The Archives of Internal Medicine

Vol. XIX

JANUARY, 1917.

No. 1

THE CLINICAL VALUE OF AMBARD'S COEFFICIENT OF UREA EXCRETION *

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In the study of any metabolic process account has to be taken of the excretion of waste products, the food intake, and also the various changes which this food undergoes in the body before the end-products are ready for excretion. The last constitutes the intermediary metabolism, of which our knowledge is still very imperfect. If any one of these groups of processes is studied to the exclusion of the others, very erroneous ideas regarding the metabolism will be obtained. Likewise, in the study of renal function chemical observations of any one of these processes (nitrogen intake or output, or retention of waste nitrogen) will fail to give accurate information unless something is known of the other metabolic factors. Little value can be attached to the finer changes in the level of the blood urea, or total nonprotein nitrogen, as a gage of renal function, unless the protein intake is known. Widal¹ suggested this precaution several years ago, but reference to the patient's diet is of rare occurrence in studies of renal function by the tests of retention. The necessity of such information is constantly increasing because of the popularity of low protein diets in the treatment of the azotemic type of nephritis. With the diet devised by Mosenthal and Richards² reductions of 75 per cent. in the level of the total nonprotein nitrogen are of frequent occurrence, so that values of from 30 to 35 mg. are not unusual, even in severe nephritis. An estimation of the protein intake should be given, therefore, in every case in which conclusions regarding renal function are being drawn from studies of the waste nitrogen of the blood.

The excretion of various substances in the urine has also been used in testing renal function. These tests are of a qualitative and quantitative nature.

* Submitted for publication July 21, 1916.

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1. Widal and Javal: *Compt. rend. Soc. de biol.*, 1904, **56**, 301.

2. Mosenthal, H. O., and Richards, A. E.: *THE ARCHIVES INT. MED.*, 1916, **17**, 329.

To make a qualitative test of renal function, a somewhat copious diet³ is given at fixed intervals, and the variation in the volume and specific gravity of the urine is studied in two-hour periods during the day. The night voiding is collected in one specimen and studied as a whole. The normal reaction to these three meals is a markedly variable specific gravity during the day, with an output of from 65 to 75 per cent. of the water during this period and the excretion of a small amount of highly concentrated urine at night. No attention is paid to the relative intake and output of nitrogen and salt, their concentration being the criterion on which a decision is based. These test diets give valuable information in the study of renal function in nephritis, both in the early and late stages of the disease.

Ambard⁴ has followed the same general principles in his studies of renal function by the determination of the kidney's maximal concentrating power. He has found a diminution of the maximal concentration to be one of the earliest signs of impaired function. With each advance in the renal injury there was a corresponding diminution in the maximal concentration.

Siebeck⁵ and his associates have also applied the same principles in their studies of the concentrating and diluting powers of the kidney. Their results confirm Ambard's findings.

There is one possible exception to the conclusions stated above. In severe anemia, with a marked hydremia of the blood, a low, fixed specific gravity is a constant finding. Whether hyposthenuria in such cases is of renal origin or a result of the constitutional changes has not been decided. A few cases show a decreased phenolsulphonephthalein output and an increased coefficient of urea excretion, pointing to definite renal involvement. In other cases these changes are absent and no direct evidence of kidney insufficiency can be obtained.

As quantitative tests to determine the reaction of the kidney to an overload of the ordinary metabolic products, large amounts of urea, sodium chlorid and water are added to a standard diet and the results are studied. No attention is paid to the concentrating power of the kidney, and all normal requirements are satisfied by the excretion of a certain proportion of the added substances within a given time.

The phenolsulphonephthalein test is the only test dependent on the excretion of foreign substances at present in common use. It requires no description.

According to Mosenthal and Richards² very little information

3. Mosenthal, H. O.: *THE ARCHIVES INT. MED.*, 1915, **16**, 733.

4. Ambard, L.: *Physiologie normale et pathologique des reins*, Paris, 1914, p. 9.

5. Hefter and Siebeck: *Deutsch. Arch. f. klin. Med.*, 1914, **114**, 497. Doll and Siebeck: *Ibid.*, **116**, 549.

regarding the intermediary metabolism can be obtained from a determination of the nitrogen balance. Even in severe nephritis there is no relation between the amounts of nitrogen retained and the level of the waste nitrogen in the blood. The discrepancy between the intake and output cannot be regarded as an evidence of renal insufficiency. The nitrogen balance cannot be used for the quantitative study of renal function.

An ideal quantitative method, however, would be a direct comparison of the processes of the intermediary metabolism with those of excretion, in other words, a comparison of the concentration of the waste nitrogen in the blood with its rate of excretion in the urine. Under such conditions the unknown factors would be reduced to the rate of blood flow through the kidney and the functional activity of that organ. Such studies have been made possible by the work of Ambard and his associates.

Lamy and Mayer⁶ endeavored to compare the concentration of urea in the blood with the rate of excretion in the urine. They did not recognize the importance of the rate of blood flow, and consequently were not able to find any relation between the two values. Five years later Ambard and Moreno⁷ announced their laws of renal function. They were three in number, and reduced the study of kidney activity to a physicochemical basis. The blood urea was regarded as a stimulus acting on the renal cells. The rate of excretion of urea was the response of the kidney to that stimulus. In their opinion the rate of circulation through the kidney was the chief factor governing the concentration of the urine. A dilute urine was a sign of a high rate of blood flow, while a diminished blood supply was shown by the increase in the concentration of the urine and a consequent diminished output of water and of urea.

The first law dealt with the relation of the rate of output of urea to the concentration of urea in the blood. The rate of output was found to vary directly with the square of the concentration of urea in the blood, if the concentration of urea in the urine remained constant. In other words, if the quantity of urea in the blood were doubled, the amount excreted in a given time would be quadrupled.

According to the second law, the rate of excretion of urea varied inversely with the square root of the concentration of urea in the urine, if the blood urea remained constant. Under these conditions a quadrupling of the concentration would result in a halving of the rate of output.

6. Lamy and Mayer: *Jour. de physiol. et de pathol. gén.*, 1905, **7**, 679.

7. Ambard, L.: *Compt. rend. Soc. de biol.*, 1910, **69**, 411, 506. Ambard, L., and Weill, A.: *Jour. de physiol. et de pathol. gén.*, 1912, **32**, 217.

The third law was a combination of the first and second. If the concentration of the urea in the blood and urine varied simultaneously, then the rate of output would vary directly as the square of the concentration of urea in the blood, and inversely as the square root of that in the urine.

The following formula, used in calculating the coefficient, is derived from the third law by the addition of correction factors for the patient's weight and for a standard urinary concentration of 25 gm. of urea per liter.

$$K = \frac{Ur}{D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}$$

K = coefficient of urea excretion.

Ur = grams of urea per liter of blood.

D = output of urea in grams per twenty-four hours.

P = weight of the patient in kilograms.

C = grams of urea per liter of urine.

70 = standard weight.

25 = standard concentration of urea in the urine.

All weights and concentrations are compared to the standards of 70 and 25.

The normal value of the constant is from 0.06 to 0.09. With a decreasing kidney efficiency there is a rise in the constant, and with an increasing function the coefficient falls.

The analytical methods used by the French had been so inaccurate that this work remained practically unknown in this country until McLean and Selling⁸ repeated the work, using more accurate methods, and found the coefficient to have the same degree of constancy that Ambard had found four years previously.

In a second paper McLean⁹ discusses the laws of function somewhat fully. He concludes that "the excretion of urea and chlorids in the normal individual is carried out according to definite laws capable of numerical expression." He finds, however, that in normal, healthy adults the laws of function are not followed so closely as by individuals living under conditions of ward routine. In the former he finds a tendency to a low concentration of blood urea, and a greater output of urea than is justified by the laws of function. In the latter cases, the blood urea is uniformly higher and the laws of function are followed more closely. These variations from the laws of function are considered merely as signs of the ready response met with in healthy young adults, living an active life. The validity of this conclusion is strengthened by the fact that variations from the laws of function are always in the direction of a hyperfunction of the kidney.

8. McLean, F. C., and Selling, L.: Jour. Biol. Chem., 1914, **19**, 31.

9. McLean, F. C.: Jour. Exper. Med., 1915, **22**, 212.

Recently, Addis and Watanabe¹⁰ have applied Ambard's laws to the results obtained in the studies of urea excretion in normal students. They find a very marked discrepancy between the laws of function and the results actually obtained. The most serious differences are seen in the second law, in which variations of 150 per cent. from the theoretical values are not uncommon. In the application of the first law the variations are of a less serious character. They conclude that the variations in urea output cannot be explained by the concentration of urea in blood and urine. The subjects of these experiments are of the same type as those which McLean finds to show the greatest variations from normal.

In the present series of forty normal hospital patients, it was possible to test the validity of Ambard's laws of function in a number of instances.

A number of cases had identical concentrations of urea in the blood. In these cases, according to Ambard's second law, the expression

$$\text{Rate of output} \times \sqrt{\text{Conc.}^n \text{ of urea in the urine}} \times \frac{70}{\text{Kg. of body wt.}}$$

should be a constant in each group of cases. The maximum error in this law was 47 per cent. but the average error was 20 per cent. This was decidedly lower than those reported by Addis and Watanabe.

In the same way, twelve groups of from two to five cases each were found having the same concentrations of urea in the urine. According to the first law

$$\frac{\text{Concentration of urea in blood}}{\sqrt{\text{Rate of output} \times \frac{70}{\text{Kg. of body wt.}}}}$$

should be a constant for each group. The adherence to this law of function was remarkably good. In very few of the cases did the factor show a variation of more than 10 per cent. from a normal value. The maximum variation was 30 per cent., the average in the neighborhood of 8 per cent.

It is evident from the above that the laws of function are followed more closely by individuals living under routine conditions than by those living on a more luxurious diet and subject to the strain of active life.

It has been claimed¹⁰ that the mathematical form of the coefficient is the real basis of its constancy and that the laws of function play absolutely no rôle in the attainment of this end. Addis and Watanabe claim that Ur is a relatively constant value and that it is the dominant factor in keeping the coefficient constant. On the other hand, D and C are the factors which are subject to considerable variation. The effects

10. Addis, T., and Watanabe, C. K.: Jour. Biol. Chem., 1916, **24**, 203.

of these variations are minimized by the fact that the greater variant is present as its fourth root, and the lesser as its square root. While their assumption is partly true, the fact remains that the blood urea is not always a constant value. In a series of nephritics here presented there are instances of enormous variations in the blood urea, without any corresponding change in the coefficient of urea excretion. While, strictly speaking, the laws of function may be mathematically inaccurate, and the formula from which the coefficient is calculated may tend to hide these inaccuracies, still there is a very definite relationship between the concentration of the urea in the blood and in the urine and its rate of excretion. Under similar conditions of urine concentration the rate of urea excretion is always greater with a high concentration of blood urea than with a low one. Similarly, in the presence of a stationary blood urea concentration the amounts of urea excreted under conditions of polyuria and low urinary concentration are greater than when the volume is small and the concentration high.

In spite of the lack of mathematical accuracy, the normal coefficient of urea excretion falls within comparatively narrow limits.

Objection has been made to the original form of the coefficient because the normal value is not a whole number, and because a diminishing renal function causes a rise in the coefficient. Balavoine and Onfray¹¹ have advocated the use of a formula giving the normal coefficient a value of 1, and so arranging the equation that a diminution in renal function would cause a drop in the constant. Their suggestion was not well received in France.

Ambard¹² has suggested a means of calculating the functional capacity of a damaged kidney in terms of percentage of the normal. For example, if, after the injection of urea, a normal individual presents a blood urea of 0.7 gm. per liter, his rate of output should be 100 gm. per twenty-four hours, at the standard concentration of 25 per 1,000. This gives a coefficient of 0.07. If a nephritic with a similar concentration of blood urea excretes only 25 gm. at the standard concentration, his rate of output is reduced to a quarter of the normal. His coefficient under these conditions would be 0.14, because

$$K = \frac{\text{Blood urea}}{\sqrt{\text{Rate of output}}} = \frac{0.7}{\sqrt{25}} = 0.14$$

Again, if the rate of output were reduced to one-ninth the normal, or 11.11 gm., the coefficient would be

$$\frac{0.7}{\sqrt{11.11}} = 0.21.$$

11. Balavoine and Onfray: *Presse méd.*, 1912, **21**, 786.

12. Ambard: *Physiologie normale et pathologique des reins*, Paris, 1914, p. 200.

The absolute functional value of the kidney can also be obtained from the coefficient by the use of the following equation:

$$\left[\frac{\text{Normal coefficient}}{\text{Pathologic coefficient}} \right]^2 = \text{Functional value of the kidney in terms of normal.}$$

If we apply this formula to the first case, $\left[\frac{0.07}{0.14} \right]^2 = 0.25$, that is, the functional capacity of the kidney is reduced to one fourth of the normal value. This corresponds to the theoretical diminution in the rate of output. The same applies to the second case. $\left[\frac{0.07}{0.21} \right]^2 = 0.11$, or one ninth of the normal value.

McLean's index⁹ is based on this modification of the original coefficient. In his opinion the average normal coefficient is 0.08, and this is used in the fraction

$$\left[\frac{\text{Normal } K}{\text{Pathologic } K} \right]^2$$

instead of 0.07. To simplify calculation, the expression

$$\frac{Ur}{\sqrt{D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}}$$

is substituted for the pathologic constant, and to avoid the use of decimals, the resultant is multiplied by 100. The formula

$$I = \frac{D \sqrt{C} \times 8.96}{Wt. \times Ur^2}$$

is obtained by simplifying the above fraction. *I* is the index of urea excretion. The normal value of the index is 100 and the maximal range is between 80 and 250. The index expresses the functional capacity of the kidney in percentage of normal.

So much work has been published in the European journals in which the original coefficient is quoted, and the normal index shows such enormous variations that it seems unnecessary to have added this new value. However, the index of urea excretion has been included in the tables for purposes of comparison.

In the present series the total nonprotein nitrogen and the urea nitrogen of the blood, and the excretion of phenolsulphonephthalein will be compared with the coefficient of urea excretion.

METHODS

The concentration of urea in both urine and blood normally shows great variations in the course of the day, particularly in relation to meals. This makes it impossible to compare the concentration of

blood urea at any one time with the daily output of urea. Ambard avoided this difficulty by studying the renal activity over a comparatively short period, the time chosen being as remote as possible from a meal rich in protein. The majority of our studies were made two to three hours after breakfast. The amount of urea excreted in the test interval, calculated for a twenty-four-hour period, therefore, represents the quantity of urea which would be eliminated in a day, provided the concentration of the urea in the blood and urine remained constant during the whole twenty-four hours. The latter is a condition impossible of attainment under any circumstances.

Theoretically, the shorter the period of observation, the more accurate should be the results. In the wards of a general hospital, however, it is impossible to depend on the absolute punctuality with which specimens are obtained. To lessen the effect of this error, a longer period has been used than that suggested by Ambard and McLean.

Half an hour before the first voiding, the patient is given 200 c.c. of water. This insures a free diuresis during the test period, and facilitates the prompt collection of specimens. The first specimen of urine is discarded. Exactly two hours after the first voiding, the patient again empties the bladder. The second specimen represents the amount of urine secreted during the period of observation. It is measured carefully to within 1 c.c. and is used for analysis. Midway between the voidings 10 c.c. of blood are drawn into a tube which contains a drop of saturated potassium oxalate solution to prevent clotting. The concentration of urea in this specimen represents the average level of the blood urea during the test period.

The urea in the blood and urine may be determined accurately by Marshall's urease methods.¹³ The procedures are simple and rapid. Duplicate determinations are unnecessary after one has become familiar with the technic.¹⁴

From the results of the foregoing analyses the twenty-four-hour output of urea (D) is calculated. The concentration of the urea in the blood (Ur) and in the urine (C) and also the patient's weight in kilograms (P) are substituted in the formula

$$K = \frac{Ur}{D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}$$

13. Marshall, E. K.: Jour. Biol. Chem., 1913, **14**, 283; *ibid.*, **15**, 487.

14. Urease-Dunning tablets have been used exclusively. Two 25-mg. tablets were found sufficient to digest 5 c.c. of urine in three hours at 37 C., while the urea in 5 c.c. of blood was completely decomposed by three tablets in thirty minutes at 37 C. Each batch of enzyme should be tested for preformed ammonia and a suitable correction applied, if necessary.

The solution of the equation gives the value of K , which is the coefficient of urea excretion.¹⁵

In determining the total nonprotein nitrogen of the blood Folin's¹⁶ method of precipitation and digestion was used. A combination of heat and aeration was employed in removing the ammonia from the digestion mixture.

In making the phenolsulphonephthalein test Rowntree and Geraghty's¹⁷ technic was followed in the determination of the rate of excretion. The two-hour output was recorded, as no marked significance could be attached to the hourly excretions. In cases with marked edema the dye was injected intravenously and the amount excreted in the first hour was recorded.

TYPES OF CASES STUDIED

The series contains a considerable number of individuals with no cardiorenal changes, mostly hospital patients. Cases of fever, hyperthyroidism and myxedema are included. Cardiac cases are presented in the stage of decompensation, and also when well compensated. The group of nephritics contains examples of all the usual types of nephritis, both acute and chronic. There are cases of mercury bichlorid and salvarsan poisoning, and also three cases of polycystic kidney.

NORMAL CASES

With few exceptions, the cases presented in this group are ward patients in whom the cardiorenal system is normal on routine examination. All persons convalescing from acute infections, diabetics with severe acidosis, and cases of hyperthyroidism are excluded, even though the urine be free of albumin and casts.¹⁸

Ambard gives 0.07 as the normal value of the coefficient, with normal range of from 0.06 to 0.08. In a series of 107 determinations, McLean finds the maximum normal range of the coefficient to be from 0.05 to 0.09 (index 235-80). He considers any coefficient above 0.09 (index below 80) distinctly abnormal, unless the reduced rate of urea excretion can be accounted for. An insufficient water intake is a possible cause of increased values of the coefficient in quite normal

15. The use of an ordinary 10-inch slide rule greatly facilitates the calculation, reducing the whole operation to approximately sixty seconds. McLean (Footnote 9) has devised a special slide rule for the determination of his index, but this is unnecessary in the calculation of the original coefficient.

16. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1912, **11**, 527.

17. Rowntree, L. G., and Geraghty, T.: *THE ARCHIVES INT. MED.*, 1912, **10**, 284.

18. It has been found that many of these cases do not have a normal renal function. The phenolsulphonephthalein excretion is increased, and the rate of urea excretion is much greater than is justified by the concentration of urea in the blood.

TABLE 1.—NORMAL CASES

Case Number	Medical Number	Urea N Mg. per 100 C.c. Blood	Coefficient	Index	'Phthal- ein Output, % 2 hr.	Diagnosis
301		9	0.053	228	55	Psychoneurosis
302	H. G.	12	0.054	220	..	
303		14	0.056	204	..	Primary anemia
304	34128	20	0.058	190	..	
305	34365	10	0.062	167	62	Psychoneurosis
306	D. S. L.	13	0.062	167	60	
307	D. S. L.	10	0.066	147	..	
308	D. S. L.	7	0.058	190	..	
309	34717	16	0.063	161	..	Primary anemia
310	34331	14	0.064	156	57	Cerebral arteriosclerosis
312	35118	10	0.067	143	56	Neurasthenia
314	34680	14	0.072	124	66	
315	33714	14	0.072	124	76	Syphilis, tertiary
316	33629	17	0.073	120	..	Primary anemia
317	33692	16	0.074	117	60	Gastroptosis
319	34967	19	0.075	114	65	Diabetes mellitus
320	35011	11	0.076	111	47	Colloid goiter
321	33986	16	0.077	108	67	Multiple sclerosis
322	34688	14	0.077	108	..	Syphilis
323	34817	11	0.077	108	..	Primary anemia
325	34716	20	0.078	105	..	
326	34634	13	0.079	102	50	Neurasthenia
327	35097	18	0.079	102	60	Syphilis, tertiary
329	34674	23	0.081	97	66	
330	35102	14	0.082	95	51	Obesity
332	34915	11	0.082	95	57	Pyloric stenosis
333	35315	13	0.083	93	55	Neurasthenia
335		16	0.085	89	60	Chronic appendicitis
336		10	0.087	85	67	
337	34195	17	0.087	85	55	General paresis
339	34709	17	0.092	76	55	Intestinal parasitism
340	34657	20	0.092	76	79	Psychoneurosis

persons. These effects of dehydration are guarded against by the ingestion of water before the test period. The findings in our series of forty normal persons are given in Table 1. They are arranged in the order of increasing coefficients. The concentration of blood urea is given in every case, and the phenolsulphonephthalein output is included whenever the figures are available.

The coefficients vary from the minimum of 0.053 to a maximum of 0.092, with an average value of 0.074. This is somewhat lower than the average normal (0.08) given by McLean.

Of the forty cases, twenty-two, or 56 per cent., had coefficients between 0.065 and 0.085, while 82.5 per cent. had values between 0.06 and 0.09.

Normal values of blood urea have been found to vary between narrow limits. Folin and Denis¹⁹ give the normal variation as from 11 to 14 mg. of urea nitrogen per 100 c.c. However, when clinical material without renal involvement is studied, the results are found to be much higher. According to Folin and Denis,¹⁹ the usual range in such persons is from 10 to 26 mg. per 100 c.c.

In the present series the blood urea nitrogen varies from 7 to 23 mg. per 100 c.c., with an average of 14.4 mg. Of the forty cases, less than 50 per cent. have a concentration of urea nitrogen between 10 and 15 mg., and fully 40 per cent. have a concentration above 15 mg. While relatively few normals present concentrations above the upper normal limit of 25 mg. per 100 c.c. suggested by Rowntree and Marshall,²⁰ still the urea nitrogen approaches this limit in a great number of persons. McLean has found that the laws of function are followed much more closely in cases with a blood urea nitrogen above 14 mg. than in those having a lower concentration of urea in the blood.

Reference to Table 1 will show the entire absence of relationship between the level of the coefficient and that of the blood urea. In many cases the higher values of blood urea are associated with very low coefficients, and vice versa. (In Case 4, $U-N = 20$ mg., $K = 0.058$; in Case 24, $U-N = 8$ mg., $K = 0.078$; in Case 25, $U-N = 20$ mg., $K = 0.078$.) These findings offer definite proof that the level of Ur is not the dominant factor in the formula

$$\frac{Ur}{\sqrt{D \times \frac{70}{P} \times \frac{\sqrt{C}}{25}}}$$

It is evident that the effects of the variations in Ur are adequately met by corresponding variations in the rate of output. The narrow limits

19. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14**, 29.

20. Rowntree, L. G., and Marshall, E. K.: Tr. Assn. Am. Phys., 1914.

of the normal coefficient (from 0.06 to 0.09) show that while the laws may not be mathematically exact, still they are at least correct in principle.

According to the originators of the phenolsulphonephthalein test, normal persons should excrete from 50 per cent. to 75 per cent. of the dye in two hours. The phenolsulphonephthalein excretion is given in twenty-eight of the forty normals. Two persons failed to excrete 50 per cent. or over, but in both instances the output (47 per cent.) was extremely close to that figure. The output ranged from 47 per cent. to 79 per cent. with an average of 60.2 per cent. There was no absolute relationship between the rate of output and the level of the coefficient, the high and low excretions of the dye being spread irregularly throughout the group. In every instance, however, the values of both phenolsulphonephthalein and coefficient are within normal limits.

Cases Having a Low Coefficient.—It has been shown that in normal individuals, errors of from 10 to 20 per cent. in the first law of function are to be expected. If, however, in certain groups of cases variations of from 50 to 200 per cent. are of frequent occurrence, and are always in the same direction, one would be justified in assuming that the underlying cause must be some change in renal function.

Four groups of cases have been observed in the present series, which show consistently low coefficients of urea excretion. They are (1) the various fevers, (2) cases of hyperthyroidism, (3) cases of primary hypertensive cardiovascular disease, and (4) cases of early chronic diffuse nephritis, with varying grades of edema and salt retention. In general, they show a normal or somewhat low concentration of urea in the blood, a high rate of urea excretion, a variable concentration of urea in the urine, and a high phenolsulphonephthalein output.

Cases of Fever: Variations of renal function during fever are not unknown. Schlayer²¹ mentions fever as one of the extrarenal factors capable of changing renal function. Ambard and Hallion²² have shown experimentally that the rate of excretion of urea is depressed by lowering the temperature of curarized dogs, without any accompanying change in the level of the blood urea. This fall in output amounted to 12 per cent. for each degree of change. Riste and Kindberg²³ showed a definite lowering of the coefficient in early amyloid disease. They believed this depression was due to the early amyloid changes in the kidney, but, in all probability, a large part of the change was caused by the fever associated with the tuberculous

21. Schlayer: *Beihefte z. med. Klin.*, 1912, **8**, 211.

22. Ambard and Hallion: *Compt. rend. Soc. de biol.*, 1912, **72**, 931.

23. Riste, Leon, and Kindberg, K.: *Jour. d'urol. med. et chir.*, 1913, **3**, 561.

process. Achard and Leblanc²⁴ have presented a short series with low coefficient in which are included several cases of fever. They considered the relative increase in the rate of excretion to be a part of the general loss of central control seen in hyperpyrexia.

A considerable variety of cases has been observed, including pneumonia, typhoid fever, acute rheumatic fever, malaria, tuberculosis, pyelophlebitis and acute gout. Observations have been made during both fever and convalescence, and also during intermissions in the fever.

In a majority of cases there was no oliguria; the albumin varied from a heavy cloud to a faint trace, and was completely absent at times. Casts were not constantly present. There was no obvious relationship between the presence or absence of albuminuria and cylindruria and the level of the coefficient.

In Table 2 the various cases are grouped according to the diagnosis, and the arrangement of the subgroups is in the order of ascending coefficients.

The maximum range of the coefficient²⁵ lies between 0.116 and 0.032, with an average value of 0.051. This is 31 per cent. lower than the average normal coefficient. The coefficient is below 0.06 in 77 per cent. of the cases, and in 55 per cent. is below 0.05, while in the normals no constant was lower than 0.053. These low values of the coefficient are not due to an excessive lowering of the blood urea. The average is 12.7 mg. urea nitrogen per 100 c.c., as compared with the normal of 14.4 mg.

The chief point of interest is that with a slightly lowered blood urea there is associated an enormous increase in the rate of output of urea. This is not associated with a marked change in any *one* of the functions of the kidney. It is not the result of a polyuria, or of any marked increase in the concentrating power; sometimes one condition is present, sometimes the other. While the average rate of urea excretion for a blood urea of 0.308 gm. per liter is 17.2 gm. per twenty-four hours, the average in fever for a similar concentration is 36.4 gm., an increase of more than 100 per cent (Table 3). This cannot be regarded as an evidence of hyperpermeability of the renal epithelium. Any kidney capable of raising the concentration of urinary urea to a level 80 times that in the blood can scarcely be called a hyperpermeable organ. The increased rate of output indicates an increased functional activity of the kidney.

24. Achard and Leblanc: Presse méd., 1914, **22**, 365.

25. The highest coefficient (0.116, Case 414) was obtained in a moribund case. It is probable that cardiac failure was largely responsible for the impaired kidney function. Cloudy swelling was the only change at necropsy.

TABLE 2.—FEVER AND CONVALESCENCE

Date	Case No.	Medical No.	Temperature, F.	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $D \times \frac{A}{P} \times \frac{V}{V_{25}}$	Gm. Urea per Liter of Blood, Ur	Urea Nitrogen, Mg. per 100 C.c. Blood	Coef. K	Index	'Phthal- ein Output, % 2 Hr.	Diagnosis	Albumin in Urine
1/ 8/16	400	35269	104.5	17.7	84.1	0.299	14	0.033	588	..	Lobar pneumonia, third day.....	++
1/10/16	...		104.5	26.7	80.2	0.299	14	0.033	588	64		++
1/11/16	...		100.5	30.7	48.7	0.45	21	0.064	156	..		+++
1/12/16	...		99	18.4	44.1	0.407	19	0.061	172	..		++
1/14/16	...		99	32.4	41.6	0.386	18	0.059	184	..		+
1/17/16	...		100	15.3	25.8	0.257	12	0.051	246	73		+
1/22/16	...		99	6.5	13	0.278	13	0.077	108	77		0
1/26/16	...		98.5	10.1	20.5	0.257	12	0.067	197	..		0
3/10/16	401		98.5	31.6	44	0.235	11	0.036	494	..	Lobar pneumonia, day of crisis.....	0
3/19/16	...		98	15.7	27	0.15	7	0.029	762	..		0
4/26/15	402	34022	104.5	21.4	31.8	0.235	11	0.042	390	..	Lobar pneumonia.....	F. T.
5/11/15	...		98	25	32.6	0.364	17	0.064	156	..	Lobar pneumonia.....	0
3/18/15	403	33873	108	22.5	42.1	0.235	11	0.045	315	..	Lobar pneumonia.....	+
4/17/15	...		98	13.6	15	0.278	13	0.072	124	..	Lobar pneumonia.....	0
1/17/16	404	35274	103.5	9.2	27.2	0.278	13	0.053	228	70	Lobar pneumonia.....	0
1/19/16	...		103.5	5.6	22.3	0.257	12	0.047	290	..		T
1/20/16	...		99.5	17.2	43.5	0.321	15	0.049	267	..	Crisis.....	+
1/21/16	...		99	32.8	51.5	0.321	15	0.045	315	..		-
1/22/16	...		99.8	28.6	39.4	0.3	14	0.048	278	..		0
1/24/16	...		97	27.1	35.2	0.214	10	0.036	494	74		0

1/26/16	...	...	97	21.4	28.2	0.257	12	0.048	278	..		-
1/29/16	...	...	97	5.9	13.8	0.214	10	0.057	197	..		-
405	34066	...	100.2	16.7	33.6	0.364	17	0.063	161	..	Lobar pneumonia.....	++
406	34794	...	101.5	11.2	20.4	0.296	14	0.065	152	..	Bronchopneumonia.....	+
407	35319	...	103.5	29.1	57.1	0.493	23	0.065	152	..	Lobar pneumonia.....	++
...	...	...	98.5	15.1	38.8	0.257	12	0.041	380	..		T
408	35081	...	103	17.9	45.6	0.45	21	0.067	143	..	Lobar pneumonia, died 3 days later	+
409	34679	...	104	17.9	65.6	0.257	12	0.032	623	68	Typhoid fever.....	+
...	...	...	100	10.7	16.7	0.214	10	0.032	236	..	Typhoid hematuria.....	+
11/ 8/15	...	...	98	3.6	6.7	0.171	8	0.066	147	59	Typhoid fever.....	T
11/23/15	...	...	98.8	6.6	13.4	0.193	9	0.053	228	65	Typhoid fever.....	T
12/14/15	...	...	98	5.6	8.7	0.171	8	0.038	190	69	Typhoid fever.....	T
4/ 7/16	...	...	104	17.6	37.2	0.235	11	0.039	421	82	Typhoid fever.....	0
1/11/16	410	35159	104	7	18.4	0.171	8	0.04	400	78	Typhoid fever.....	T
1/26/16	...	...	99	4.3	13.9	0.15	7	0.04	400	..	Typhoid fever.....	0
2/ 2/16	...	...	98	8.3	22.9	0.278	13	0.053	190	81	Typhoid fever.....	0
3/ 2/16	...	...	98.2	2.8	8.2	0.107	5	0.037	468	..	Typhoid fever.....	0
8/20/15	412	34255	102	9.1	30.2	0.235	11	0.043	346	..	Typhoid fever.....	F. T.
9/20/15	...	...	98	6.5	10.9	0.3	14	0.063	74	..		0
9/11/15	413	34709	104	8.6	19.7	0.193	9	0.044	331	61	Typhoid fever.....	T
9/29/15	...	...	98	3.2	14.6	0.248	12	0.065	152	..		0
9/15/15	414	34782	102.6	23.4	61	0.384	17	0.047	290	67	Typhoid fever.....	+
9/29/15	...	...	102	20.6	15	0.452	21	0.116	47	..	Typhoid fever, died 3 days later....	++
415	34769	...	104	15.1	26.6	0.272	13	0.053	228	59	Typhoid fever.....	F. T.
8/20/15	416	34619	104	7.9	21.2	0.342	16	0.075	114	..	Typhoid fever.....	T
9/ 9/15	...	...	98.5	20.5	20	0.353	17	0.079	102	..		0

TABLE 2.—FEVER AND CONVALESCENCE—(Continued)

Date	Case No.	Medical No.	Temperature, F.	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $70 \sqrt{C} \times \frac{D}{P} \times \frac{1}{\sqrt{25}}$	Gm. Urea per Liter of Blood, Ur	Urea Nitrogen, Mg. per 100 C.c. Blood	Coefficient K	Index	'Phthal- ein Output, % 2 Hr.	Diagnosis	Albumin in Urine
9/15/15	...		99	3.5	7.9	0.275	13	0.097	68	50		0
417	34994		101.6	9.2	9.7	0.285	11	0.076	111	..	Typhoid fever.....	T
418	35126		100	30.9	53.7	0.278	13	0.038	444	72	Tuberculous meningitis, died 3 days later	++
12/10/15	...		101	26.7	47.5	0.343	16	0.05	236	..		++
11/20/15	419		102	22.8	30.7	0.257	12	0.046	303	80	Pulmonary tuberculosis; broncho-pneumonia	F. T.
11/21/15	...		99.8	12.6	19.5	0.214	10	0.049	267	..		T
11/22/15	...		100	4.9	12.4	0.321	15	0.095	71	60		T
11/23/15	...		100.2	11.7	16.1	0.235	11	0.059	184	68		T
11/26/15	...		99.8	3.8	10.5	0.235	11	0.073	120	58		T
12/ 1/15	...			8.4	17.8	0.257	12	0.061	172	..		0
12/14/15	...		100.5	7.2	14.2	0.214	10	0.057	107	78		0
12/ 3/15	420		102	6.2	11	0.214	10	0.064	137	56		F. T.
12/14/15	...		101	21.4	39.8	0.257	12	0.041	380	90	Tuberculosis, pleurisy.....	0
12/30/15	...		100	8	19.9	0.171	8	0.038	442	68		0
1/26/15	...		98	7.7	16.1	0.257	12	0.064	156	63		0
2/27/15	...		98	3.8	7.8	0.214	10	0.076	111	61		0
421			102.5	31.6	35	0.3	14	0.051	246	..	Acute rheumatic fever.....	T
422			98.6	9.7	11.4	0.171	8	0.051	246	..	Pylephlebitis.....	0
...			103.6	4.7	9.4	0.171	8	0.055	211	..		0
423			101			0.214	10	0.047	220	..	Acute gout.....	0
424	35184½		96.4	15.5	42.2	0.364	17	0.056	204	..	Malaria.....	0

Associated with this improved nitrogen excretion, there is a well-marked increase in the phenolsulphonephthalein excretion, the average for two hours being 70.5 per cent., compared with a normal of 60.2 per cent.

The cause of this disturbed condition of renal function must be common to all fevers, as there is a complete agreement of the results in all cases. The only features in common are increased temperature and the presence of a toxemia.

The effect of heat on the rate of metabolism has been thoroughly studied. Pflüger²⁶ found that heating curarized animals caused an increase in the rate of gas exchanges of approximately 10 per cent. for each degree (C.) of rise. Linser and Schmid²⁷ found increases in the neighborhood of 13 per cent. for each degree of rise, while Voit²⁸ confirmed these findings by studies on the nitrogen excretion under similar conditions.

TABLE 3.—AVERAGE VALUES OF UREA EXCRETION IN A GROUP COMPRISING HYPERTHYROIDISM, MYXEDEMA AND COLLOID GOITER

Description	Gm. Urea per Liter Blood, Ur	Urea N, Mg. per 100 C.c. Blood	Corrected Rate of Output for 24 Hr. $D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}$	Rate of Output Calcu- lated for $Ur=0.308$	Coeffi- cient	Index	'Phthal- ein Output, 2 Hr.
Normal.....	0.308	14.3	17.2	17.2	0.074	116	60.2
Fever.....	0.272	12.7	28.6	36.4	0.051	246	70.5
Convalescent.....	0.238	11.1	13.4	22.5	0.065	152	63.2
Hyperthyroid.....	0.233	10.9	19.4	33.8	0.053	228	71.8
Hypertension.....	0.22	10.3	17	33.2	0.053	224	65.7
Chronic diffuse nephritis.	0.21	9.8	13.6	29.2	0.057	197	68.2

In moderate grades of fever, however, the nitrogen excretion frequently increases from 100 to 150 per cent., in spite of a low nitrogen intake. This excessive rise has been regarded as an evidence of the toxic destruction of body protein.

Applying these considerations to renal function, we should expect the cells to share in the generally increased metabolism due to hyperthermia, and the rate of output of urea to increase from 10 to 13 per cent. for each degree of fever.

In these cases, however, the rate of output is frequently doubled, while a simple hyperthermia of 3 degrees (C.) would only account

26. Pflüger: Arch. f. d. ges. Physiol., 1878, **18**, 303, 356.

27. Linser, P., and Schmid, J.: Arch. f. klin. Med., 1904, **79**, 514.

28. Voit: Sitzungsberichte der Gesellschaft für Morphologie u. Physiologie, 1895, **2**, 120, quoted by Lusk: Science of Nutrition, 1909, p. 313.

for a rise of 30 per cent. Again, if the increased rate of excretion were due entirely to an overheating of the cells, the rate of output should vary directly with the temperature. Observations on cases of pneumonia at the time of crisis, and of septicemia with intermittent fever show that there is no mathematical relation between the height of the fever and the rate of excretion. The very moderate changes caused by the hyperthermia are overshadowed completely by some other factor.

The toxins must be regarded, then, as the more important etiologic agents in this increased rate of excretion. It is known that they increase the rate of protein destruction to a marked degree, that is, they stimulate the processes of catabolism. The kidneys also share in this stimulation, and this remarkable increase in the rate of function is the result. This stimulation can go on to outspoken injury of the cell with the production of an acute toxic nephritis. In these cases there is a marked oliguria, with retention of nitrogen and elevation of the coefficient, showing a serious temporary kidney insufficiency. The damage in this instance is due to a destructive action of the toxins, rather than the milder changes which cause irritation only.

The most constant pathologic finding in fever is a cloudy swelling of the organs. Virchow²⁹ suggests that in some stages, at least, cloudy swelling may be an evidence of hyperactivity and hypernutrition of the cell, rather than of actual degeneration. Schilling's³⁰ work supports this view. The hyperactivity of the febrile kidney, shown by the above functional studies, would seem to agree with Virchow's suggestion.

All the determinations in the group were made after the temperature had been normal for at least four days.

The averages of the coefficient and phenolsulphonephthalein output show a marked return to normal. Their values are 0.065 and 63 per cent., compared with febrile averages of 0.051 and 70.5 per cent. In spite of this rise, there is a marked fall in the average blood urea, but this is offset by a still greater fall in the rate of output. These findings coincide closely with the accepted ideas of metabolism in convalescence. There is an increase in the anabolic activities, the tissues throw less waste nitrogen into the blood, and the output of urea diminishes.

While the above considerations apply to a majority of the cases, there are some coefficients which do not return to normal. A few of these cases show casts, a persistent trace of albumin, and a high rate of phenolsulphonephthalein excretion. These kidneys have suffered

29. Virchow: *Reizung u. Reizbarkeit*, 1858, **14**, quoted in Ziegler's *Lehrbuch der allgemeinh Pathologie*, Jena, 1901, p. 206.

30. Schilling: *Virchows Arch. f. path. Anat.*, 1894, **135**, 470.

permanent damage and present in a more or less typical form the functional picture seen in early chronic diffuse nephritis (Group 4).

Cases of Hyperthyroidism: The same marked increase in general metabolism is seen also in exophthalmic goiter. Indeed, Magnus-Levy³¹ reports increases in oxygen consumption of from 50 to 70 per cent. over normal figures. Friedrich Müller³² reports a patient weighing 29 kg., with exophthalmic goiter, who lost weight on a diet containing 68 gm. of protein and 58 calories per kilogram. This points to a greatly increased destruction of protein and fat. The nitrogen excretion frequently rises to very high levels. At times this can be referred to superalimentation, but there is frequently a large negative nitrogen balance. This marked increase in metabolism has been attributed to the tremor present in exophthalmic patients; but calorimetric determinations during sleep have shown that there is no diminution in heat production when there is complete absence of tremor.³¹

With a view to estimating the extent to which the kidney participated in this accelerated metabolism, the coefficient of urea excretion was determined in a number of cases of hyperthyroidism. At the same time two cases of myxedema were studied and one case of colloid goiter. The results are presented in Table 4, and the average values for the group are to be found in Table 3. The cases were outspoken instances of toxic goiter, with varying grades of exophthalmos and tachycardia. In no case was the temperature above 99.5, consequently hyperthermia could not be accepted as an explanation of the findings. A majority of the cases showed tremor, emotional disturbances and loss of weight. Three cases (Cases 459, 461 and 462) showed varying grades of myocardial insufficiency, with chronic passive congestion.

In this series of twelve cases the minimum coefficient is 0.024 (McLean's index 1110), and the maximum 0.079. The average of the 19 determinations is 0.053. The highest coefficient among the cases with outspoken hyperthyroidism, and without cardiac insufficiency, is 0.058. The average blood urea is distinctly lower in this group than in normal cases, but the blood urea and coefficient are absolutely independent of each other. Case 460 shows a blood urea nitrogen of 7 mg. and a coefficient of 0.067, while in Case 450 a blood urea nitrogen of 9 mg. is associated with one of 0.024. Again, Case 461, with a blood urea nitrogen of 13 mg., has a coefficient of 0.047. The consistently low coefficients cannot be related, therefore, to this slight depression of the blood urea, but it is quite possible that the relatively

31. Magnus-Levy and von Noorden: *Metabolism and Practical Medicine*, English translation, 1907, p. 995.

32. Müller, F.: *Deutsch. Arch. f. klin. Med.*, 1893, **51**, 335, 361.

low blood urea may be the result of the increased rate of excretion of urea.

All these cases show a high phenolsulphonephthalein output, the average excretion being 71.8 per cent. in two hours. This is 11.6 per cent. higher than the normal average.

TABLE 4.—HYPERTHYROIDISM

Date	Case No.	Medical No.	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}$	Gm. Urea per Liter Blood, Ur	Urea Nitrogen, Mg. per 100 C.c. Blood	Coefficient	Index	'Phthal-ein Output, 2 Hr.
	450					9	0.024	1,110	72
	451					8	0.036	494	75
	452	35150	12.3	21.9	0.193	9	0.041	331	
12/19/15	453		5.2	13	0.171	8	0.047	290	78
1/22/16	...		12.4	21.3	0.235	11	0.051	246	89
12/18/15	454	S. 38841	10.7	24.4	0.234	11	0.047	290	80
12/19/15	...		6.5	18.9	0.257	12	0.058	190	
1/22/16	...		12.4	22.4	0.257	12	0.054	220	52
	455					9	0.053	228	64
	456					11	0.053	228	72
1/24/16	457	S. 38946	22.5	22.5	0.257	12	0.054	220	
2/16/16	...		8.1	11.7	0.235	11	0.058	190	
	458	S. 38280	5.9	9.5	0.171	8	0.055	211	73
	459		9.4	13.2	0.21	10	0.057	197	
	460	S. 38557	5	5.1	0.15	7	0.067	142	
12/13/15	461		10.4	19.8	0.321	15	0.072	124	64
1/24/16	...		15.3	34.7	0.278	13	0.047	290	71
3/ 6/16	...					14	0.051	247	
	462					17	0.079	102	
Myxedema 11/17/15	475		19	7.3	0.257	12	0.067	68	55
12/ 2/15	...		23.7	14.9	0.3	14	0.072	124	65
11/17/15	476	34982				15	0.125	41	53
11/23/15	...					22	0.11	53	47

Both these tests show a marked increase in the functional power of the kidney in the uncomplicated cases. The response of the kidney to the stimulus of the blood urea is greater than normal, consequently the rate of output is decidedly higher than usual and the coefficient is depressed. This increased renal activity is probably a local manifestation of the general acceleration of metabolism caused by the hyperactivity of the thyroid gland.

Partial strumectomy, or ligation of vessels, has been done on three of these patients (Cases 454, 457 and 461). One left the hospital unimproved. One (Case 457) showed a distinct increase in glucose tolerance, and some clinical improvement, as evidenced by a gain in weight, but practically no change in the coefficient. He was observed for only three weeks after operation. The third (Case 461) is still in the hospital. She is improving slowly, but so far the coefficient has not shown any marked tendency to return to normal. This slow return to normal after operative interference suggests the possibility that the internal secretion of the thyroid has a definite toxic action resulting in irritation of the kidney tissues. The circumstance that hypertension may develop in thyroid disease³³ also makes it possible that changes have occurred in the smaller vessels throughout the body and that the vascular system of the kidney has suffered at the same time. There is a noteworthy similarity between the above functional findings and those in primary hypertensive vascular disease.

In colloid goiter there is absolutely no change from normal, either in the coefficient or in the phenolsulphonephthalein output.

The findings in two cases of myxedema were particularly interesting. Schwartz and McGill³⁴ noted a somewhat low concentration of blood urea in a case of myxedema. Two cases in the present studies showed normal concentrations of blood urea (12 and 14 mg. *U-N*). In one case the coefficient was 0.097 and in the other 0.125, while there was a low normal excretion of phenolsulphonephthalein. Both cases showed a marked clinical improvement following the administration of thyroid extract. The blood urea increased to a moderate degree and there was a distinct lowering of the coefficient.

Marshall and Davis³⁵ have shown that removal of the suprarenals produces a marked impairment of renal function, as measured by the level of blood urea and the phenolsulphonephthalein excretion. This impairment is not due to any failure of circulation, and is undoubtedly caused by the removal of the internal secretion of the glands. The above clinical findings are in close accord with their experimental results, and furnish additional proof of the widespread activities of the glands of internal secretion as regulators of metabolism.

Primary Hypertensive Cardiovascular Disease:³⁶ There were ten cases in this group. All had a systolic pressure above 160 mm. of mercury. In almost every instance the patients complained of some manifestation of the increased blood pressure, such as headaches, transient attacks of vertigo, mild signs of cardiac embarrassment, or

33. Janeway, T. C.: *Bull. Johns Hopkins Hosp.*, 1915, **26**, 341.

34. Schwartz and McGill: *THE ARCHIVES INT. MED.*, 1916, **17**, 42.

35. Marshall and Davis: Personal communication to the author.

36. Janeway, T. C.: *THE ARCHIVES INT. MED.*, 1913, **12**, 755.

vague neurasthenic symptoms. They came for consultation purposes, so that prolonged observations were not possible. Slight cardiac hypertrophy was the only physical finding common to the whole group. The output of urine was somewhat increased, traces of albumin were present in a majority, but casts were found in less than half the cases.

One patient (Case 0, Table 5) has been seen at intervals during eight months. He has shown marked symptomatic improvement and a slight drop in blood pressure, but no change in the urinary picture or in the level of the coefficient.

In these cases the average blood urea nitrogen is 10.3 mg. per 100 c.c., with a range of from 7 to 20 mg. The level of the blood urea is very low in most cases, but in two a high blood urea had no effect on the value of the coefficient. Associated with this

TABLE 5.—PRIMARY HYPERTENSIVE CARDIOVASCULAR DISEASE

Case No.	Medical No.	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}$	Gm. Urea per Liter Blood, Ur	Urea Nitrogen, Mg. per 100 C.c. Blood	Coefficient	Index	'Phthal-ein Output, 2 Hr.
0	34088	21.3	15.1	0.193	9	0.05	257	76
		9	13.1	0.171	8	0.048	278	70
10					9	0.05	256	60
14					12	0.051	246	63
1	35486	5.4	14.5	0.193	9	0.051	246	70
5	35552	8.2	14.8	0.214	10	0.055	212	58
6		16.2	17.8	0.235	11	0.056	204	53
12	35239	30.6	50.9	0.406	19	0.057	197	58
7	35477	4.9	6.7	0.15	7	0.058	190	64
18	33777	11.3	10.5	0.193	9	0.059	181	85

depressed blood urea is an increased rate of output. For an average blood urea nitrogen of 10.3 mg. there is an output of 17 gm. per day, or, recalculated for a normal concentration of 14.4 mg., the output is 33.2 gm. This shows an increase of 100 per cent. over the normal response of the kidney to the same concentration of urea in the blood. As a result of this increased rate of output, the coefficient shows a marked depression, the average value being 0.0535. The phenolsulphonephthalein excretion shares in this increased renal function, the average output being 5 or 6 per cent. above the normal average.

According to Fischer,³⁷ every case of pure hypertension shows a change in the smaller vessels of the body. These vascular changes

37. Fischer: Deutsch. Arch. f. klin. Med., 1913, **109**, 469.

are associated with a loss of vasomotor control, and vascular crises are the result. The same conditions are present in the arterioles of the kidney. There is an increased irritability of the organ, which is shown by an exaggerated response to stimuli of all kinds. The depression of the coefficient is a means of gaging the intensity of this pathologic change. This condition has been described by Schlayer²¹ in his various studies of renal function, and the above findings are confirmatory of certain phases of his work.

The primary stage of irritation is of particular value in explaining the outspoken pathologic changes seen in cases of primary contracted kidney in which the functional findings have been normal. These cases are in the second stage of the disease. Having gone through the initial period of irritation (Fig. 1, *A*, *B*, *C*), they have returned to an apparently normal function (*C*), although the damage has progressed. Any further advance in the pathologic process will be shown promptly by functional evidence of renal insufficiency.

Fig. 1.—State of renal function as shown by progressive renal involvement. *A*, normal; *B*, increased; *C*, “pseudo” normal; *D*, decreased. The heavy horizontal line indicates the normal level. (After Schlayer.)

Early Chronic Diffuse Nephritis: Cases of chronic diffuse nephritis showing a hyperpermeability to phenolsulphonephthalein have been described by Sellards,³⁸ Pepper and Austin,³⁹ and Baetjer.⁴⁰ There were ten similar cases in the present series; a few showed edema at the time of observation and all showed a marked interference with the excretion of sodium chlorid. The urine was highly albuminous (from 3 to 7 per 1,000, Esbach), and casts were frequently present. The specific gravity was high. The nonprotein nitrogen of the blood was low in the four cases reported by Baetjer. We found the same condition in our own series. The blood urea was below normal in every case except one. This patient presented an extreme oliguria during one stage of his illness, and at this time his blood urea rose to

38. Sellards, A. W.: Bull. Johns Hopkins Hosp., 1912, **23**, 298.

39. Pepper and Austin: Am. Jour. Med. Sc., 1913, **145**, 254.

40. Baetjer, W.: THE ARCHIVES INT. MED., 1913, **11**, 593.

triple its former value. The rate of output was reduced in this instance to such a degree that the coefficient rose from 0.05 to 0.214. With the secretion of a larger volume of urine the coefficient promptly fell to its former level. As a rule, however, the rate of output was much greater than that normally found with low concentrations of blood urea and the coefficient was depressed. The average value for the ten cases was 0.057. The phenolsulphonephthalein output was never below 56 per cent. and in a majority of cases exceeded 65 per cent.

TABLE 6.—EARLY CHRONIC NEPHRITIS

Date	Case No.	Medical No.	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}$	Gm. Urea per Liter Blood, Ur	Urea Nitrogen, Mg. per 100 C.c. Blood	Coefficient	Index	'Phthal-ein Output, 2 Hr.
	11	34529				10	0.052	237	69
	2	34369	29.4	37.9	0.321	15	0.053	227	65
	3		7.11	18.9	0.235	11	0.054	220	78
1/ 7/16	8	35138	4.6	12.3	0.193	9	0.055	212	71
1/17/16	...		4.6	6.3	0.15	7	0.059	184	
1/18/16	...		14.7	14.5	0.193	9	0.051	246	67
1/19/16	...		3.2	8.9	0.15	7	0.05	256	
	4	35443	19.6	21.8	0.257	12	0.055	212	56
		34679				8	0.058	190	69
	9	33745	7.3	6.2	0.171	8	0.068	138	70
	11	34529	8.9	9.3	0.257	12	0.07	130	69

In these cases the early inflammatory process has caused a cellular irritation, which is again made evident by an increased response to stimulation. These cases also go through a second stage, in which the usual functional tests are normal, and a later stage, in which the damage is so marked that the functional tests show progressive impairment of renal function.

The last two groups of cases are presented to emphasize the fact that irritation is the earliest sign of renal disease, no matter whether the process be of the vascular or of the diffuse type, and it should be remembered that increased function is one of the first evidences of this irritation. An excessively low blood urea in the presence of a normal protein intake, a coefficient persistently below 0.055, or a phenolsulphonephthalein output of more than 70 per cent. should be regarded, therefore, with suspicion, as being possible indications of an early stage of renal damage.

CASES WITH INCREASED COEFFICIENTS OF UREA EXCRETION

Increased coefficients

Myocardial insufficiency; variable, with changes in circulatory system

Nephritis

Constant

Variable

With changes in the clinical picture

Acute nephritis

Progressive renal insufficiency

Effect of myocardial insufficiency

Without changes in the clinical picture

Effect of fixation of specific gravity and interference with water excretion

Basal coefficient

Myocardial Insufficiency.—The patients in this group presented some type of pure cardiac disease of a valvular or myocardial nature. Cases of nephritis with failing compensation have been excluded. A number of the patients were followed from the stage of extreme myocardial insufficiency through the period of recovery to a complete restoration of the circulatory equilibrium. Some did not improve during their stay in the hospital. Twelve died; of these, seven came to necropsy. Six of the latter showed typical chronic passive congestion of the kidney. One (Case 276) showed a few arteriosclerotic scars of the kidney, with a marked chronic passive congestion superadded.

Tests of Renal Function in Chronic Passive Congestion.—Blood Nitrogen: In chronic passive congestion, the chief functional defect lies in the inability of the kidney to excrete water and sodium chlorid. The concentrating power for nitrogen is rarely interfered with, and little evidence of nitrogen retention in the blood is to be expected, except in the severe cases. The work of Frothingham and Smillie,⁴¹ Tileston and Comfort,⁴² Rowntree and Fitz,⁴³ and other observers confirms this assumption.

The present group, taken as a whole, shows moderate increase in the blood urea. The average urea nitrogen is 19.9 mg. per 100 c.c., compared with the normal average of 14.4 mg. In moderate chronic passive congestion there is no constant change in the level of the blood urea, with improvement in the circulatory condition. Indeed, many of these cases show a rise in the blood urea following a return of cardiac compensation. This is due to the increased protein intake during convalescence.

In some of the more outspoken cases of myocardial insufficiency (Cases 276, 277, 278 and 279) a definite fall in the blood urea accompanies the return of compensation. In no case does this exceed 12 mg.

41. Frothingham and Smillie: THE ARCHIVES INT. MED., 1914, **14**, 541.

42. Tileston and Comfort: THE ARCHIVES INT. MED., 1914, **14**, 620.

43. Rowntree and Fitz: THE ARCHIVES INT. MED., 1913, **11**, 258.

TABLE 7.—MYOCARDIAL INSUFFICIENCY

Date	Case No.	Medical No.	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $D \times \frac{1.73}{\sqrt{C}} \times \frac{1.73}{\sqrt{P}}$	Gm. Urea per Liter of Blood, Ur	Urea Nitrogen, 100 C.c. Blood	Coefficient	Index	'Phthal- ein Out- put, 2 Hr.	Degree of Chronic Passive Conges- tion	Diagnosis
2/ 1/15	250	32538	15.7	19.2	0.235	11	0.054	222	..	0	Aortic insufficiency
3/ 1/15	251	33659	6.4	12.4	0.257	12	0.074	117	51	+	Mitral regurgitation
2/23/15	...		3.6	19.9	0.3	14	0.067	140	..	0	Mitral regurgitation
8/12/15	252	33767	21.2	18.4	0.342	16	0.08	100	46	±	Aortic insufficiency
8/18/15	...	34587	15.2	4.5	0.407	19	0.193	17	..	++	Aortic insufficiency
9/ 3/15	...		12.3	4.5	0.364	17	0.171	22	40	+	Aortic insufficiency
9/11/15	...		14.4	10.6	0.364	17	0.112	51	..	±	Aortic insufficiency
253	...		25	26.8	0.471	22	0.091	77	42	0	Aortic insufficiency
254	253	33888	25.2	27.8	0.386	18	0.081	98	35	±	Myocarditis; auricular fibrillation
255	254	33727	15.4	15.8	0.321	15	0.082	95	..	±	Myocarditis
257	255	33614	12.8	19.2	0.386	18	0.088	83	59	0	Bacterial endocarditis
5/31/15	257	34579	18.7	21.4	0.413	16	0.089	80	48	±	Myocarditis
6/19/15	260	34271	4.6	10.8	0.321	15	0.068	67	..	+	Myocarditis
261	...		21.9	27.7	0.314	15	0.06	178	36	0	Myocarditis
5/21/15	261	34723	10.3	10.6	0.321	15	0.068	67	48	+	Myocarditis
5/29/15	262	34687	14.6	17.1	0.406	19	0.099	65	58	±	Mitral stenosis
263	...		27.6	19	0.462	22	0.106	57	..	±	Mitral stenosis
	263	33869	24.1	10.3	0.321	15	0.1	64	..	±	Myocarditis

266	38627			0.235	11	0.108	55	85	±	Bacterial endocarditis
267	34873	4.7	3.1	0.192	9	0.117	46	..	+	Myocarditis; secondary anemia
268	33989	20.6	10.6	0.385	18	0.119	45	..	+	Myocarditis; auricular fibrillation
269	34250	12.5	9.6	0.385	18	0.124	42	55	+	Aortic insufficiency; myocarditis
...		18.1	34	0.6	28	0.105	58	..	±	
270	33978	22.1	23.6	0.642	30	0.132	37	17	+	Myocarditis; auricular fibrillation
272	34945	23.9	12.7	0.499	23	0.14	33	..	+	Myocarditis
...		11.4	6.7	0.321	15	0.123	42	48	±	Myocarditis
273	34764	26.2	8.9	0.416	19	0.140	33	24	+	Myocarditis
...		17.5	17.4	0.364	17	0.087	92	49	0	Myocarditis
...		24.7	21.8	0.428	20	0.089	81	45	0	Myocarditis
274	34631	22.8	8.4	0.438	20	0.147	29	38	+	Aortic insufficiency
...		19.7	10.8	0.471	22	0.143	31	..	+	Aortic insufficiency
...		31.4	34	0.624	29	0.108	55	32	±	Aortic insufficiency
275	34601	24.7	21	0.706	33	0.154	27	21	++	Aortic stenosis; fibrillation
...		25.6	19	0.706	33	0.161	25	40	++	Aortic stenosis; fibrillation
276	33696	7.4	5.9	0.406	19	0.155	27	40	+	Myocarditis; arteriosclerosis
...		13.8	9.3	0.278	13	0.091	70	60	0	
...		17.9	13.9	0.278	13	0.075	114	..	0	
277	33599	11	11.3	0.556	26	0.166	23	50	+	Myocarditis; hypertension
...		22.2	23.8	0.342	16	0.07	111	..	0	
...		19.4	14.1	0.385	18	0.103	60	..	±	
278		20.7	9.4	0.526	25	0.172	21	42	+	Myocarditis; mitral insufficiency
...		8.7	15.3	0.385	18	0.089	65	58	0	
280	34654	12.5	8.1	0.706	33	0.248	10	37	++	Mitral stenosis; auricular fibrillation

of urea nitrogen per 100 c.c. One of these cases subsequently came to necropsy, and the kidneys showed a few arteriosclerotic scars. Rowntree and Fitz⁴³ suggested that this retention might be due to some slight renal change which was not demonstrable under normal conditions, but which became apparent under the extra strain put on the kidneys by the failing circulation.

Phenolsulphonephthalein Excretion: In well compensated heart conditions and the milder forms of passive congestion, Rowntree and Fitz⁴³ have found little interference with the excretion of dye. In outspoken myocardial insufficiency the excretion was much diminished, but returned to normal with restoration of circulatory equilibrium. These observations were confirmed in the present series.

The coefficient of urea excretion has been determined at least once in all cases, and repeatedly in a number of instances.

In well-compensated cardiac disease there is very little change from normal, the average coefficient being 0.082. The highest value under these conditions is 0.103 and the lowest 0.054.

In forty-one determinations there were outspoken evidences of myocardial insufficiency. The average coefficient in these cases is 0.124, with a maximum variation of from 0.074 to 0.248. There is a general relationship between the degree of decompensation and the height of the coefficient in all these cases: the more evident the passive congestion, the higher the coefficient. The most striking agreement, however, is found in those determinations done on the same individual under varying conditions of myocardial sufficiency and insufficiency.

Case 252 is a good example. The diagnosis was syphilis of aorta, aortic insufficiency and myocardial insufficiency. On the patient's first admission, his coefficient was obtained after compensation had been reestablished. It was normal (0.08). The blood urea nitrogen was 16 mg. and the phenolsulphonephthalein excretion 46 per cent. Six months later he returned. He was very edematous and extremely dyspneic. There was marked oliguria, the daily output rarely exceeding 500 c.c. Chronic passive congestion had evidently impaired his renal function, as his power of concentrating urea was markedly diminished. The blood urea had increased slightly, but the coefficient had risen to 0.193, an increment of over 200 per cent. After six days' rest and a restricted fluid intake, there was some clinical improvement, and the blood urea nitrogen dropped to 17 mg. There was no diuresis, the rate of output was essentially the same as on the previous occasion, and the coefficient showed no marked change. In the course of the next two and a half weeks, the patient lost most of his edema, there was a moderate polyuria, and at the time of the third determination, the coefficient had dropped to 0.112. This change was not accompanied by any fall in the blood urea, but was due entirely to the increased rate of urea excretion. The fourth observation was made shortly after the disappearance of myocardial insufficiency. There was a good output of urea, and, in spite of an increased blood urea, the coefficient had returned to normal. The phenolsulphonephthalein excretion was not determined at the height of passive congestion, but subsequent determinations did not show any marked change from the output obtained on the first admission.

Practically every case in which serial determinations were done showed the same relation between the coefficient and the degree of myocardial insufficiency present. In a majority of cases the coefficient shows no relation whatever to the level of the blood urea, indeed a lowering of the coefficient is frequently associated with a rise in the latter value.

Eighteen of the patients had coefficients below 0.12 and four of these died. In thirteen, the coefficient was above 0.12, with nine fatalities. Of the four fatal cases with coefficients below 0.12, two of the patients died of bacterial endocarditis without obvious chronic passive congestion; the other two showed no myocardial insufficiency at the time of observation, and died in subsequent exacerbations. Five of the thirteen fatal cases in the second group showed a temporary improvement, and during this time the coefficient returned to normal values.

The rise in the coefficient should not be regarded as having the same significance in chronic passive congestion as in nephritis. The rise in the latter case is the result of definite anatomic changes in the renal cells. In chronic passive congestion the fundamental cause lies in the failure of the heart to supply a sufficient quantity of blood to the kidneys. This imperfect circulation results in an oliguria. There is a secondary factor, the actual functional deterioration of the cell, due to its impaired blood supply. This prevents the attainment of a requisite degree of concentration to offset the effects of the oliguria. The resultant of these two factors is that the rate of output does not reach the level demanded by the concentration of urea in the blood, and there is a rise in the coefficient. With a return of normal circulatory conditions, the kidney shows a complete recovery of functional activity.

In cardiac disease there is no great change in the level of the total nonprotein nitrogen or urea of the blood. The urea nitrogen forms a somewhat larger proportion of the total nonprotein nitrogen in the more severely decompensated cases than it does normally. The coefficient of urea excretion affords an excellent means of following the effects of passive congestion on renal function. The more severe grades of chronic passive congestion cause marked rises in the constant. Cases with a coefficient about 0.12 usually come to a fatal issue within a relatively short period. In a majority of cases the phenolsulphonephthalein excretion is diminished in marked passive congestion and returns to normal with the reestablishment of normal circulatory conditions.

Nephritis: Ambard,⁴⁴ Widal, Weill and Vallery-Radot⁴⁵ and McLean⁹ have shown that changes in the functional capacity of the

44. Ambard, L.: *Physiologie normale et pathologique des reins*, Paris, 1914.

45. Widal, Weill and Vallery-Radot: *Presse méd.*, 1914, **22**, 565.

diseased kidney can be followed with great exactness by the coefficient of urea excretion. They have found a marked fixation of the coefficient when the disease was stationary, a gradual rise during the progress of the condition, and a fall if the disease showed a tendency to subside. Widal has compared the excretion of urea to the escape of a fluid through an opening of variable size. If it is escaping at a given rate, under a known pressure, it will be necessary to increase that pressure if the size of the orifice is to be diminished without interfering with the rate of output. These laws of hydrostatics hold absolutely within certain wide limits. The same general considerations apply to renal function. Under normal conditions a satisfactory rate of output can be maintained with comparatively low concentrations of urea in the blood. As the amount of healthy kidney tissue is decreased by disease, interference with the rate of urea excretion becomes more outspoken, and a higher concentration of blood urea is required to maintain the original rate of output. The coefficient, therefore, assumes a higher level than previously, but should remain constant at this new value until a further change in renal function occurs. Ambard, however, points out that these conditions prevail only in the presence of a sufficient output of water and that in the oliguric stages of nephritis variations in the coefficient, which cannot be explained by actual changes in the kidney function, are to be expected.

The coefficient is particularly useful in the study of those cases of nephritis which show a retention of nitrogen. In the early stages of chronic diffuse nephritis, with a maximum involvement of the salt excretion, the results are not so dependable. Indeed, there may be an irritation of the kidney, with an actual hyperactivity in the excretion of nitrogen in certain stages, as has been shown previously. In the absence of any marked interference with the chlorid elimination, however, the coefficient may be relied on to indicate an impaired nitrogen excretion in a considerable number of cases, long before any impairment has been shown by a retention of nitrogen in the blood.

There are 162 cases of nephritis in the present series, but the findings will be tabulated in only forty-one cases, which were studied repeatedly. These results will be used for an analysis of varying factors which may cause changes in the value of the coefficient. The whole series will be utilized for the general discussion and observations on prognosis.

Acute Nephritis: There were eighteen cases of acute nephritis, seven of which were observed repeatedly. Possible etiologic factors were known in ten instances. Four were associated with purpura, one followed erysipelas, one followed salvarsan therapy, and two were cases of mercury poisoning. In one case there was a history of prolonged exposure to cold and wet.

TABLE 8.—ACUTE NEPHRITIS

Date	Case No.	Medical No.	Total Non-protein Nitrogen, Mg. per 100 C.c. Blood	Urea Nitrogen, Mg. per 100 C.c. Blood	Percentage of Total Non-protein as Urea Nitrogen	Coefficient	Index	'Phthal-ein Out-put, 2 Hr.
4/10/15			..	34		0.116	...	40
4/13/16			..	16		0.062	...	
4/16/16			..	11		0.069	...	55
4/18/14	160	20990	..	45		0.13	38	*
5/10/14			..	39		0.104	59	
5/ 2/14	162	20948	..	44		0.134	36	15
5/30/14			..	22		0.079	108	50
2/19/15	85	33695	44	27	61.5	0.172	21	40†
3/ 1/15			20	10	50	0.063	163	65
10/23/15	95	34901	60	46	76.7	0.232	12	
10/26/15			60	45	75	0.203	16	48
11/ 1/15			57	36	63.2	0.162	24	
11/ 3/15			49	27	55.1	0.124	42	
11/ 9/15			..	24		0.107	56	44
11/16/15			..	22		0.119	45	
11/30/15			30	22	73.3	0.111	52	50
12/ 6/15			19	12	63.2	0.074	117	
12/ 8/15			14	9	64.3	0.054	219	58
12/13/15			16	9	56.1	0.061	172	63
12/23/15	132	S. 36610	129	117	90.8	0.4	4	15
12/26/15			..	45		0.179	3	23
9/29/15	119	34753	178	148	83.2	1.09	0.5	‡
9/30/15			170	141	83	1.36	0.3	T.
10/ 2/15			125	102	81.6	0.55	2.1	11
10/ 4/15			78	55	70.5	0.41	3.8	
10/ 6/15			42	23	54.8	0.186	18	27
10/ 8/15			26	11	42.4	0.124	42	35
10/13/15			22	8	36.4	0.064	156	45
10/18/15			22	11	50	0.12	53	

* The diagnosis was acute nephritis; purpura.

† The diagnosis was salvarsan poisoning.

‡ The diagnosis was mercury bichlorid poisoning.

The results were similar in every case. During the acute stage there was a variable grade of oliguria and a well-marked retention of nitrogen, as shown by studies of the blood. The coefficient showed a rise corresponding to the severity and duration of the disease, and there was a consistent diminution in the phenolsulphonephthalein output. The highest values were found in Cases 95, 119, and 132. In Case 95 the nephritis was associated with a septicemia, and was probably of a focal nature. The second was a case of mercury bichlorid poisoning. The patient had been anuric for six days before examinations were begun. Case 132 was of an acute nephritis, with complete suppression of urine for two days after the onset. The two determinations were made during the period of recovery, but the coefficient was not obtained after complete recovery.

In every case clinical improvement was accompanied by a rapid change in the functional tests. The blood urea fell to normal levels, the rate of excretion of urea increased and there was a marked drop in the coefficient. The phenolsulphonephthalein excretion also increased and resumed a normal rate of output. Those cases in which a chronic nephritis followed the subsidence of the acute lesion gave evidence of this in the persistence of some elevation of the constant and an impaired phenolsulphonephthalein excretion. In those patients with perfect recovery the coefficient and phenolsulphonephthalein resumed absolutely normal figures.

Chronic Nephritis: The findings in chronic nephritis have been confirmatory in nature to a considerable degree. Ambard and McLean have both noted marked increases in the coefficient, corresponding to the grade of renal insufficiency present.

Reference to the work of Folin,⁴⁶ Frothingham,⁴¹ Tileston⁴² and others quoted previously shows the wide range of normal values of urea nitrogen. The upper limit of normal is between 20 and 25 mg. Of sixty-six cases in the earlier stages of nephritis, only twenty-two showed urea nitrogens above 20 mg., and only six were above 25 mg.; yet all had coefficients above 0.09 (the upper normal limit), and many showed outspoken increases in the constant. In this same group the urea nitrogen was 15 mg. or less in twenty-nine cases. It is evident from this that the coefficient picks out instances of early impairment long before the blood urea shows any definite increase. In the severer cases there was a more evident agreement between the blood urea and the level of the coefficient. Of forty-one determinations on cases having a coefficient between 0.15 and 0.3, the blood urea was above 25 mg. in thirty-three and above 20 mg. in thirty-seven instances, with only two cases below 15 mg. Both these patients, Cases 88 and 92, were

46. Folin, O., and Denis, W.: Footnotes 16 and 19.

on a low protein diet at the time, their levels of blood urea nitrogen having been 19 and 65 mg., respectively, before the diet was commenced. In one instance, Case 92, the change in level of the blood urea had caused no noticeable change in the value of the constant, while in Case 88 the disappearance of a moderate passive congestion readily explained the lowered coefficient.

The Relation of the Total Nonprotein Nitrogen to the Urea Nitrogen: In a considerable number of cases the total nonprotein nitrogen was determined synchronously with the blood urea nitrogen. Folin and Denis⁴⁶ found that 50 per cent. of the total nonprotein nitrogen was present as urea nitrogen in healthy adults, but that in normal clinical material the proportion ranged from 41 to 74 per cent. While this range of variation has been noted in the milder cases of nephritis, an almost complete disappearance of the lower values has been found in the more severe cases. In thirty-eight determinations on persons having a coefficient between 0.09 and 0.15, twenty-one had less than 60 per cent. of the total nonprotein nitrogen as urea nitrogen; while in seventy-one determinations on cases with a constant above 0.15, only eleven had less than 60 per cent. of the total nonprotein nitrogen as urea nitrogen. The ratio of total nonprotein nitrogen to urea nitrogen seems to have a much more intimate relation with the degree of nitrogen retention than it does with the level of the coefficient. The lower percentages are almost always associated with the low values of blood nitrogen. In those cases in which the blood nitrogen was varied by dietary procedure (Cases 117, 88, 92, 54 and 35), the fall in the blood urea always took place much more rapidly than did that of the total nonprotein nitrogen, with the result that even in severe cases the proportion frequently sank below 50 per cent., and went to 43 per cent. on two occasions. In chronic nephritis a low percentage of urea nitrogen has little significance. Percentages above 75 are seen rarely in the milder cases, but they become increasingly frequent in the severer ones.

The Independence of the Coefficient and the Blood Urea: If Addis and Watanabe's¹⁰ criticisms of the coefficient are founded on fact, and if the coefficient really maintains its constancy only by reason of the relative fixation of the blood urea, one would be justified in making the following assumption:

1. In cases of chronic nephritis, in a stationary condition, the coefficient should follow the concentration of urea in the blood. Every rise or fall in the blood urea should be reflected by a corresponding variation in the coefficient.
2. If the clinical condition of the patient is showing marked variations during the period of observation, then the variations in the blood

urea, and consequently the coefficient, should reflect the functional condition with accuracy.

3. If the disease should be rapidly advancing, and yet the blood urea should be reduced by dietary measures, then the coefficient should follow the blood urea, and indicate an apparent improvement in the presence of an outspokenly progressive impairment of renal function.

In dealing with the first assumption, reference may be made to Cases 92, 97, 110 and 84. In Case 92 (Fig. 2) variations in the blood urea nitrogen from 59 to 15 mg. per 100 c.c. produced a maximum variation in the constant of from 0.224 to 0.292. In this case the rate of output, corrected for urinary concentration, amounted to 29.7 gm.

Fig. 2.—Independence of the coefficient of blood urea excretion in chronic nephritis. The coefficient remains constant, while the blood urea and the urea output vary. In this and the following illustrations the full, dark line indicates the coefficient of urea excretion (K), the figures being given in the first column at the left; the dotted line indicates the blood urea in thousandths (Ur), the figures being given in the second column from the left; the parallel dash line indicates the V corrected rate of output $= V D$, etc., the figures being given in the third column; the dash line indicates the concentration of the urine in thousandths (C), the figures being given in the fourth column; and the parallel lines indicate the volume of urine, expressed in the figures of the fifth column.

of urea for the initial concentration in the blood. With the drop in the blood urea to 25 per cent. of its former value, the rate of output dropped to 2.09 gm. in the 24 hours, or 7.01 per cent. of its original rate. The other cases all show the same absolute relationship between the rate of excretion and the concentration of urea in the blood. Judged from the blood urea alone, these patients should be considered

as markedly improved, while in reality their functional power has shown no obvious change.

The phenolsulphonaphthalein excretion in these cases was constant, pointing to an unchanged condition of renal function.

The acute nephritides furnish the best examples of the agreement of the blood urea, the coefficient, and the clinical condition of the patient. Such cases cannot be used as arguments against the validity of the coefficient.

The third condition is somewhat difficult of attainment, but Case 35 fulfils all requirements.

The patient, C. C. (Med. No. 35242), 35 years of age, was perfectly well until nine months before admission, when headaches began. They became progressively worse. He had marked nycturia; gastro-intestinal disturbances appeared, and he lost a great deal of weight. Visual disturbances commenced one week before admission.

Physical examination showed evident loss of weight, no marked pallor, some exophthalmos, lungs with few râles at the bases. The region of cardiac dullness was 4 by 14 cm. There was relative mitral insufficiency. The blood pressure was 240 systolic, 140 diastolic. There was marked arterial thickening. The liver edge was palpable 2 cm. below the costal margin. The eyegrounds showed extreme hemorrhagic albuminuric retinitis. The urine specific gravity was 1.015. There was albumin, 2 parts per thousand, with numerous hyaline and granular casts. The phenolsulphonaphthalein excretion in two hours was 40 per cent.

A diagnosis was made of chronic diffuse nephritis, secondary contracted kidney, chronic uremia, hypertension and arteriosclerosis.

On account of severe headache, he was put on low protein diet. The blood urea nitrogen dropped from 17 mg. to 13 mg. and then to 7 mg. With this drop there was an even greater rate of fall in the twenty-four hour output of urea, and as a result, the coefficient rose from 0.103 to 0.129. The phenolsulphonaphthalein excretion dropped to 34 per cent. in the course of a few days.

Under treatment his headaches decreased, but otherwise his condition was unchanged. He died two months later in typical uremic convulsions. In this particular instance the coefficient and phenolsulphonaphthalein tests showed the true progressive character of the disease, in spite of the drop in the blood urea and the symptomatic improvement.

From the cases given above it is evident that there can be no absolute relationship between the blood urea and the coefficient. In the mild and moderately severe cases the value of the coefficient depends on the functional capacity of the kidney, and any variation in the value has its underlying cause in some functional change in the kidney itself.

Causes of Variation in the Coefficient in Chronic Nephritis: The foregoing cases show conclusively that simple variations in the blood urea have no effect on the level of the coefficient. Therefore, the

most obvious cause of the variability in the constant will be an actual change in the patient's condition. This may be due to changes in circulatory mechanism or to definite changes in renal function.

In myocardial insufficiency the onset of passive congestion is rapidly followed by a rise in the coefficient, which falls again quite as rapidly with the subsidence of the condition. Case 28 shows the effect of an increasing grade of cardiac insufficiency, a marked increase in the coefficient, with very slight change in the blood urea, while Case 52 is an example of a change in the opposite direction. Case 88 shows the effect of chronic passive congestion on the coefficient in a severe case of nephritis. The coefficient falls from 0.192 to 0.154 with an improvement of the circulatory condition, then, as chronic passive congestion returns, rises again to 0.172. In this particular instance the level of the blood urea also shows large variations, due to the dietary regimen. This patient died of cardiac failure two weeks later.

Actual Changes in Renal Function—Improvement: The fall of the coefficient during improvement has been discussed under acute nephritis.

By dietary methods, having as their basis a prolonged reduction in the protein intake, we have been able repeatedly to reduce the blood urea to normal and even low normal values, but in only one case has this been followed by any apparent functional change in the kidney. In Case 84, after a low protein intake of two months' duration, the coefficient fell from 0.168 to 0.066. It subsequently rose to 0.087. That this variation was not due merely to a change in the blood urea concentration is shown by the fact that on one occasion the coefficient was 0.163, with a blood urea nitrogen of 12 mg., and one month later was 0.087, with blood urea nitrogen of 13 mg. This patient had been admitted five times during the preceding three years, and on each occasion his phenolsulphonephthalein excretion had been approximately 40 per cent. On the last admission his output was 31 per cent., but with the falling Ambard, his phenolsulphonephthalein rose to 63 per cent. and finally 72 per cent. In other words, there seemed to be a definite functional improvement in this case, which, to the best of our knowledge, had been in a stationary condition for the preceding thirty-six months.

Advance in the Severity of the Disease: The coefficient affords an excellent means of studying the progress of functional impairment. Table 9 presents numerous examples of a rising coefficient, associated with increasing renal insufficiency. In these cases an increase in the level of blood urea usually accompanies the rising constant. If such a condition occurred with a stationary lesion of the kidney, the rate of output would increase to a corresponding degree and the coefficient would not change. A rise in the coefficient indicates an inadequate

response on the part of the kidney to an increased stimulation in the form of increased concentration of blood urea. According to the stage of disease, the increase may be slow or rapid. In Case 164 the coefficient rose from 0.172 to 1.12 in six weeks, and death occurred shortly after the latter determination. In Cases 116 and 114 the change was equally rapid.

Other cases have advanced much more slowly. Case 96 presented a coefficient of 0.24 in 1915. Eight months later the value was 0.34 and one year later 0.414. The phenolsulphonephthalein output fell from 10 per cent. to 3.5 per cent., and finally to zero in the same time. Another case (Case 124) merely advanced from 0.101 to 0.153 in three months, while others (Case 92, etc.) were absolutely stationary.

Changes in the Coefficient Which Are Not Due to Actual Changes in Renal Function: These changes are only seen when kidney function is in an extremely embarrassed condition.

Certain cases of marked renal insufficiency in the present series showed marked changes in the value of the coefficient, quite independent of any change in the functional efficiency of the organ. Some explanation of these findings was sought in view of their apparent disagreement with the laws of function.

The use of test meals for renal function has shown that the most constant qualitative finding in moderately severe nephritis is loss of concentrating power.³ This eventually progresses until there is a loss of diluting power as well⁵ and the concentration of the urine becomes practically constant throughout the day. Under these conditions the second law of function becomes nonexistent, and the rate of output varies directly as the square of the concentration of urea in the blood. The only means of changing the rate of output is by a variation of the urinary volume, and in such persons a rise in the blood nitrogen is met by a corresponding grade of polyuria. Cases 110 and 112 are examples of this condition. In both cases there is approximate fixation of the urea concentration. In the former case the blood urea drops, and in the latter there is a considerable rise. In each instance the burden of changing the rate of output falls on the volume of urine excreted. In the first case there is an almost perfect response, with a constant coefficient; in the latter (Case 112) the rise in volume is not quite sufficient and there is a definite increase in the constant.

In the later stages of nephritis, even this water-regulating mechanism may be lost, and the rate of output becomes a relatively fixed quantity. As a result the formula

$$K = \frac{\text{Blood urea}}{\sqrt{\text{Corrected rate of output}}} \text{ becomes } K = \frac{\text{Blood urea}}{\sqrt{\text{Constant factor}}}$$

or, in other words, the coefficient varies directly with the blood urea,

because the rate of output has become a constant. The best example of this condition is Case 102 (Fig. 3).

Another possible condition would be the inadequacy of the water output. The frequency with which a diurnal oliguria and nocturnal polyuria are associated in nephritis is well known. If, therefore, the concentration were fixed, and a coefficient were determined during the period of nocturnal polyuria, and again during the oliguria period of the day, the coefficient should vary in direct proportion to the water output. The last four determinations of the coefficient in a case of polycystic kidney (Case 111, Fig. 4) show this condition remarkably well. The blood urea is relatively constant, while the volume, corrected rate of output, and value of the coefficient agree absolutely. The final intense grade of oliguria was precipitated by the ingestion of an enormous quantity of water, given in the hope of producing a polyuria. This is a good example of a fatigue reaction in a badly damaged kidney and is of the same type as that produced in many cases of chronic diffuse nephritis by a sudden overload of salt.

In this case the changes in the value of the coefficient were not associated with any clinical change in the patient. At first sight they seem to be obvious proof of the inaccuracy of the coefficient and the laws of excretion. Closer examination, however, proves them to be the natural outcome of the functional conditions present.

In patients with a regular advance in the kidney lesion, the importance of oliguria in producing the terminal renal insufficiency is beautifully shown in Figure 5. The fixation of concentration is almost complete, although it shows a slight tendency to rise with the progressive increase in the blood urea. The volume and rate of output continually diminish, and finally there is the onset of the premortem protein catabolism, with a tremendous rise in the coefficient and blood urea, associated with a marked fall in the urine volume and rate of excretion. This progressive impairment is also reflected by the constant fall in the phenolsulphonephthalein output.

Basal Coefficient: In dealing with physiologic problems we are accustomed to speak of stimuli as being minimal, optimal and maximal. By the last is meant a stimulus of such a strength that it will elicit the maximal response from the tissue under examination. Any further increase in the stimulus will cause no increased response; on the contrary, it may produce actual damage and the response be diminished rather than augmented.

It is conceivable that similar conditions might exist in cases of nephritis with a marked impairment of concentrating power. Within certain limits of blood urea concentration, the kidney would be capable of excreting the theoretical quantities of urea, and the coefficient would remain constant. If the blood urea rose above these limits, and pre-

Fig. 3.—The coefficient of urea excretion varies directly with the blood urea in the later stages of nephritis. For key to the diagram see the legend of Figure 2.

Fig. 4.—Case of variation of the coefficient of urea excretion with changes in the urine volume. For key to the diagram see the legend of Figure 2.

Fig. 5.—Importance of oliguria in producing the terminal rise of the coefficient. For key to the diagram see legend of Figure 2.

Fig. 6.—Case of direct variation of the coefficient of urea excretion with the blood urea. The rate of urea output remains constant while the urea in the blood is high; when the latter falls, the rate of output begins to vary in relation to the blood urea. For key to the diagram see legend of Figure 2.

sented a supramaximal stimulus, the rate of output would not increase to a corresponding degree, but would remain a relatively fixed quantity. Under these conditions the coefficient would vary directly with the blood urea. The reappearance of a constant coefficient would signify the return of the blood urea within the foregoing limits of concentration and below the critical concentration.

Case 95 (Fig. 6) is of interest in this connection. During the acute stage there was a considerable nitrogen retention. In the first five determinations, however, there was a progressive fall, both in the blood urea and in the coefficient. During this period the rate of output remained practically constant, a good example of a maximal response to a supramaximal stimulus. As soon as the blood urea fell below the critical concentration, the rate of output began to vary in relation to the blood urea.

Case 117 (Fig. 7) is another example of the same condition in a chronic nephritis with the diffuse type. There was marked albuminuria and cylindruria. The specific gravity was fixed in the neighborhood of from 1.010 to 1.012. On admission, the blood urea nitrogen of this patient was 53 mg. per 100 c.c., and the coefficient 0.75. After a period of improvement his protein intake was increased and the blood urea nitrogen rose to 88 mg. The coefficient, however, fell to 0.458. One month later the coefficient was 0.425. He then became worse; there was a marked retention of nitrogen, and the coefficient rose to 1.305. A low protein dietary reduced the level of the blood urea. The coefficient followed it closely during the first part of its fall, but when the coefficient reached the value of 0.525, it became constant. The concentration of urea continued to fall, but each diminution was accompanied by a corresponding change in the rate of output, so that the coefficient resumed its independence of the blood urea concentration. A subsequent rise of the blood urea nitrogen to 64 mg. was associated with a prompt rise in the constant, while subsequent falls below 50 mg. did not produce any marked depression in the coefficient. As the fatal issue approached, renal function became more and more impaired and there was a progressive increase in both blood urea and the coefficient.

After the initial exacerbation of the disease, the phenolsulphonephthalein excretion remained constantly between 5 per cent. and 7 per cent., and showed no such variations as those seen in the coefficient during the same period.

The second case is of particular interest. It raises the question as to whether two types of nitrogen retention should not be recognized. The first type is characterized by a fairly rigid adherence to the laws of function, and every change in blood urea concentration is accompanied by a corresponding change in the rate of excretion. The retention may be regarded as a purely physiologic means of over-

Fig. 7.—Variation of the coefficient of blood urea excretion with the blood urea in a chronic nephritis of diffuse type. For key to the diagram see legend of Figure 2.

coming the increased resistance to the passage of urea through the damaged kidney. The result of such a retention is a coefficient somewhat above the normal, but constant in value. In the second type of retention the conditions are somewhat different. If the kidney were stimulated to its maximal capacity by that portion of the retained urea necessary to produce a maximal response, then the excess above this level would act merely as an overload. It would not have any favorable effect on the rate of urea excretion, and would be of a distinctly pathologic nature. It should be regarded as an accumulation of nitrogen, rather than a retention. Under such conditions the value of K would vary directly with the concentration of the blood urea. If, however, the blood urea fell below the critical concentration, which marked the division between the pathologic accumulation and the physiologic retention of nitrogen, the kidney would again be able to respond to variations in the blood urea by corresponding variations in the rate of output, and the coefficient would again become a constant. The coefficient would be independent of the concentration of urea in the blood just so long as the blood urea remained below the critical concentration. Reference to Case 117, Table 9, will show that before the exacerbations in October the kidney had quite a wide margin of safety. Concentrations of blood urea nitrogen up to 88 mg. were not sufficient to cause any variations in the coefficient. At a later period 50 mg. seemed to be the value and any rise above the level caused marked rise in the coefficient. It seems justifiable to assume that no absolute change in the functional capacity of the kidney took place during this time, but that the variations in the coefficient were merely the result of this *accumulation* of nitrogen in the blood.

The term "basal coefficient" might be applied to the value of the coefficient below which it is impossible to go, no matter how low may be the value of the blood urea. It represents the actual functional power of the kidney more accurately than do the higher values of the coefficient obtained during the period of nitrogen accumulation.

McLean⁴⁷ has described an accumulation of nitrogen in certain cases of nephritis, caused by the limitation of the fluid intake. In the present instance there was no restriction of fluids and the condition was produced by the actual inability of the kidney to excrete either water or urea.

PROGNOSIS

While tests of function should be regarded as valuable aids to an accurate prognosis, they should never be allowed to dominate the picture. A diagnosis of the type of lesion and a proper valuation of the many factors in the disease complex are of even greater importance.

47. McLean, F. C.: Jour. Exper. Med., 1915, **22**, 366.

TABLE 9.—CHRONIC NEPHRITIS

Date	Case No.	Medical No.	Total Non-protein Nitrogen, Mg. per 100 C.c. Blood	Urea Nitrogen, Mg. per 100 C.c. Blood	Percentage of Total Non-protein Nitrogen Present as Urea Nitrogen	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $\frac{70 \sqrt{C}}{D \times -x - \frac{P}{\sqrt{25}}}$	Gm. Urea per Liter of Blood, Ur	Coefficient	Index	Phthalate Output, 2 Hr.	Diagnosis
3/10/15	23*	33336	28	17	60.8	15.4	14.9	0.364	0.094	72	50	Chronic diffuse nephritis; secondary contracted kidney
3/17/15	...		35	21	60	18.6	24.6	0.45	0.091	78	..	
3/ 1/15	24	33786	25	15	60	13.5	10.7	0.321	0.097	70	35	Primary contracted kidney; myo-cardial insufficiency
4/25/15	...		..	14		4.1	5.6	0.299	0.126	40	32	
5/20/15	26*	33605	33	25	75.8			0.535	0.098	67	41	Chronic diffuse nephritis; secondary contracted kidney
6/22/15	28	34208	30	15	50	9.1	10.7	0.321	0.098	67	42	Chronic diffuse nephritis; secondary contracted kidney
12/ 2/15	...		..	17		7.7	8.7	0.364	0.123	42	57	
12/ 7/15	35*	35242	26	17	65.5	12.1	12.5	0.364	0.103	60	40	Chronic diffuse nephritis; secondary contracted kidney; uremia
12/ 13/15	...		23	13	56.5	4.9	6.9	0.278	0.106	57	34	
12/13/15	...		16	7	43.7	4	1.3	0.15	0.129	38	..	
1/21/16	...		..	19		14.8	8.7	0.406	0.137	34	32	
2/ 8/15	39	33557	50	33	66	19.3	45.1	0.706	0.105	58	55	Chronic diffuse nephritis
2/23/15	...		30	20	66.6	12.7	25	0.428	0.085	80	..	
3/ 5/15	...		20	18	62	23.4	40.7	0.385	0.061	175	..	
3/17/15	...		26	15	57.7	13.6	36.2	0.322	0.053	228	65	
4/ 4/15	44*	33921	23	17	69.5	6.1	9.3	0.364	0.112	53	55	Arteriosclerosis; arteriosclerotic kidney
3/20/15	52	33887	20	12	60	8.9	4.9	0.257	0.116	48	66	Primary contracted kidney; myo-cardial insufficiency

4/ 6/15	...		22	13	59.1	11.9	9.6	0.278	0.097	70	..	Primary contracted kidney; no myocardial insufficiency
8/28/15	54*	34404	..	24		7.1	18.5	0.514	0.118	46	35	Chronic diffuse nephritis; secondary contracted kidney
12/ 3/15	...	35075	..	16		1.2	1.1	0.344	0.331	5.8	24	Chronic diffuse nephritis; secondary contracted kidney; uremia
1/ 8/16	...		108	86	79.5	6.3	9.7	1.84	0.59	1.8	11	
1/14/16	...		73	50	68.5	3.3	3.6	1.07	0.57	1.9	14	
1/24/16	...		41	27	66	2.1	1.9	0.579	0.41	3.9	14	
4/ 3/15	65	34005	25	15	60	11.9	5.8	0.321	0.134	36	15(?)	Primary contracted kidney
4/27/15	...		36	27	75	21.2	14.3	0.578	0.158	26	34	
6/19/15	...		..	27		19.2	16.4	0.578	0.142	32	20	
4/29/15	70*	34100	39	34	87.3	19.4	26.9	0.729	0.14	33	25	Chronic diffuse nephritis
5/21/15	...		111	88	79.2	22.2	32.0	1.884	0.334	5.7	T	Chronic diffuse nephritis; uremia
	71*	35182	32	17	53.1	19.7	6.6	0.364	0.141	32	55	Primary contracted kidney; cerebral arteriosclerosis
1/17/16	74*	35264	..	10		5.8	2.2	0.214	0.144	31	34	Primary contracted kidney; chronic diffuse nephritis
3/18/16	...		..	98		8.5	7.3	2.1	0.775	1	0	Primary contracted kidney; chronic diffuse nephritis; uremia
5/24/15	84	34239	35	28	89	15.4	12.7	0.6	0.168	23	45	Chronic diffuse nephritis
8/12/15	...		..	61		20	65.8	1.305	0.161	25	37	
11/13/15	...		..	23		7.9	1.9	0.483	0.361	5	..	
11/16/15	...		..	26		16.2	16.1	0.557	0.139	33	31	
11/29/15	...		24	12	50	10.3	7.3	0.257	0.095	71	54	
12/ 8/15	...		14	5	35.7	2.4	2.6	0.107	0.066	144	63	
12/20/15	...		18	8	44.5	3.6	4.6	0.171	0.08	100	72	
12/30/15	...		..	13		13.8	10	0.274	0.087	84	70	
4/28/14	164†	20982	..	42			27.6	0.904	0.172	22	19	Chronic diffuse nephritis; secondary contracted kidney
5/25/14	...		..	77			27.8	1.65	0.212	6.6	..	

* Cases ending fatally.
† Cases in which original hypobromite methods were used for analysis.

TABLE 9.—CHRONIC NEPHRITIS—(Continued)

Date	Case No.	Medical No.	Total protein Nitrogen, Mg. per 100 C.c. Blood	Urea Nitrogen, Mg. per 100 C.c. Blood	Percentage of Total Non-protein Nitrogen Present as Urea Nitrogen	Gm. Urea per Liter of Urine, G	Corrected Rate of Output per 24 Hr. $D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}$	Gm. Urea per Liter of Blood, Ur	Coef. of Index	Index	'Phthal- ein Output, 2 Hr.	Diagnosis
6/ 6/14	...		..	178			11.4	3.799	1.12	0.5	0	
1/12/16	88*	35287	23	19	82.5	8.3	4.5	0.407	0.192	17.4	24	Ch. dif. nephritis; secondary cont'd kidney; myocardial insufficiency
1/23/16	...		24	12	50	6.3	2.8	0.257	0.154	27	23	
2/24/16	...		30	26	66.6	10.6	10.5	0.556	0.172	22	..	
3/ 8/15	91*	34717	..	37		13.5	13.5	0.792	0.216	13.7	51	Chronic diffuse nephritis; secondary contracted kidney
3/13/15	92	33757	80	59	73.8	13.5	29.7	1.261	0.224	12	23	Chronic diffuse nephritis; secondary contracted kidney
3/17/15	...		74	65	87.8	11.5	17.5	1.391	0.332	5.7	..	
11/20/15	...		65	53	81.5	13	24.8	1.135	0.228	9.5	22	
11/23/15	...	35042	97	61	63	10.1	13.8	1.309	0.358	5.0	17	
11/23/15	...		70	41	58.5	8.5	9	0.877	0.292	7.5	..	
11/23/15	92		38	24	63.2	2.9	3.6	0.515	0.272	8.7	23	
12/ 8/15	...		22	15	68.2	2.3	2.1	0.322	0.224	12.8	18	
12/13/15	...		32	21	65.6	4	3.1	0.45	0.254	9.9	22	
12/20/15	...		54	39	72.2	6.8	8.5	0.835	0.289	7.7	..	
4/14/15	96	34837	..	35		13.1	9.7	0.749	0.24	11	10	Chronic diffuse nephritis; secondary contracted kidney
10/11/15	...		..	41		7.3	6.8	0.891	0.341	5.5	3.5	
5/16/16	...		87	49	53.3			1.049	0.414	3.7	T	

6/ 8/14	171†	21252	..	64				32.2	1.37	0.241	11	..	Primary contracted kidney; arterio-sclerosis
6/19/14	...		..	43				10.6	0.924	0.285	8	..	Primary contracted kidney; uremia
9/ 4/15	97*	34691	..	28			12.9	5.9	0.606	0.245	10.7	18	Primary contracted kidney; uremia
9/20/15	...		..	53			19.7	24.4	1.141	0.232	12	17	Chronic diffuse nephritis; secondary contracted kidney; uremia
1/15/16	98	35282	..	51			14	16.8	1.09	0.266	9	16	Chronic diffuse nephritis; secondary contracted kidney; uremia
1/28/16	...		..	32			11.7	6.7	0.685	0.265	9	15	Chronic diffuse nephritis; secondary contracted kidney; uremia
8/26/15	102*	34507	..	35			5	6.2	0.75	0.302	7	22	Chronic diffuse nephritis; secondary contracted kidney; uremia
9/15/15	...		..	47			4.5	4.9	1.018	0.457	3	9	Chronic diffuse nephritis; secondary contracted kidney; uremia
9/27/15	...		..	98			4.8	5.6	2.102	0.891	0.8	0	Chronic diffuse nephritis; secondary contracted kidney; uremia
10/14/15	...	34637	110	80	73	5.1	7	1.715	0.85	1.5	..	..	Chronic diffuse nephritis; secondary contracted kidney; uremia
10/24/15	...		132	78	51.2	4.8	8.3	1.67	0.53	1.9	0	0	Chronic diffuse nephritis; secondary contracted kidney; uremia
2/16/16	105		..	44			11.7	7.3	0.941	0.349	5.2	15	Chronic diffuse nephritis; secondary contracted kidney; uremia
2/23/16	...		54	35	64.8	8.7	5	0.749	0.336	5.7	7	7	Chronic diffuse nephritis; secondary contracted kidney; uremia
3/18/16	...		..	60			7.4	5.2	1.284	0.563	2	..	Chronic diffuse nephritis
4/ 1/16	...		82	66			6.1	2.7	1.41	0.86	0.9	..	Chronic diffuse nephritis
1/ 9/14	174*†	20575	..	65				12	1.336	0.401	4	0	Chronic diffuse nephritis; uremia
4/ 3/14	...		..	211				23.8	4.505	0.924	0.7	0	Chronic diffuse nephritis
4/28/14	...		..	321				16.7	6.86	1.68	0.2	0	Primary contracted kidney; uremia
3/ 4/15	107*	33799	81	64	79	7.7	10	1.37	0.434	3.4	13	13	Primary contracted kidney; uremia
3/12/15	...		96	60	62.5	5	5.2	1.284	0.567	1.9	..	..	Primary contracted kidney; uremia
3/26/15	...		102	85	83.3	7.5	7.7	1.82	0.665	1.4	2.5	2.5	Primary contracted kidney; uremia
4/ 9/15	...		94	84	80.4	6.2	6	1.796	0.742	1.1	0	0	Primary contracted kidney; uremia
4/20/15	...		102	155	80.8	8	2.8	3.318	1.99	0.2	0	0	Primary contracted kidney; uremia
2/ 9/15	108*	33643	40	23	57.5	3.3	1.3	0.492	0.436	3.4	28	28	Primary contracted kidney; uremia

* Cases ending fatally.

† Cases in which original hypobromite methods were used for analysis.

TABLE 9.—CHRONIC NEPHRITIS—(Continued)

Date	Case No.	Medical No.	Total Non-protein Nitrogen, Mg. per 100 C.c. Blood	Urea Nitrogen, Mg. per 100 C.c. Blood	Percentage of Total Non-protein Nitrogen Present as Urea Nitrogen	Gm. Urea per Liter of Urine, C	Corrected Rate of Output per 24 Hr. $D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}$	Gm. Urea per Liter of Blood, Ur	Coefficient	Index	'Phthal- ein Output, 2 Hr.	Diagnosis
2/25/15	...		78	66	84.9	8.6	4.7	1.415	0.65	1.6	0	Polycystic kidney
9/ 3/15	110*	34684	..	53		5	5.7	1.135	0.475	2.8	T	
9/15/15	...		..	40		4.8	3.5	0.86	0.46	3	5	
2/ 5/16	111		86	70	81.5	6.6	10	1.498	0.48	2.8	0	Polycystic kidney
2/10/16	...		112	90	80.3	7.4	8.4	1.926	0.665	1.4	0	
2/19/16	...		86	69	80.3	5.5	4.3	1.476	0.714	1.3	0	
3/ 3/16	...		92	62	67.4	6.8	13.6	1.327	0.359	5	0	Chronic diffuse nephritis; secondary contracted kidney; uremia
3/11/16	...		..	52		5.7	5.7	1.112	0.466	2.9	0	
3/12/16	...		..	57		5	2.4	1.22	0.793	1	0	
9/14/15	112*	34725	..	76		6.1	7.5	1.629	0.597	1.8	T	Chronic diffuse nephritis; secondary contracted kidney; uremia
9/24/15	...		..	120		5.8	9.9	2.568	0.815	0.9	0	
10/ 4/15	...		181	163	90					..	..	
1/20/16	114*	35306	..	142		8.1	24.5	3.143	0.659	1.5	0	Chronic diffuse nephritis; secondary contracted kidney; uremia
1/26/16	...		..	178		9.6	9.7	3.818	1.23	0.4	0	
3/ 8/16	116*	35586	..	89		6.9	6.6	1.917	0.742	1.2	T	
3/18/16	...		..	113		9.4	3.7	2.523	1.31	0.4	T	Chronic diffuse nephritis; secondary contracted kidney
8/19/15	117*		..	53		5.4	2.3	1.131	0.75	1.1	..	

8/28/15	...		..	68		7.2	17	1.88	0.458	3	18
9/ 6/15	...		..	63		6	9.6	1.349	0.425	3.5	14
10/ 7/15	...		125	99	79.2	4.4	3.5	2.119	1.125	0.5	5
10/14/15	...		145	125	87	6.4	4.3	2.7	1.305	0.4	..
10/21/15	...		123	103	83.9	3.3	6.9	2.2	0.836	0.9	7
10/28/15	...		66	49	74.3	3.4	4	1.049	0.524	2.3	5
11/ 5/15	...		55	32	58.2	2.1	1.7	0.685	0.525	2.3	5
11/ 9/15	...		88	64	72.8	2.4	2.9	1.37	0.8	1	..
11/16/15	...		95	63	66.4	5.1	4.6	1.349	0.631	1.6	..
11/23/15	...		79	55	69.8	2.9	3.3	1.177	0.65	1.5	6
11/30/15	...		41	30	73.1	1.9	2.1	0.642	0.445	3.2	..
12/ 7/15	...		32	23	71.9	1	0.9	0.492	0.52	2.4	..
12/11/15	...		36	26	72.3	1.7	1.7	0.557	0.43	3.5	..
12/30/15	...		..	32		2.3	2.9	0.676	0.396	4.1	..
1/13/16	...		08	52	76.5	5	2.7	1.112	0.682	1.4	5
1/25/16	...		03	45	71.5	3.9	3.6	0.964	0.509	2.5	..
2/12/16	...		..	79		4.1	0.8	1.69	1.872	0.2	..
2/24/16	...		192	149	77.6	9.8	5.4	3.187	1.37	0.3	T
3/ 3/16	...		216	170		10.8	5.2	3.64	1.591	0.2	T
3/10/16	...		..	174		6.1	1.9	3.725	2.67	0.1	..
3/25/14	177+†	20603	..	173		10.6	13.9	3.725	0.995	0.6	0
4/16/14	...		..	419		15.9	1.3	8.96	7.95	..	0

Primary contracted kidney; uremia

* Cases ending fatally.
† Cases in which original hypobromite methods were used for analysis.

In vascular nephritis death is due so frequently to extrarenal accidents (vascular or cardiac) that extreme renal insufficiency is somewhat unusual. In such cases the presence of a relatively unimpaired renal function should not be regarded as necessarily warranting a favorable prognosis. For example, Case 71 was a cerebral arteriosclerotic, with some evidences of a vascular nephritis. The functional tests showed slightly damaged kidney (55 per cent. phenolsulphonephthalein excretion, coefficient 0.141), yet he died two weeks later of cerebral hemorrhage. We have had very little opportunity of following the cases of primary contracted kidney over long periods. Such patients have usually come for consultation on account of symptoms referable to hypertension rather than to any renal insufficiency and have not remained in the hospital. Of fifty-eight patients examined, forty-eight had coefficients below 0.2. Thirty-three of these have been traced, and of these, only five are dead. One died of uremia, three of cerebral hemorrhage, and one with extreme myocardial insufficiency. Of the ten patients with coefficients above 0.2, nine have been followed and eight of these are dead. Six died in the hospital in coma, two died of cerebral hemorrhage shortly after their discharge. Extreme myocardial insufficiency was present in three of the eight patients during their terminal illness. It is evident from the foregoing that functional signs of renal insufficiency occur only in the last stages of the disease. Coefficients above 0.175 in chronic vascular nephritis justify a very guarded prognosis.

The cases of chronic diffuse nephritis can be divided into three distinct types:

1. Those which remain stationary over prolonged periods, in spite of an outspoken renal insufficiency. The functional tests have a peculiar value in identifying these cases and in giving evidence of the onset of a progressive lesion, which under ordinary circumstances is the final event.

2. Other cases show a progressive course, with constantly increasing renal insufficiency. In these the coefficient and phenolsulphonephthalein test enable us to follow the rate of progress and thus assist in an accurate prognosis.

Seventy-one determinations have been done on thirty-nine such cases in which the coefficient was below 0.2. Thirty of these patients have been traced and ten have died, six in uremic coma. Seventy-six determinations have been done on twenty-six patients with coefficients above 0.2. Twenty-one of these patients have been traced and fifteen of them are dead. Eleven died in uremia within a short time of observation, and most of them had more or less severe myocardial insufficiency. It is evident from the foregoing that here again individuals with a coefficient above 0.2 have an expectation of life measured in

months, although the danger is not so immediate as in those cases of vascular nephritis with an equally high coefficient.

3. In three cases (Cases 23, 26 and 35) the functional studies gave no inkling of the severity of the lesion. These were all examples of rapidly progressive uremia. The history was the same in every instance. There were severe headaches, visual disturbances, nausea, vomiting and loss of weight. Hypertension, cardiac hypertrophy, diffuse vascular thickening, and extreme grades of albuminuric retinitis were present in every case. They showed normal blood ureas, coefficients below 0.14 and phenolsulphonaphthalein excretions above 40 per cent. These patients all died in convulsions within five months of the time of observation. None of these cases came to necropsy. From the history, Case 114 was probably another member of the group, seen, however, in the last stages. At necropsy a moderate grade of secondary contracted kidney was found. In these cases a comparison of the severity of the symptoms and physical signs, with the mild grade of functional impairment, gave a perfectly definite picture. The absence of outspoken functional impairment should not be misleading. The prognosis in these cases was measured in weeks.

While in a majority of cases the functional findings are of great assistance in the making of an immediate prognosis (as in those cases with a coefficient above 0.2), we are still at a great disadvantage in those cases having only a moderate grade of impairment. Under ordinary conditions a low coefficient (below 0.12) which remains at approximately the same level for some time justifies a good prognosis. One should be extremely careful in giving a favorable opinion with values above 0.15, as a coefficient at this level means that a large proportion of the active renal tissue has been damaged, and any extra strain put on the organ will undoubtedly cause serious renal insufficiency.

Practically every patient with a coefficient steadily above 0.35 has died within six months. Every one of these patients, however, had such outspoken signs of renal insufficiency that the information gained by functional study was merely of a confirmatory nature.

SUMMARY

1. The laws of function are not followed with mathematical exactness in young and active individuals, but under routine conditions they are remarkably accurate. They are correct in principle.
2. The coefficient of urea excretion is subject to certain variations in normals, but any value below 0.06 or above 0.09 should be regarded as abnormal unless the excessive variation can be readily explained.
3. The coefficient is absolutely independent of the blood urea concentration. Its level is governed by the condition of renal function.

4. The coefficient is depressed in fever, in hyperthyroidism, in hypertension with early changes in the renal arterioles, and in early chronic diffuse nephritis. The depression is an evidence of increased renal activity due to irritation.

5. The coefficient is raised in myxedema.

6. There is an increase of the coefficient in myocardial insufficiency. Opinions are divided as to whether this is the effect of an extrarenal factor (the circulation) or whether there is a definite anatomic lesion in the passively congested kidney.

7. The coefficient is above normal in nephritis with renal insufficiency. This increase is more evident in chronic diffuse nephritis than in the vascular type, due to the greater frequency of renal insufficiency in the former cases. The coefficient shows an increase long before there is any evidence of nitrogen retention in the blood. The coefficient gives an excellent means of following the changes in renal function and of measuring the rate of progress of the disease.

8. There is a marked uniformity in the results of the phenolsulphonephthalein test and the coefficient in all stages of nephritis. In the later stages there is also a close agreement between the nonprotein nitrogen of the blood and the coefficient.

9. In a few severe cases the coefficient varies without there being any evident change in the clinical condition; the causes of these variations have been discussed.

10. The prognostic value of the coefficient is considerable. Values above 0.2 are seen only in the severe cases, while constants persistently above 0.3 are found only in persons with a maximal impairment of renal function. A coefficient above 0.2 has a graver import in vascular nephritis than in that of chronic diffuse type.

11. For an accurate prognosis repeated determinations of the coefficient are of the greatest importance.