# STUDIES OF UREA EXCRETION. VIII. THE EFFECTS ON THE UREA CLEARANCE OF CHANGES IN PROTEIN AND SALT CONTENTS OF THE DIET

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In the study of the effects of protein-rich and protein-poor diets on nephritic kidneys, relatively little attention has so far been paid to the changes in functional activity. Indications suggesting that such changes exist are to be found in the observations of Addis and Drury (1) that the "maximum urea clearance" can be slightly but definitely increased by a meal of protein-rich food, and in the recently published findings of Jolliffe and Smith (2) that in dogs fed on a cracker-meal diet low in protein, the urea clearance is markedly lower than on a high protein diet.

It appeared desirable, therefore, to obtain more definite information concerning the effects of protein on the function of human nephritic kidneys. As criterion of renal function, the standard urea clearance of Möller, McIntosh and Van Slyke (5) has been employed. The cases presented are unselected, except that those were discarded which showed evidence during the preliminary observational period that activity of the nephritic process was causing a progressive lowering of renal function at the time, and also a few in which infections or exacerbations occurred during the experimental period and were likely to change the renal function. These two types of cases were excluded because they were subject to such rapid changes that it would have been difficult to tell whether functional changes under different regimes were due to change in regime or in renal pathology. The patients used were those in which the renal condition appeared to be in a fairly steady state.

In order to obtain evidence of the effect of salt also on the urea clearance, similar studies were carried out with diets containing large and minimal amounts of sodium chloride. The salt variation had no significant influence on the urea clearance. We shall therefore not detail this part of the work, but merely record its negative results. In one instance the ingestion of 65 grams of sodium chloride and its subsequent excretion at high concentration in the urine had no detectible influence on the urea clearance. It was not found possible, by feeding diets poor in salt, to reduce the plasma chloride to such low concentrations as are

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said by many French writers to cause a nitrogen retention. Diets which reduced the urinary NaCl output to less than 1 gram per day, however, were without effect on the urea clearance.

## METHODS

The usual methods of estimating and calculating the clearance have been employed (5). Urea in both blood and urine has been estimated gasometrically by the method of Van Slyke (7), in the former in 1 cc. samples of whole blood obtained by venipuncture, in the latter in a volume of urine appropriate to the urea concentration anticipated. Duplicate analyses made in all cases agreed within 1 per cent.

After admission to hospital and routine investigation each patient was kept for a week or more on a normal diet containing about 75 grams protein per day. During this time urea clearance determinations, usually eight in number, were made with the patient in bed, for the dual purpose of obtaining average values for the individual on a normal diet, and of making sure that no marked spontaneous change in the urea clearance was taking place. A diet containing 40 grams of protein per day was then given for at least five days before fresh clearance determinations were made. These having been obtained, the protein of the diet was once more increased either to the original 75, or in most cases to 120, grams per day. Rise of the urea clearance during this third period in each of the recorded cases (except the anomalous Bo) was taken as evidence that the depressed clearance in the second period was indeed associated with the low protein diet, and was not an expression of a progressively destructive nephritic process active at the time.

## RESULTS

Thirteen cases of nephritis have been successfully examined in this manner, and the results are indicated graphically in Figure 1. All the clearance values obtained on a given individual are plotted in a single column. The thirteen columns thus represent the thirteen cases studied and are arranged in order of decreasing renal function. The figure at the bottom of each column is the mean standard urea clearance for that individual on a normal diet, expressed in cubic centimeters of blood per minute. The individual clearance values obtained have been plotted as percentages of this figure. Thus in each case an ordinate value of 100 per cent represents the average standard urea clearance for that subject on a normal diet. To take an example, the first column represents observations on the patient M. On a normal diet his mean standard urea clearance was 77.6 cc. per minute. Individual clearance determinations, plotted as small circles, varied from 112 per cent to 79 per cent *of this value*. On a low protein diet the urea clearance fell to between 51 per cent and 62.5 per cent of the original 77.6 cc., i.e. to between 39.6 and 48.5 cc.

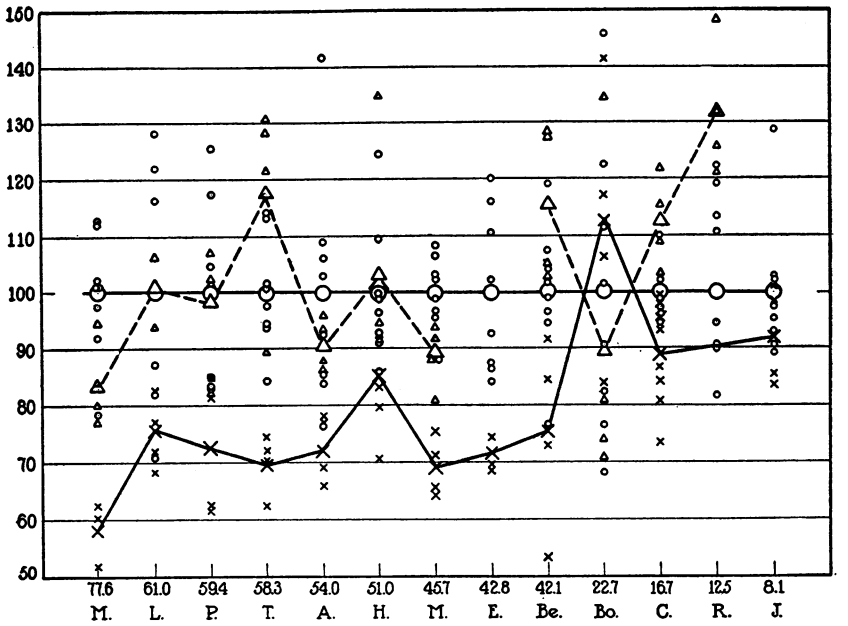


FIG. 1. EACH COLUMN OF SYMBOLS SHOWS STANDARD UREA CLEARANCE VALUES FOR AN INDIVIDUAL WHOSE MEAN STANDARD UREA CLEARANCE ON NORMAL DIET (ABOUT 75 GRAMS PROTEIN PER DAY) IS RECORDED ALONG THE LOWER MARGIN

Ordinates represent clearance values expressed for each subject as percentages of his average clearance on a diet with 75 grams of protein.

o = values obtained on normal diet (75 grams protein per day),
o = mean of these values,
× = values obtained on low protein diet (40 grams protein per day),
× = mean of these values,
Δ = values obtained on high protein diet (120 grams protein per day),
△ = mean of these values.

per minute, as shown by the small crosses. When the daily protein intake was increased to 120 grams the standard clearance rose once more to between 77 per cent and 94 per cent of the original mean, i.e. to between 59.7 and 73.0 cc. per minute, the individual clearances being indicated by the small triangles.

The figure shows that when renal function is unimpaired, or only slightly impaired by the nephritic lesion, as in the first 9 cases, the urea clearance is reduced by from 15 to 40 per cent by diminishing the protein intake from 75 grams to 40 grams per day. Of the remaining cases, with seriously impaired renal functions, two showed a slight reduction of the urea clearance, about 10 per cent, and one was exceptional in having a urea clearance higher on the low protein than on a protein rich diet. No

explanation of this anomalous case is offered. In the remaining case, that of R, the low protein diet was not administered, as her plasma proteins were low and it was felt that such a regime would provoke a recurrence of the edema to which she was liable. This case is included, however, because she showed a well marked rise in her urea clearance when the protein intake was increased to 120 grams per day.

The effect of high protein regime was more irregular than that of the low. Of the eleven cases which had the high protein intake during the third period, the clearances of four rose to well above the figures for the first or moderate (75 grams) protein diet period, those of three others returned to the original values, and those of a further three rose well above the low protein diet figures, but failed to return completely to the original level. The remaining case Bo was again anomalous showing an effect precisely the reverse of the other twelve, her clearance being reduced on the high protein diet.

## DISCUSSION

In 11 out of the 12 nephritic patients who have been examined a definite reduction in the urea excretory activity of the kidneys has been demonstrable on a low protein diet, when this activity has been estimated by the standard urea clearance test.

In this respect our data confirm the observations of Keutmann and McCann (3) which appeared when our experimental work was nearing completion. Keutmann and McCann studied 4 cases of hemorrhagic Bright's disease, and found that the urea clearance was usually higher on high protein than on low protein diets.

In our cases, the effect of low protein diet in reducing the urea clearance is relatively less when the renal activity is already seriously impaired by disease. This fact is in accord with other evidences that the kidney shows a tendency to diminishing variability of activity as the nephritic lesion progresses. Possibly in this instance it is due to retained metabolites stimulating the kidney to a sustained maximal effort.

In all cases the rise in urea clearance caused by increasing the protein intake was accompanied by a rise in the blood urea concentration. However, it appears probable that the kidneys are stimulated by some protein metabolite other than urea. Möller, McIntosh, and Van Slyke (5) found that, when the urea nitrogen content of the blood was increased from the usual normal range of 10 to 16 mgm. per 100 cc. to two or three times as much by feeding urea, the clearance value was not affected. Addis and Drury (1) found that, when the blood urea was first similarly raised by urea ingestion, and later a protein meal or 20 grams of glutamic acid was taken, the meal or amino acid caused a definite decrease in the clearance. The increase in clearance after food or glutamic acid occurred despite the facts that the blood urea had some hours before passed the peak of the

rise which followed urea ingestion, and was falling; and that the amount of urea formed from the food or glutamic acid was insufficient to check the fall in blood urea. It appears probable, therefore, that the stimulus to increased blood urea clearance was something other than urea itself.

In this connection it is of interest that the hypertrophy of the kidneys, which many workers have produced by feeding a high protein diet, could not be fully duplicated by Osborne, Mendel, Park and Winternitz (6) nor by MacKay, MacKay and Addis (4), by feeding urea alone, a fact which tends to suggest that such hypertrophy also is related to the stimulating effect of products other than urea formed from a protein diet.

There is, it is true, one gap in the experimental evidence required to confirm the application of this explanation to our results. All the data available on men have been obtained by starting with subjects in ordinary protein nutrition, with the usual blood urea nitrogen levels of 10 to 16 milligrams per 100 cc. To obtain by urea administration the same blood urea changes that are produced by increasing the protein intake from 40 grams to 75 or more grams, one would need to use subjects who had previously been on a diet containing as little as 40 grams of protein. If urea administration to such subjects did not stimulate a rise in the clearance, it would appear clear that the increased clearances obtained in our subjects by increased protein administration were not due to the accompanying rise in blood urea.

## SUMMARY

The urea clearance was not affected, in either normal or nephritic subjects, by variations in the sodium chloride content of the diet.

Raising the protein content of the diet from 75 grams to 120 grams was also without consistent effect on the urea clearance.

However, lowering the protein intake from 75 grams to 40 grams was accompanied by depression of the clearance in 11 out of 12 subjects *with normal or nearly normal renal function.* In these subjects the clearance on the low protein diet was only 60 to 80 per cent as great as on the 75 gram diet.

In three patients with renal function *below half normal*, the clearance on low protein remained 90 per cent or more of the clearance on the 75 gram diet.

In interpreting subnormal urea clearances as measures of renal function, allowance should be made for the fact that on very low protein diets the lower limit of normal variation may extend down to 50 per cent of the usual normal average, instead of to the 70 per cent minimum found under ordinary conditions (5). In subjects with markedly depressed function, however, the clearance appears to be relatively fixed, and little influenced by protein restriction.

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