RENAL FUNCTION AND THE AMOUNT OF FUNCTIONING TISSUE

THE RATIO: $\frac{\text{UREA IN ONE HOUR'S URINE}}{\text{UREA IN 100 C.C. OF BLOOD}}$ AFTER GIVING
UREA AND WATER *

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This is the first of a short series of papers, the outcome of an attempt to draw quantitative structural deductions from functional results. The few methods used are discussed and criticized only in reference to the question as to whether the results give information in regard to the amount of secreting tissue in the kidney. This narrow point of view has been adopted because the purpose of the inquiry is entirely utilitarian and clinical. All manifestations of renal function have an intrinsic interest from the standpoint of physiology, but it is maintained that only those from which we can draw quantitative conclusions about the amount of tissue in the kidney are of immediate and practical clinical importance.

Such an idea is foreign to nearly all the recent work on this subject. Nevertheless, from the time of Bright up to about the beginning of the last decade, the hope that functional methods might ultimately be used as a measure of the extent of a renal lesion was probably the main incentive to clinical investigation into the function of the kidney. But since Schlayer's papers were published, that is to say, during the very time when technical methods were so perfected as greatly to facilitate the mechanical side of the work, this hope appears to have been abandoned. Schlayer is largely responsible for this modern attitude of disillusion. He demonstrated that there was no quantitative relation between the function of the kidney, as he determined it, and the amount of damage it had suffered experimentally or through disease. But while he rejected the idea of drawing quantitative structural inferences from functional work, he believed that functional methods were of value in detecting, if not the amount, at least the location of disease in the kidney. He thought he could determine whether disease affected mainly the vessels or mainly the tubules. However, it was soon shown that it was impossible to make such a distinction by functional methods. This failure to draw even qualitative anatomic deductions from functional results had a marked psychologic effect; all the more, because, at the same time, the limitations of histologic methods were emphasized. Instances were cited in which no evidence of renal damage was obtained by microscopic examination, although there had been obvious indications of a failure of renal function, and, on the other hand, cases were

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reported with apparently normal function in which gross manifestations of structural derangement were found. In view of all these facts, the tendency of clinical investigators has certainly been to give up what seemed to be a hopeless attempt, to take what they did have—the functional results—and to try to establish classification and treatment on a functional rather than on an anatomic basis.

This view will not be held permanently. At best it is only a confession of failure, the result of inadequacies in present day functional and histologic methods. It can serve only as a preparation for a renewed attempt on the problem of the relation between renal function and structure, the problem which Bright set before himself nearly a century ago.

Improvement in functional methods has been mainly technical. We can now measure more easily, and also more accurately, the amounts of various substances eliminated by the kidney. But in other respects there has been little change. In particular, a fundamental principle applicable to all functional methods, when they are to be used for structural deductions, has been neglected almost entirely. Unless the functional manifestation is the maximal effort of which the organ to be tested is capable, no structural inferences can be drawn from it. For instance, it might be possible, from a measurement of the force exerted, to make a fairly accurate prediction as to the amount of muscular tissue concerned in some action, such as weight lifting—but only if the effort put forth were the greatest the muscles could perform. Thus, two different amounts of muscle tissue might both raise a 10 pound weight. No deduction as to their relative size could be made. But if it were to be found that in one case 50 pounds was all that could be lifted, while in the other case 100 pounds was the maximum, it would be legitimate to conclude, other things being equal, that one was twice as large as the other. In the kidney also the functional output must be at a maximum if quantitative deductions in regard to the amount of the secreting tissue are to be drawn.

In the above example the deduction as to the amount of muscular tissue from the functional result would be valid only if the conditions were such that extramuscular factors were equally operative. So, also, if renal function is to be used as a measure of the amount of secreting tissue, the extrarenal circulatory and nervous factors concerned in excretion must be uniform.

THE UREA RATIO TEST

The Ratio: $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 C.c. of blood}}$ after giving urea and water.

The development and some of the theoretic aspects of this test were dealt with in 1917.¹ Since then the technic has been modified as a

1. Addis: *J. Urol.* **1**:263, 1917.

result of further work on animals² and on man.³ In its present form the method has been in use for two years in clinical work on Bright's disease, and it seems unlikely that any further considerable change will be required, although much remains to be done in regard to the establishment of standards of normality. Only the practical application of the test will be dealt with in this paper.

Two essential conditions are required. One is that the kidney should be placed under circumstances which call for great activity in urea excretion. The other is that there should be an absence of certain specific renal stimulants and depressants. The first is met by the administration of an amount of urea which will raise the concentration of urea in the blood reaching the kidney, while at the same time a diuresis is induced by water drinking. The second is fulfilled if the test is carried out in the morning, before the subject has taken food, and if the collections of urine and blood are not commenced until three hours after the urea has been taken.

The details of the procedure used in clinical work are as follows: At 6 a. m. the patient slowly drinks about 1,000 c.c. water in which urea is dissolved. When the blood urea concentration is between 15 and 25 mg. per hundred c.c., 30 gm. urea are given. If the blood concentration is already as high as 60 mg. of urea per hundred c.c., no urea need be taken. At intermediate blood urea levels appropriate quantities of urea are administered, so that when the first blood is collected it should have a concentration of between 60 and 90 mg. of urea per hundred c.c. At 7 a. m., and every hour thereafter until 11 a. m., the patient drinks two glasses of water. No breakfast is given. Urine is voided every hour, but at 9 a. m., the time at which urination is completed is noted to within thirty seconds, and at 10 a. m., 11 a. m. and 12 noon urine is passed directly into special bottles and the exact time noted. The patient must be instructed to make each voiding as complete as possible, and to take the time at the end, and not at the beginning of urination. For women a special commode is used with a large funnel emptying into a removable bottle. Blood is obtained at the middle of each of the three hourly periods over which urine is collected. The urea content of these urine and blood specimens must be estimated with a high degree of accuracy, for even small errors may markedly influence the ratio if they happen to be in opposite directions for the blood and for the urine.

When these conditions are observed the rate of urea excretion is governed by only two factors, the concentration of urea in the blood

2. Addis, Barnett and Shevky: *Am. J. Physiol.* **46**:1, 22, 39, 52, 1918. Addis, Shevky and Bevier: *Am. J. Physiol.* **46**:11, 129, 1918. Addis, Foster and Barnett: *Am. J. Physiol.* **46**:84, 1918.

3. Addis and Drury: *Proc. Soc. Exper. Biol. & Med.* **23**:24, 1920.

and the amount of secreting tissue in the kidney. Since the concentration of urea in the blood is determined, it follows that the ratio: $\frac{\text{rate of urea excretion}}{\text{urea in 100 c.c. of blood}}$, or as we measure it, $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$, is a measure of the amount of secreting tissue in the kidney.

When the amount of secreting tissue in the kidney is constant, the rate of urea excretion varies directly with the blood urea concentration. In the same normal adult individual the amount of renal tissue may be assumed to remain nearly constant, and if this statement is true, there should be a direct proportion between the amounts of urea in an hour's urine and the amounts of urea in 100 c.c. of blood, so

Fig. 1.—The amount of urea in one hour's urine is directly proportional to the amount of urea in 100 c.c. of blood, when the amount of renal tissue is constant, and when certain conditions are observed. Observations on the same subject at different levels of blood urea concentration.

that the rates plotted against their respective blood urea concentrations should fall in a straight line. Figure 1 shows a series of hourly rates measured in the same individual. The blood urea concentrations were varied by administering varying quantities of urea.

These experiments show that when the amount of renal tissue is constant there is a direct relation between the rate of urea excretion and the blood urea concentration, so that changes in the level of urea concentration in the blood between 20 and 120 mg. are associated with corresponding changes in the rate of urea excretion.

It should be emphasized that this is not a general law. It holds true only under the special and peculiar conditions which have been

outlined. We have many rates, observed in the subject from whom the measurements shown in Figure 1 were obtained, which show how far the rate of urea excretion may vary from any direct relation with the blood urea concentration, and we have already given many instances of great variations in the rate in spite of a constant blood urea concentration.⁴ These variations are of particular interest and importance as showing the high degree of adaptability inherent in the mode of action of the kidney, and its freedom from subjection to merely physical and mechanical conditions. But when we wish to deduce the size of the kidney from its function, all this complex mechanism of adjustment, of concurrent or alternating inhibition and excitation, must be merged in the drive toward the maximum rate of excretion allowable under the circumstances. The fact that such a direct relationship between blood concentration and rate of excretion can be demonstrated, is an indication that we have succeeded in attaining this unity of action, and that under these special conditions all the circulatory and nervous factors concerned in renal activity are working together towards one end.

When the amount of renal tissue varies, the ratio: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ is directly proportional to the amount of secreting tissue in the kidney. This again, of course, is no general law, but is true only under the specific conditions described. The detailed proof will require much further work, but there is already sufficient evidence that it is at least approximately true. It has already been shown, though at that time the conditions under which the ratio ought to be measured were only imperfectly understood, that the loss of renal substance involved in the removal of one kidney,⁵ or the variable loss arising from differing degrees of uranium intoxication,⁶ was revealed by the degree of depression in the ratio. We are now engaged in a study of the relation between the weight of the kidneys and the magnitude of the ratio in rabbits. It appears that in the rabbit every 10 gm. of renal tissue—the average weight of both kidneys in a medium sized animal—will yield a ratio of approximately 1.75. In man the average weight of both kidneys is about 300 gm. If there is a direct relation between the magnitude of the ratio and the size of the kidney, we should, accordingly, expect to find that the average ratio in man was 1.75×30 , or 52.5. Our present average for normal adults is 50.4—a sufficiently close agreement.

In Table 1 all the ratios obtained from normal persons under these conditions are given. There are 163 in all. The number of persons is

4. Addis and Watanabe: *J. Biol. Chem.* **27**:249, 1916.

5. Addis and Watanabe: *J. Biol. Chem.* **28**:251, 1916.

6. Watanabe, Oliver, and Addis: *J. Exper. M.* **28**:359, 1918.

thirty-one. Almost all of them were medical students between 23 and 30 years of age. In a few cases the amount of urea taken varied, but in the great majority 30 gm. were given. The average ratio is 50.4, the standard deviation ± 6.61 and the variability (the standard deviation as a percentage of the average) 13.1 per cent.

Part of the variability in the ratios obtained from different normal persons is no doubt due to differences in the amount of renal tissue

TABLE 1.—RATIOS OBTAINED FROM NORMAL ADULTS AFTER ADMINISTRATION OF UREA AND WATER

Name	Ratio	Name	Ratio	Name	Ratio	Name	Ratio
Dru.	56.9	Add.	45.1	Geo.	43.5	Nak.	43.0
	58.8		45.4		42.0		48.0
	56.0		42.3		38.5		47.0
	58.4		44.0		39.7		45.0
	57.6		51.4				
	54.4		42.9	Jae.	60.8	Ank.	48.4
	53.0		45.6		60.8		48.8
	54.6		44.8		61.4		56.0
	57.7		43.5		54.9		
	58.5		50.9			War.	45.9
	54.2		49.6		39.2		49.1
	54.0		43.3	New.	39.2		51.0
	53.6		41.9		39.8		
	49.1		50.9		39.6	Dia.	48.2
	50.4		47.8		38.3		45.5
	57.4		43.1		35.9		48.0
	55.3		45.3		38.5		
	52.4		49.3			Ves.	46.7
	56.1		44.3	Pis.	45.1		43.8
	55.0		50.7		58.7		53.8
	52.6		42.4		42.5		
	51.2				51.4	Dun.	50.5
	55.2	Jen.	54.1		55.3		48.5
	53.8		48.3		47.1		41.9
	58.4		51.1				
	57.4		46.6	Kol.	60.7	Moo.	50.0
	61.1				61.7		49.0
	58.5	Hun.	58.4		57.6		46.1
	53.4		58.2		58.2		
	56.4				56.9	Bin.	49.0
	57.6	Aze.	55.9		54.2		52.3
	59.0		52.6		56.0		47.7
	61.1						
		Har.	38.6	Col.	66.5	Sea.	54.5
Col.	41.2		38.1		59.4		55.1
	45.6		36.7		65.9		55.9
	44.2						
	47.4	Chr.	43.7			Kel.	51.5
			48.6				51.6
Swe.	45.9			Cim.	52.4		
	49.6	Pro.	46.3		47.8		
	45.8		54.0		44.8		
			54.4			Pie.	51.1
Sei.	44.7			Mye.	46.0		47.0
	49.7				48.0		46.2
	50.2	Nor.	53.2		48.5		
	55.6		56.9		39.5	Nap.	53.0
	54.5		58.6		41.0		55.6
	56.1		64.8		40.0		54.6

they possess. The true variability, i. e., the fluctuations due to the influence of other physiologic factors then the size of the kidney and to errors in collection and chemical technic, can be gaged in a rough way from the variability of the ratio in a single person. We have thirty-three ratios in the subject Dru. and the variability is only 5.1 per cent., as compared with 13.1 per cent. in the group. Some means should be found whereby the effect of these variations in the amount

of renal tissue in normal persons could be discounted. It is highly desirable for adults, and in dealing with children it is absolutely necessary, for their ratios are, of course, much lower than those obtained from adults, so that no direct comparison is possible. There is no doubt some relation between body weight and renal weight, and in the case of children we correct the ratio by reference to a curve drawn from average figures given by Vierordt⁷ on the percentage of kidney weight to body weight at different ages. But we have not found any data from which the reliability of this correction can be calculated.

Fig. 2.—Provisional separation of ratio obtained in adult men or women into those which can be regarded as within the limits of normal variation (normal ratios), those which are regarded as beyond these limits (abnormal ratios), and those which cannot with any certainty be described as either normal or abnormal (doubtful ratios).

It seems likely that the relationship is far from being a close one. Warthin,⁸ who has been interested in this subject, thinks that the most reliable estimate of the range of variation in renal weight in adults is from 110 to 145 gm. for the right kidney, and from 150 to 180 gm. for the left, and he is impressed with the variability of the relation between kidney weight and body weight. Stewart⁹ recently published some figures which showed that kidney weight varied more

7. Vierordt: Arch. f. Anat. u. Physiol. Anat. Abt., Suppl. **62**: 1890.

8. Warthin, Practical Pathology, Ed. 2, George Wahr. Ann Arbor, Mich., p. 155.

9. Stewart, Am. Physiol. **57**:45, 1921.

directly with body surface than with body weight. We are at present collecting data on this question. In the meantime, it seems preferable to use the ratio without attempting any correction for adults even though the range in which there is doubt as to whether normality or abnormality exists is thereby considerably widened. From the average and standard deviation of the ratios obtained from normal persons we have calculated the odds that any normal person would have as low or a lower ratio than those given in Table 2. The limits of the normal, the doubtful and the abnormal are provisionally and arbitrarily indicated. They are also shown in Figure 2.

Examples of the application of this method in clinical work will be given in a later paper of this series. We have found it of value in the diagnosis, prognosis and treatment of Bright's disease.

TABLE 2.—THE ODDS THAT ANY NORMAL PERSON WILL HAVE AS LOW OR A LOWER RATIO THAN THOSE GIVEN IN THE TABLE

Ratio	Odds	
50.4 or less.....	1 in 2	Normal
40.5 or less.....	1 in 15	
39.8 or less.....	1 in 18	Doubtful
39.2.....	1 in 22	
38.5.....	1 in 28	
37.9.....	1 in 35	
37.2.....	1 in 44	
36.5.....	1 in 56	
35.9.....	1 in 72	
35.2.....	1 in 93	
34.5.....	1 in 122	
33.9 or less.....	1 in 162	Abnormal
33.2.....	1 in 213	
32.6.....	1 in 286	
31.9.....	1 in 385	
31.2.....	1 in 527	
30.6.....	1 in 741	
27.9.....	1 in 1,630	

CONCLUSIONS

1. Under certain special conditions, when the amount of secreting tissue in the kidney is constant, the amount of urea excreted in the urine in one hour is directly proportional to the amount of urea in 100 c.c. of blood sampled during that period.

2. Under certain special conditions, when the amount of secreting tissue in the kidney varies, the ratio: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ is directly proportional to the amount of secreting tissue in the kidney.

3. The conditions under which the ratio: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ becomes a measure of the amount of secreting tissue in the kidney are, first, that the urea excreting capacity be placed under a strain so that all the secreting tissue is called to full activity, and second, that there be an absence of the effect of certain specific renal stimulants and depressants.