells of the kidney. But since we know that urea is not secreted by the glomeruli, and have reason to conclude that a large part of the water of the urine is, it seems likely that the concentration of the blood which leaves the glomeruli is higher than that of the systemic blood in proportion to the amount of water abstracted from it in the glomeruli. In experiments in which the volume of urine is very large, it is conceivable that the difference thus produced might lead to appreciable error.

The estimation of urea in the urine was done in duplicate. As in the case of the blood urea, the greatest source of error is
probably not the technical one, which can be measured, but one arising from the conditions under which the experiments were conducted. Especially, we believe, in cases in which the urine volume was small, considerable error may sometimes have resulted from incomplete emptying of the bladder. The subjects, however, were asked to take special pains to make urination complete, and where the urine volumes were small, the periods over which the rate of excretion was determined were lengthened. In such cases more than one estimation of blood urea concentration was sometimes made for each period.

Part of the data has been given in tabular form in a previous paper, though a considerable number of observations made since that time have been added.

All the observations made under these varying physiological conditions have been plotted in Fig. 1. The general trend reveals the existence of a relationship between the concentration of urea in the blood and the rate of urea excretion. The curve shows the theoretical quantitative effect of any given degree of change in blood concentration, other factors remaining constant. The degree of scattering indicates to what extent other factors than blood concentration may modify the rate of excretion.

There are certain defects in the data which have to be considered as probably detracting from the accuracy of the curve. Of these, the sources of error we have described above in the estimation of the rate of excretion and of the blood urea concentration cannot be considered as important in relation to the extent of the scattering seen in the graph. Appreciable errors were certainly only occasional, whereas the scattering is general. The most important and probable cause of a deflection of the curve from its true course would be a want of balance between instances of acceleration and of depression of the rate of excretion due to other causes than changes in blood concentration. The drinking of large quantities of water tends to accelerate the rate of excretion, and abstention from water to decrease it, apart from any alteration in blood concentration. There is a fairly even distribution of observations made under

\[2\text{ The curves were drawn for us by Mr. Otis, of Stanford University, by means of a method he has described which is called the "method of rank correspondence."} \quad \text{Otis, A. S., School and Society, 1916, iv, 716, 750.}\]
these two conditions in the subjects who took no urea, but in those experiments in which urea was administered, there are too many taken from water drinking experiments. This may account in part for the slight alteration in the direction of the curve at the higher levels of blood urea concentration as opposed to the lower. Yet even if such experiments are excluded, there is a definite tendency after the administration of urea for the rate of excretion to be greater than would be expected from observation of the result of alteration in blood concentration in experiments in which no urea was given. It has been noted from observation of the renal vessels in animals that urea injections may be followed by an apparent increase in the rate of flow of blood through the kidneys. It may be that part of the acceleration of the rate of excretion in man after the ingestion of urea is due to this cause, as well as to the increased urea concentration of the blood.

Although the absolute differences between the rates of excretion observed at each level of blood concentration increase as the concentration rises, yet relatively they become steadily smaller. Thus at 0.03 per cent the probable range of variation is over 200 per cent of the average, whereas at 0.09 per cent it is only about 75 per cent. Since it is the relative and not the absolute differences which measure the degree of variability in kidney function, we may conclude that the urea-excreting function of the kidneys tends to become more uniform the greater the urea concentration of the blood. When there is only a small amount of work to do there are great differences in the rate of work, but when the load is increased, the output becomes less variable.

The great variability in the rates of excretion at every grade of blood concentration is of particular interest in relation to the high degree of uniformity in the 8 to 24 hour rates at which subjects excrete urea added to a constant diet. The differences in these experiments were no greater than those which might have resulted from individual fluctuations in the rate of protein catabolism. This uniformity cannot be ascribed only to the equality of conditions as regards food and water intake, for we have recorded instances in these subjects where the rates of

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Addis and Watanabe, J. Biol. Chem., 1916, xxvii, 249. There was no egg given with the noonday meal, as is incorrectly stated in this paper.
excretion during short periods of time showed a variation not markedly lower than that shown in Fig. 1, even when the blood concentration was constant. We believe that the uniformity arose mainly from the fact that the rate was observed over long periods of time (8 to 24 hours), while in the experiments given in this paper the time of observation was relatively short (15 to 120 minutes). Though kidneys which are called on to perform equal amounts of work may vary their rate of work widely from hour to hour, their total performance for the day is relatively uniform. If this is the true explanation, we may conclude that those unknown factors which cause the kidney to alter its rate of work have only a temporary and evanescent effect, and that a depression of kidney activity during 1 hour of the day is counter-balanced by a later acceleration, so that the total output remains the same.

The fact that in twenty-nine young adults a high grade of uniformity was found in the 8 to 24 hour rate of excretion of administered urea indicates that there were no fixed individual peculiarities in the kidneys of that group. The subjects of the present observations include all of the above group, and the additional subjects were similar in their age and freedom from evidence of kidney disease. It seems therefore improbable that the scattering shown in Fig. 1 can be due to permanent individual differences in kidney structure. But it is possible to give direct evidence in regard to this point from our data. A considerable number of observations (110) were made on one subject under all the various experimental alterations in food and water intake. Fig. 2 shows the curve and the degree of scattering in his case. Since the kidneys of this individual show as great a variability as is manifested by the kidneys of all the other subjects, we may conclude that permanent anatomical differences are not responsible for the variations in the rate of urea excretion independent of changes in blood concentration during short time intervals. The causes of these variations must be sought for among temporary, irregular, and counterbalancing alterations in the environment of the kidney.

In the next paper evidence is presented showing that alterations in the urea concentration of the urine play no appreciable part in the production of these variations.
Fig. 2. The effect of changes in blood urea concentration on the rate of urea excretion. Observations on a single individual.
CONCLUSIONS.

1. A curve has been constructed which indicates the effect of changes in blood urea concentration on the rate of urea excretion in man.

2. The wide scattering of the observations from which the curve was constructed shows that other factors than blood urea have a pronounced effect on the rate of urea excretion.

3. There is a relative decrease in the degree of scattering, as the blood urea concentration increases. This is interpreted as indicating that the greater the stimulus to increased work in excreting urea, the less subject the kidney becomes to influences tending towards variability in its rate of work.

4. The variability in the rate of urea excretion at every level of blood urea concentration during the short periods of time chosen in these experiments is in marked contrast to the uniformity in the rate of excretion of administered urea over periods of 8 to 24 hours. This is taken as indicating that unknown factors lead to short-lived variations in the rate of excretion, and that these variations tend to counterbalance one another over longer periods.

5. The degree of scattering in one individual is as great as the scattering in the whole group. This makes untenable the hypothesis that permanent individual peculiarities, such as might arise from anatomical differences in kidney structure, are responsible for the variability in the rate of urea excretion revealed by the scattering shown in Fig. 1 for the group.
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