STUDIES OF UREA EXCRETION. II.

Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults[1]

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DEFINITION AND CALCULATION OF THE MAXIMUM AND STANDARD BLOOD UREA CLEARANCES

Investigations by Marshall and Davis (1914), Pepper and Austin (1915), Addis and Watanabe (1916), and by Addis, Barnett, and Shevky (1918) have shown that when the urine volume is fairly large the rate of urea excretion is directly proportional to the blood urea content. Expressed in other words, with abundant urine the urea excretion per minute equals the urea contained in a constant volume of blood. This volume of blood in a normal adult is about 75 cc.

Austin, Stillman, and Van Slyke (1921) demonstrated in three normal subjects that the direct ratio between blood urea content and urea excretion rate holds only when the urine volume is above a certain limit (about 2 cc. per minute in adults), which they called the "augmentation limit." When the urine volume fell below the augmentation limits of the subjects studied, the urea excretion rate was found to fall also, and on the average, in proportion to the square root of the volume: e.g., if, blood urea remaining constant, the urine volume were diminished from 2 to 0.5 cc. per minute, the urea excretion rate would be halved.

The conception of these authors is confirmed in this paper by observation on 7 other subjects, and the augmentation limit in normal adults has been found to range from 1.7 to 2.5 cc. of urine per minute.

When the urine volume output is at any point *above the augmenta-*

[1] The first paper of this series was by Austin, Stillman, and Van Slyke (1921 on "Factors Governing the Excretion Rate of Urea."

tion limit, urea excretion proceeds at maximum speed, and the output per minute represents the urea content of a maximum blood volume. This blood volume, averaging in normal men about 75 cc. per minute, we shall for convenience term the *maximum blood urea clearance, or simply the maximum clearance.* It represents the volume of blood which one minute's excretion suffices to clear of urea when the urine volume is large enough to permit a maximum urea output. The value of the maximum clearance, C_m, is calculated from the observed urea concentrations of the blood and urine, B and U, and the urine volume, V, in cubic centimeters per minute, by the formula,

$$\textit{Maximum clearance} = C_m = \frac{U\,V}{B}$$

The concentration ratio, $\frac{U}{B}$, indicates the number of cubic centimeters of blood the urea content of which is represented in 1 cc. of urine. $\frac{U}{B} \times V$ therefore indicates the number of cubic centimeters of blood represented in the urea content of the V cubic centimeters of urine excreted in 1 minute.

Below the augmentation limit the volume of blood, the urea content of which is represented in one minute's excretion, (the blood urea clearance per minute) is not a constant, but varies, on the average, in proportion to the square root of the urine volume. In order to compare excretions below the augmentation limit, therefore, they must either be observed with a standard, constant, urine volume output, or, if observed with other urine volumes, the excretion rates must be corrected for the urine volume effect. It is practically impossible to fix the urine volume at a definite standard, but, by means of the square root rule of Austin, Stillman, and Van Slyke, the urea excretion that would accompany such a standard urine volume can be calculated from the excretion measured with any other volume below the augmentation limit.

The formula for the calculation is developed as follows:

If C is the observed blood urea clearance (the cubic centimeters of blood, the urea content of which is excreted in 1 minute) with any urine volume output, V, below the augmentation limit, then with the standard urine volume, V_s, the corresponding *standard clearance*, C_s, may be calculated by the square root rule as

$$C_s : C = \sqrt{V_s} : \sqrt{V}$$

or

$$C_s = C\sqrt{\frac{V_s}{V}}$$

The standard urine volume that we have adopted is 1 cc. per minute. This value not only simplifies calculation because it is represented by unity: it presents itself also as a natural standard, because it is approximately the average rate of urine excretion for normal adults (1440 cc. for 24 hours; Addis (1923) found 1345 cc. as the average). Consequently the observed volumes will on the average differ less from it than from any other volume. Substituting therefore 1 for V_s we obtain

$$C_s = C\sqrt{\frac{1}{V}}$$

For convenience in calculation it is desirable to substitute in place of the observed clearance, C, the figures directly determined by analysis, viz. the urea concentrations, U and B, in urine and blood respectively, and the urine volume, V. As shown above in connection with the calculation of the maximum clearance, the observed clearance is estimated as $C = \frac{UV}{B}$. We therefore substitute $\frac{UV}{B}$ for C in the equation $C_s = C\sqrt{\frac{1}{V}}$ and obtain:

$$\textit{Standard clearance} = C_s = \frac{U}{B}\sqrt{V}$$

For the condition that the urine volume is below the augmentation limit.

The standard clearance indicates the efficiency with which the kidneys excrete urea when the urine volume is at the average normal level of 1 cc. per minute. The maximum clearance indicates the maximum efficiency

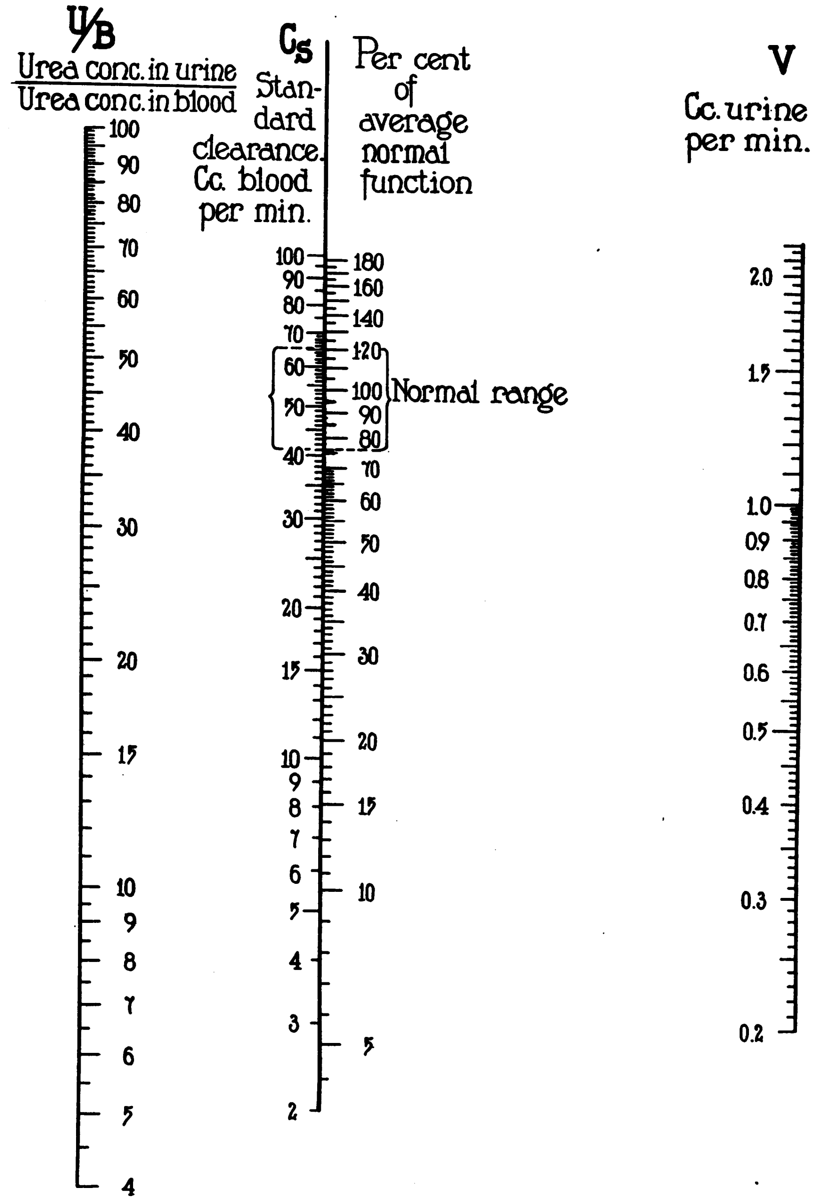

FIG. 1. LINE CHART FOR CALCULATING MAXIMUM BLOOD UREA CLEARANCE, $C_m = \frac{U V}{B}$, FROM U, B, AND VALUES OF V ABOVE THE AUGMENTATION LIMIT

Connect observed U/B and V values by a straight line. Where the line cuts the inner scale read C_m value or per cent of average normal renal function.

For subjects differing markedly from usual adult size, a correction is introduced by multiplying the observed V value by the factor $\frac{1.73}{\text{sq. m. surface area}}$ (see next paper), and using the V value thus corrected for the calculation of C_m.

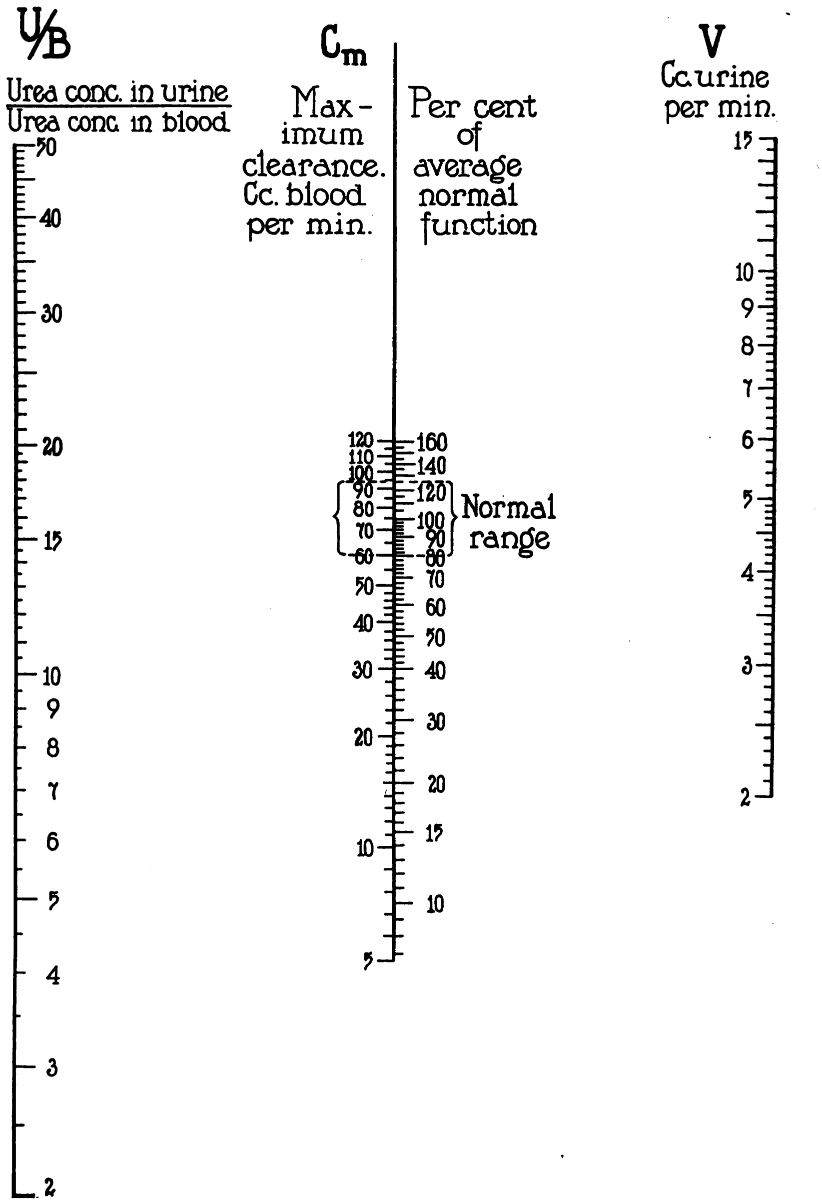

FIG. 2. LINE CHART FOR CALCULATING STANDARD BLOOD UREA CLEARANCE, $C_s = \frac{U\sqrt{V}}{B}$, FROM U, B, AND VALUES OF V BELOW THE AUGMENTATION LIMIT

Connect observed U/B and V values by a straight line. Where the line cuts the inner scale read C_s value or per cent of average normal renal function.

For subjects differing markedly from usual adult size, a correction is introduced by multiplying the observed V by the factor $\frac{1.73}{\text{square meters surface area}}$ (see next paper), and using the V value thus corrected for the calculation of C_s.

of urea excretion with high urine volumes. The maximum clearance is normally about 40 per cent greater than the standard clearance, the mean values being 75 cc. of blood per minute for the maximum and 54 cc. for the standard. Usually, though not always, in pathological conditions both values are affected to approximately the same degree.

For use in the above formulae for calculating C_s and C_m, any convenient units of urea or urea N concentration, e.g. grams per liter, milligram per 100 cc., may be used to express the urea concentrations, U and B so long as the *same* unit is used for both U and B. This follows from the fact that in each formula U and B appear only in the ratio $\frac{U}{B}$, so that both U and B may be multiplied by any factor without changing the value of $\frac{U}{B}$ ratio, or of the C_s or C_m calculated therefrom.

The unit for expressing values of V, however, can not be changed without changing the numerical values of C_s and C_m.

CALCULATION OF CLEARANCE VALUES

If the urine volume exceeds 2 cc. per minute, as observed in an adult, or as corrected for body size (see next paper) in a child, the *maximum clearance* is calculated.

If the volume thus observed or corrected is less than 2 cc. per minute, the *standard clearance* is calculated.

It is advantageous as a rule to calculate both clearances in percentages of the mean normal C_s and C_m. Urea excretions observed with ordinary urine volumes and calculated in terms of C_s are thus rendered directly comparable with excretions observed with large urine volumes and hence calculated in terms of C_m. Furthermore the percentage values thus calculated express directly percentages of average normal renal efficiency.

The percentage of average normal C_m is obtained by dividing the absolute C_m value by the mean normal C_m, 75, and multiplying by 100. Similarly the percentage of average normal C_s is obtained by dividing the absolute C_s by 54 and multiplying by 100.

$$\text{Per cent of average normal } C_m = \frac{100\ UV}{75B} = 1.33\frac{UV}{B}$$

$$\text{Per cent of average normal } C_s = \frac{100\ U\sqrt{V}}{54B} = 1.85\frac{U\sqrt{V}}{B}$$

Graphic calculation of C_m and C_s by charts of figure 1 and figure 2. Both the absolute and percentage C_m and C_s values are most readily calculated graphically by means of a slide rule, or by means of the line charts in figure 1 and figure 2 respectively. When the charts are used it is necessary to calculate by arithmetic only the value of the quotient $\frac{U}{B}$, and of V in cubic centimeters per minute, corrected for body size as outlined in the next paper if the subject is a child. A thread stretched taut across figure 1 or figure 2 intersecting the observed values of $\frac{U}{B}$ and V on the outer scales then crosses the inner scale at a point indicating both the absolute clearance and the percentage of normal.

Arithmetical calculation of C_m and C_s. For arithmetical calculation of the standard clearance the following values of the square root of V are given covering the range below the augmentation limit.

V *cc. per minute*	$\sqrt{V}$	V *cc. per minute*	$\sqrt{V}$
0.2	0.45	1.2	1.10
0.3	0.55	1.3	1.14
0.4	0.63	1.4	1.18
0.5	0.71	1.5	1.23
0.6	0.78	1.6	1.27
0.7	0.84	1.7	1.30
0.8	0.89	1.8	1.34
0.9	0.95	1.9	1.38
1.0	1.00	2.0	1.42
1.1	1.05	2.1	1.45

Example of calculation of a normal maximum clearance

Blood urea N = 15.6 mgm. per 100 cc. = B
Urine urea N = 321.0 mgm. per 100 cc. = U
Urine volume = 210 cc. per hour
= 3.5 cc. per minute = V

$$C_m = \frac{UV}{B} = \frac{321 \times 3.5}{15.6} = 72 \text{ cc. of blood cleared of urea per minute}$$

Per cent of average normal function = 1.33 × 72 = 96 per cent

Example of calculation of a normal standard clearance

Blood urea N = 14.7 mgm. per 100 cc. = B
Urine urea N = 750 mgm. per 100 cc. = U
Urine volume = 50 cc. per hour
= 0.83 cc. per minute = V

$$C_s = \frac{U\sqrt{V}}{B} = \frac{750 \times 0.91}{14.7} = 46 \text{ cc. of blood cleared of urea per minute}$$

Per cent of average normal function = 1.85 × 46 = 85 per cent

Technique for determining the blood urea clearance as a measure of renal efficiency. The necessary data are the concentrations of urea in blood and urine, and the volume of urine excreted in a measured time. The manner in which these 3 values are secured may be varied to suit conditions. As a routine procedure, however, we have found the following satisfactory:

The subject is not subjected to any previous routine, except that vigorous exercise is avoided and the previous meal should be a moderate one, preferably without coffee, which Addis and Drury (1923) have found may increase the blood urea clearance. The most desirable time of day, when excretion is least liable to fluctuations, is found according to MacKay (1928) in the hours between breakfast and lunch. The patient remains quiet while the urine is collected during two succeeding periods of 1 hour each. The chief source of error is probably the possibility of incomplete emptying of the bladder, either at the beginning or end of a period. The collection of two urine specimens affords a check on this factor. A few minutes before the end of the first hour a blood sample is drawn. Its urea content is used for calculation of the clearances during both periods. This usage is permissible, because under the conditions of the test the blood urea does not change greatly during an hour.

The maximum clearance is calculated if the urine volume observed in an adult, or if the corrected volume $V \times \frac{1.73}{\text{Sq. m. surface area}}$

in a child, exceeds 2 cc. per minute. (See accompanying Paper III of this series.)

The standard clearance is calculated if the urine volume, corrected in the case of a child, is less than 2 cc. per minute.

Physiological and pathological significance of maximum and standard blood urea clearances. The excretion rate observed with the average normal maximum blood urea clearance is what would be obtained if 75 cc. of blood per minute passed the kidneys, and all its urea were excreted. Actually a larger volume of blood perfuses the kidneys, and only a certain fraction of its urea is removed. Picard (1856) found that in dogs the urea content of blood from the renal vein was half that of blood from the artery. If a similar relation held for man, the average normal renal blood flow could be estimated at 150 cc. per minute, 50 per cent of the urea of this blood being excreted with large urine volumes and 35 per cent with the average urine volume of 1 cc. per minute.

Decrease in the volume of blood cleared of urea per minute in pathological conditions must be due to one of two causes: either the volume of blood per minute passing through the kidneys is diminished, or the proportion of its urea removed during the passage is less than normal. In cardiac decompensation presumably the flow factor is responsible for lowered renal function; and in glomerular nephritis the damaged renal vessels make diminished flow again seem certain. Whether a decrease in the proportion of urea removed from the blood also occurs or not, we have not at present the basis to surmise.

THE VARIABILITY OF THE BLOOD UREA CLEARANCE, AND ITS SIGNIFICANCE

The fact that in a given individual the probable variation of the standard blood urea clearance is $\pm$ 10 per cent, and that the maximum variation is much greater, indicates, as pointed out by Austin, Stillman, and Van Slyke (1921), that other factors in addition to blood urea concentration and urine volume affect urea excretion. Some of these factors were studied by Addis and Drury (1923), who found that the maximum clearance was increased by ingestion of a mixed meal, milk, caffein, or glutamic acid, and decreased by pituitrin or very large doses of adrenalin. The effect of adrenalin, however, was shown in rabbits by Addis, Barnett, and Shevky (1918) to vary with the dosage; up to a certain maximum it increased urea output, but greater amounts depressed the output. Ordinarily Addis (1917) believed that adrenalin and pituitrin act as antagonists in regulating renal activity.

Such influences may vary the blood clearence per minute in either of two ways. They may vary the renal blood flow without altering the percentage of blood urea removed at each passage through the kidneys. Or they may so influence the activity of renal cells that variations do result in the percentage of blood urea removed at each passage. The questions, whether and how the percentage of urea removed from the blood in the kidneys can be influenced, awaits experimental proof.

It is evident that the urea excretion rate is influenced by other factors in addition to blood urea content and urine volume, and that an erroneous impression would be created by the clearance formulae if they were assumed to express with mathematical exactness the complete effects of all factors influencing urea excretion. The width of the range of normal variation indicates the contrary. The formulae are only expressions of the effects of two factors, blood urea content and urine volume, which are in continual action and appear to be ordinarily of chief importance in regulating the urea output.

To minimize variations due to other factors Addis (1922) in determining the maximum clearance gives water and urea to the fasting subject at the beginning of a 6 hour period, and analyzes specimens of blood and urine collected during the last 3 hours of the period, during which diuresis is maintained by water drinking. In determining the standard clearance in this laboratory we have thus far set no conditions, except that the subject should be at rest and should have avoided coffee and other obvious diuretics during the preceding hours of the day. The limits of variation in our results, reported below, apply to these conditions. It appears possible that by standardizing conditions more completely the range of variation could be narrowed.

THE HISTORICAL DEVELOPMENT OF UREA EXCRETION TESTS OF RENAL FUNCTION IN NEPHRITIS

That the relatively simple conceptions of the maximum and standard blood urea clearances outlined in the preceding pages are logical developments of a long course of observation, experiment, and study by many investigators is indicated by the following historical summary.

In 1827 Bright first described the disease which has been called after him. The year after, 1828, Wöhler performed the synthesis of urea. This was the first time any organic substance had been synthesized *in vitro*.

The coincidence of these two scientific events at once created an interest in urea excretion in Bright's disease. Christison (1829) found the serum urea content increased in 3 patients out of 6, and further observed, that in these 3 cases the rate of urea excretion was slower than in the 3 others. Bright (1836) found a serum urea concentration of as much as 1500 mgm. per cent in a case of uremia. He noted that the concentrations of urea in the serum and in the urine of this patient were the same, and that while the former was increased, the latter was only about one-third of the ordinary normal value. These findings were soon confirmed by other authors, and in 1851 Frerichs, in his monograph, stated that while in acute cases of Bright's disease urine urea concentration and urea output were both normal, in chronic cases both were lower than in normal subjects on the same diet. In such cases he believed that the determination of the urea concentration of the urine could be of diagnostic value. A few years later diagnostic use of the blood urea concentration was recommended by Picard (1856).

During the second half of the nineteenth century the investigation of Bright's disease was chiefly concerned with the morphological and circulatory changes. The few isolated comments upon the usefulness of the determination of urine urea concentration (Green, 1885) or excretion rate (Cruise, 1890; Guyon, 1892) were only exceptions to the general rule.

In about 1900 interest turned to the functional aspect of disease, and the study of urea excretion was resumed. The point of view, however, was now different. Determination of the blood urea content and the urea excretion rate were carried out (separately or combined) not only for purposes of qualitative diagnosis, but in order to furnish quantitative information about the degree of functional impairment of the kidneys. The unrelated measurement of excretion rate or of urea concentration in urine was soon found to be unsatisfactory for this purpose. The reason was that both these factors are too dependent on the rate of protein catabolism and the urine volume. The influence of protein catabolism was fully recognized at the time, but that of urine volume was not.

Achard and Paisseau (1904) brought patients into nitrogen equilibrium and then added to the diet 20 grams of urea daily for some days. They measured the urea output per 24 hours, and noted the rapidity with which the superimposed amount of nitrogen was excreted. The procedure was, however, laborious, the results not very consistent. The method was abandoned, to be revived occasionally by later authors.

Other authors turned their attention to the blood urea, and neglected the excretion. The determination of blood urea was introduced into clinical medicine by Strauss (1902) and by Widal and Javal (1904). For diagnostic purposes determination of blood urea concentration has an advantage over determination of urine concentration, in that with ordinary urine volumes the blood figure is less dependent on fluctuations of water output. Other factors being constant, however, the blood urea content is proportional to the rate of protein catabolism. If a given subject breaks down into urea half as much protein daily his average blood urea will be half as high, given a constant urine volume. If the urine volume increases within the ordinary range (below the augmentation limit), the blood urea will be further diminished, increased water output washing out more urea from the blood. Both of these factors are likely to be operative in nephritis to prevent a rise in blood urea proportional to renal destruction. MacKay and MacKay (1927) in fact report data (which our own confirm) showing that many nephritics do not show blood ureas definitely above the normal maximum until more than 60 per cent of renal function has been lost.

The conception of comparing simultaneous urea determinations in blood and urine was introduced by Gréhant (1904) who used the concentration ratio $\frac{U}{B}$ as an expression of renal functional ability. However, the immense effects of urine volume changes on the urea concentration, U, in urine were not considered, in consequence of which even approximate constancy can not be obtained with this ratio. The use of the $\frac{U}{B}$ ratio was revived by Harrison (1922), who emphasized that the most consistent results were gained when the urine volumes were below 150 to 100 cc. per hour. This restriction reduces the inconsistencies introduced into the $\frac{U}{B}$ ratio by urine volume changes, but also limits the conditions under which observations can be made.

Ambard and Weill (1912) were the first to include both urea output and urine volume in attempting quantitatively to relate urea excretion to blood content. They found that urea excretion in normal subjects, and also in nephritics, was governed by two laws, relating output to blood and urine concentrations respectively. These laws were combined into the urea excretion formula of Ambard and Weill (1912), which, with numerical constants omitted, is:

$$K = \frac{B}{\sqrt{D}\sqrt{U}}$$

B and U represent, as above, concentration of urea in urine and blood, and D indicates rate of urea excretion (*débit*). Since $D = U \times V$, Ambard's formula can be written

$$K = \frac{B}{U^{\frac{3}{4}}\,V^{\frac{1}{2}}}$$

For the sake of comparison with our standard clearance formula we take the reciprocal, and have

$$\frac{1}{K} = \frac{U^{\frac{3}{4}}}{B}\sqrt{V}$$

In this form the similarity can readily be seen of Ambard's formula with our present formula, $C_s = \frac{U}{B}\sqrt{V}$, for calculating standard blood clearance. Although the influence of urine volume was not directly investigated by the French authors, a correction for urine volume is nevertheless contained in their formula and is brought out through its transcription as above. The volume factor $\sqrt{V}$ is valid, however, only for ordinary urine volumes of less than 2 cc. per minute. Above this point the volume factor should be V, and for higher urine volumes the Ambard formula becomes increasingly more inaccurate. The use of U in the ¾th power instead of in the first appears, in the light of present results, to be a complication diminishing rather than enhancing the accuracy of the formula. The introduction of the Ambard formula was, however, an important advance in estimating the effect of urine volume on urea excretion.

F. C. McLean (1915) put the Ambard formula into a more convenient form by squaring and inverting it, and adding a numerical constant, which made 100 the average normal value of this "urea secretory index."

Addis and Watanabe (1916) found a wide range of variation in results calculated from normal subjects by Ambard and Weill's formula, and presented data indicating the degree of inaccuracy of the two basic assumptions. Addis believed the urea excretion ratio, $\frac{D}{B} = \frac{\text{urea in 1 hour's urine}}{\text{urea in 100 cc. blood}}$, to be independent of urine volume (1917), and recommended its determination under certain standard conditions (1922) as a test of kidney function. These standard conditions will, except in rare pathological conditions, keep the urine volume well above the augmentation limit, and cause $\frac{D}{B}$ to represent the maximum blood clearance.

The existence of the augmentation limit was first recognized by Austin, Stillman, and Van Slyke (1921) who showed, first, that Addis' urea excretion ratio is independent of urine volume only when this is above the augmentation limit of about 2 cc. per minute, and, second, that with urine volumes below this point the excretion rate varies most nearly in proportion to the square root of the volume.

In the present paper we confirm these results on normal subjects, and in an accompanying paper we show that they hold true for nephritics also.

H. MacLean and de Wesselow (1919, 1920) in the interest of simplicity reverted to a single determination, the urea concentration in the urine, as a test of renal function. These authors prescribed certain standard conditions for its determination, designed to make the values more consistent. They gave 15 grams of urea with 100 cc. of water, and noted whether or not the urine urea concentration in the 2 subsequent hours rose above 2 per cent. If it did, they considered the kidneys fairly efficient. Gross errors due to dilute urines were excluded by rejecting tests in which the second hour's urine volume exceeded 150 cc. Their procedure was admirably adapted to its primary purpose, the rapid examination of large numbers of soldiers. In the study of nephritic patients, however, the method invites error by neglect of the blood urea. For example, if urinary function is so low that only a tenth the normal blood volume is cleared of urea per hour, the urea output will nevertheless be normal if the blood urea concentration is ten-fold the ordinary. Hence the urinary concentration will also be normal, if the volume is not increased. For this reason, in the terminal stages of nephritis, with high blood urea content, a urinary urea concentration within ordinary normal ranges may be observed, despite tremendously reduced renal ability.[2] The interpretation of figures for urea concentration in urine is therefore uncertain, unless the blood urea content is known, as well as the urine volume.

The historical sequence in which the different urea determinations were introduced as indicators of renal function, and the conditions under which they were best applicable, are summarized in table 1.

Numerical relation of the present standard clearance to previously used forms of the Austin-Stillman-Van Slyke formula. The formula $\frac{U}{B}\sqrt{V}$ expresses the number of cubic centimeters of blood *of which the urea content is concentrated into 1 cc. of urine*, when urine excretion is at the average normal rate of 1 cc. per minute. The mean normal numerical value of 54 indicates that under these conditions the kidneys concentrate the blood urea 54-fold. The standard clearance thus may be interpreted as a measure of the concentrating power, as well as the excreting ability, of the kidney. For this reason the value now called the standard clearance has, in a number of papers from this laboratory (e.g. Hiller, McIntosh, and Van Slyke (1927)) been called the "*concentration index.*" The term "standard clearance" is at pres-

[2] "Selbst die prozentige Ausscheidung des N kann noch relativ gut erscheinen, ja 1 per cent betragen, wenn bereit die tödliche Vergiftung begonnen hat" (p. 166 of Volhard and Fahr, 1914).

TABLE 1

Determination used to indicate state of kidneys' ability to excrete or concentrate urea

Functional test	Value determined	Variation, direct or inverse, with renal function	Conditions of applicability	Authors
Urea concentration in urine	U	Direct	Conditions assuring maximum concentration, viz., minimum urine volume, sufficient blood urea	Frerichs (1851) Guyon (1892) McLean and de Wesselow (1919)
Urea concentration in blood	B	Inverse	Normal diuresis and ordinary rate of protein catabolism	Picard (1856) Strauss (1902) Widal (1904)
Concentration ratio between urine and blood	$\frac{U}{B}$	Direct	Minimum or standard urine volume	Gréhant (1904) Harrison (1922)
Ambard's urea-secretory constant. Original form.	$\frac{B}{\sqrt{D \times \frac{70}{\text{weight}} \times \sqrt{\frac{U}{25}}}}$ *	Inverse	Below augmentation limit	Ambard and Weill (1912)
Addis' urea excretion ratio. (Maximum blood clearance)	$\frac{D}{B}$ or $\frac{UV}{B}$	Direct	Large urine volumes, above augmentation limit of about 2 cc. per minute	Addis and Watanabe (1916)
Standard blood clearance	$\frac{U}{B}\sqrt{V}$	Direct	Moderate and small urine volumes, below augmentation limit of about 2 cc. per minute	Austin, Stillman and Van Slyke (1921)

* U and B in this formula are expressed in grams of urea per liter urine and blood respectively. Freed of arbitrary constants, reduced to terms of U, B, and V, and inverted for comparison with other formulae, Ambard's formula becomes $\frac{U^{\frac{3}{4}}}{B}\sqrt{V}$.

ent preferred, partly because when used in conjunction with "maximum clearance" it suggests more clearly the difference in conditions under which the two respective urea excretion rates are determined.

In the above papers the formula used in calculating the "index" was $\frac{U}{B}\sqrt{\frac{V}{W}}$ instead of $\frac{U}{B}\sqrt{V}$. However, in the $\frac{V}{W}$ ratio used the volume unit was cubic centimeters per hour per kilogram, which, for a person of 60 kgm. weight, is the same as cubic centimeters per minute. Hence the values of $\frac{U}{B}\sqrt{\frac{V}{W}}$ in the above papers are approximately interchangeable with those of the present $C_s = \frac{U}{B}\sqrt{V}$. They deviate therefrom in proportion as $\sqrt{W}$ deviates from $\sqrt{60}$, but the fact that unusually low or high body weights influence the value $\frac{U}{B}\sqrt{\frac{V}{W}}$ only in proportion to their square roots, and not their first powers, diminishes the effect on the calculated clearance. E.g., a person of 50 kgm. would weigh 17 per cent less than one of 60; but the effect of this weight difference on the value of the index $\frac{U}{B}\sqrt{\frac{V}{W}}$ is only 9 per cent. Our present practice, discussed in the next paper, is to correct for wide divergence from average size by multiplying V by the factor $\frac{1.73}{\text{Sq. m. surface area}}$.

The standard clearance $\frac{U}{B}\sqrt{V}$ is, except for omission of the weight correction, identical with the excretion constant $\frac{D}{B\sqrt{VW}}$ of Austin, Stillman and Van Slyke. If in $\frac{D}{B\sqrt{VW}}$ the factor D is replaced by its equivalent, UV, the formula changes to $\frac{U}{B}\sqrt{\frac{V}{W}}$. Omission of the weight correction, W, simplifies it to $\frac{U}{B}\sqrt{V}$. The original numerical values of the excretion constant $\frac{D}{B\sqrt{VW}}$, or $\frac{U}{B}\sqrt{\frac{V}{W}}$, of these authors differed from the present clearance, and from the above discussed concentration index, because a different urine volume unit, $\frac{V}{W}$ = liters per 24 hours per kilogram, was used. A given excretion rate expressed in cubic centimeters per minute is represented by a figure $\frac{1000\ W}{1440}$, or 0.694 W, times as large as that expressing the same rate in terms of liters per 24 hours per kilogram. The average weight of the 4 men studied by Austin, Stillman, and Van Slyke was 72 kgm. If we substitute this for W in the factor 0.694 W, we find that a given excretion expressed in the terms of the above authors is to be multiplied by exactly 50 to correct it into cubic centimeters per minute. In order to convert the average value of the excretion constant obtained by Austin, Stillman, and Van Slyke into terms of the present standard clearance, the former value is consequently to be multiplied by $\sqrt{50}$, or 7.13. Their average normal constant of 7.5 therefore corresponds to a standard clearance of 53.6 cc. of blood per minute, which is nearly identical with the value calculated from the additional data yielded by other normal adults in this paper.

Numerical relationship of the present maximum clearance to the excretion ratio of Addis. The excretion ratio of Addis,

$$\frac{\text{urea in 1 hour's urine}}{\text{urea in 100 cc. blood}},$$

indicates $\frac{1}{100}$ the number of cubic centimeters of blood, the urea content of which is represented by 1 hour's secretion. The excretion ratio is determined by Addis under conditions of large urine volumes, so that the value represents maximum clearance. A normal hourly excretion equivalent to the urea content of 5000 cc. of blood corresponds to an Addis ratio of 50, which was found by him (1922) to be the average normal value. Our maximum clearance, expresses $\frac{1}{60}$ the cubic centimeters of blood, of which the urea content is represented by 1 hour's excretion. The Addis ratio is therefore converted into maximum clearance values, of cubic centimeters of blood cleared of urea per minute, by multiplying the Addis ratio by $\frac{100}{60}$ or 1.67. The mean normal value of his ratio, found by Addis to be about 50 in young men, corresponds therefore to a per minute maximum blood clearance of about $1.67 \times 50 = 83$ cc., which does not differ greatly from the average of 75 cc. found in our normal subjects.

THE CORRELATION BETWEEN URINE VOLUME AND UREA EXCRETION

The influence on urea output of urine volume changes below the augmentation limit, observed by Austin, Stillman, and Van Slyke, has been questioned by Addis and his collaborators. Addis and Drury (1923) studied the relationship between V and the excretion ratio (or blood urea clearance). They found that in rabbits changes in volume down to 2 cc. per hour had no influence on the observed clearance, $\frac{UV}{B}$. Of the 3 human subjects studied, however, only one was observed with urine volumes below 120 cc. per hour, which is the usual augmentation limit according to our data. In this subject they found the blood clearance somewhat lower with urine volumes below 50 cc. per hour than with volumes above 64 cc. per hour. Since no regular quantitative relationship between excretion and urine volume was demonstrable from their data, however, these authors concluded that the increase in urea excretion with increase in urine volume, observed over the lower volume ranges by themselves and by Austin, Stillman, and Van Slyke, was due merely to the fact that certain factors stimulated both water and urea excretion: the excretion rates of these two substances Addis and Drury conceived to be independent of each other.

As opinions still are divided we have considered it desirable to increase the number of observations covering the influence of urine volume on urea excretion in normal subjects. We have attempted to limit the factors influencing excretion as nearly as practicable to one, water. In some of the experiments data were also obtained on the effect of urea ingestion, which, however, was not observed to affect significantly the clearance values obtained.

EXPERIMENTAL

We have examined 5 normal persons between 20 and 30 years of age, all in good health and without any history of kidney disease. We also have reexamined another normal subject, now 44 years of age, (Van Slyke), on whom data were first published by Austin, Stillman, and Van Slyke, six years ago.

During each experiment (except those on Van Slyke) the person examined was kept in bed. The reasons for this were, first, that changes of position are said to influence the water excretion through the kidneys (White, Rosen, Fischer and Wood (1926)) and, second, that the kidney function of patients is nearly always examined while they are in bed, so it seems more correct to compare them with normals studied under similar conditions.

In some of the experiments urea was taken between 6 and 8 a.m.

The test began at 9 a.m. and went on for from one to seven hours. During this time the subject voided at the end of each hour, and a sample of blood (usually 0.2 cc. from the ear lobe) was drawn 10 minutes before the middle of each 1-hour period. The intention was to obtain a blood urea figure representing as nearly as possible the average value during the hour when the urine was formed. The urine takes a certain time to flow from the renal tubules to the bladder. The error which is due to this factor is lessened when the blood is taken somewhat before the middle of the collection period.

At about 8 a.m. the subjects were allowed to take bread, butter and jam. At noon bread, butter, jam, fruit and vegetables were given. Addis and Drury (1923) found that ingestion of milk or coffee accelerated urea excretion appreciably; consequently we have avoided giving them during an experiment. Addis and Drury found moderate sugar ingestion to be without effect. We have not observed any significant effect of the above, chiefly carbohydrate, meals on the urea excretion rate in our subjects.

The variations in urine volume were obtained by controlling the water intake. Each patient was examined on 2 or more days. When minimal urine volumes were desired no fluids were given from the previous evening till noon or later. High volumes were obtained by giving water freely hour by hour, either from early morning or in the afternoon following a period of desiccation. No other factors were varied, except on occasions when urea was given. As will be seen, the urea was without discernible influence on the clearance values. The variations obtained in the blood clearances with varying urine volumes may, we believe, be attributed to the variations in water regime.

Our attention has been particularly directed to the possibility of such changes in blood clearance occurring, during sudden increases or decreases of water output, as were found in dogs under certain conditions by Bourquin and Laughton (1925). These authors observed exceedingly high clearances during the onset of diuresis and a period of depressed clearances when diuresis subsided and during more or less of the postdiuretic period. It will be seen from table 1, that although sudden changes in urine volume occurred in several of our experiments, no changes in clearance of the kind described by Bourquin and Laughton are found in our data on human subjects.

The concentrations of urea in the urine and in most of the blood samples were estimated by the gasometric urease method of Van Slyke (1927). Most of the blood analyses were performed on 0.200 cc. samples by the micro-technique. In experiments numbers A 7 to A 11, however, the blood was drawn by venous puncture, and the urea concentration was estimated on samples of 3 cc. with the aeration urease method of Van Slyke and Cullen (1914).

RESULTS AND DISCUSSION

The conditions and results of all our experiments are given in tables 1 to 4.

The results for each of the 6 subjects investigated by us, and for one other from the literature (Rehberg, 1926), have been plotted in figures 3 to 9 with clearance values as ordinates and $\sqrt{V}$ as abscissae. In order to simplify the plotting by obtaining straight line curves we have laid off as abscissae values of the square root of the urine volume. According to the square root rule, this procedure should enable one to express the relationship between urine volume and blood clearance as a rising straight line below the augmentation limit; and it will be seen in the graphs that such is the case. Above the augmentation limit volume has no effect, and the excretion curve becomes a horizontal line.

The curves have been drawn in the following manner. The mean value of the clearance $\frac{UV}{B}$, in cubic centimeters of blood containing the amount of urea excreted per minute, for all points above the augmentation limit is taken, and at the corresponding height above the horizontal axis, and parallel to it, a line is drawn. Then for all points to the left of the augmentation limit the standard clearance $\frac{U}{B}\sqrt{V}$ is calculated, and the mean value is taken. This average determines the height of the curve at $V = 1$ cc. Through the corresponding point on the vertical line representing $V = 1$ cc., and through the zero point, a straight line is drawn. The position of the augmentation limit is calculated as the intersection point between this slanting line and the horizontal line first drawn.

In this way we have calculated augmentation limits from the data given by Austin, Stillman, and Van Slyke on Austin and Van Slyke our own data on six normal subjects, and finally the data given by Rehberg (1926) on himself, that were collected by him for quite other reasons, but can be used for our purpose as well.

TABLE 2

Data of experiments

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_S = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_S = 54$, $C_m = 75$
		cc. per minute	*mg. per 100 cc.*	*mg. per 100 cc.*	*cc. blood per minute*	*cc. blood per minute*	*per cent*
Experiment Number A 7 L. L. Ca. 8:15, breakfast with ca. 100 cc. of water	9–10	0.82	1003	13.1	64.3	69.3	128
Experment Number A 8 L. L. 6 a.m., 15 grams urea and 500 cc. of water. 7, 8, 9, 10 and 11 a.m., 500 cc. of water each time	9–10	12.33	238	31.7	92.7*		124*
	10–11	10.33	202	29.2	71.5*		95*
	11–12	9.75	209	28.0	72.9*		97*
Experiment Number A 9 L. L. Ca 8:15, breakfast with ca. 100 cc. of water	9–10	0.57	1460	17.6	47.0	62.6	115
Experiment Number A 10 L. L. Ca. 8:15, breakfast with ca. 100 cc. of water	9–10	0.47	1260	20.5	28.7	42.2	78
Experiment Number A 11 L. L. Ca 8:15, breakfast with ca. 100 cc. of water	9–10	0.58	?	?	43.2	56.7	105
Experiment Number 2 L. L. 7 a.m., 15 grams urea. 11 a.m., 20 grams urea and 200 cc. of water	9–10	1.33	1231	26.3	62.4	54.0	100
	10–11	1.83	1063	25.5	76.5*	56.4	104
	11–12	3.58	857	40.3	76.0		101*
	12–1	3.62	852	38.5	80.0*		107*
	1–2	2.03	1115	34.1	66.5*		89*

* Clearance figures marked * represent maximum clearance values, determined when V was above the augmentation limit for the subject. For augmentation limits see table 4.

TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_S = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_S = 54$, $C_m = 75$
		cc. per minute	*mg. per 100 cc.*	*mg. per 100 cc.*	*cc. blood per minute*	*cc. blood per minute*	*per cent*
Experiment Number 1	9–10	7.17	415	39.3	75.5*		101*
J. F. M.	10–11	8.08	324	38.5	68.0*		91*
7 a.m., 30 grams urea and	11–12	4.00	842	46.6	72.3*		96*
500 cc. of water. 10 and	12–1	2.42	1321	44.9	71.2*		95*
11 a.m., 12 noon and 1	1–2	1.63	1398	36.7	62.2	48.6	90
p.m., 5 grams, urea each time	2–3	1.67	1273	42.5	49.8	38.7	72
Experiment Number 8	9–10	0.75	1568	25.1	46.8	54.1	100
J. F. M.	10–11	0.92	1564	29.0	49.5	51.8	96
7:15 a.m., 15 grams urea.	11–12	1.08	1260	29.9	45.7	43.8	81
12:45 p.m., lunch. 1 and	12–1	0.60	1185	24.6	29.0	37.3	69
2 p.m., 1000 cc. of water	1–2	1.03	1366	24.7	57.2	56.2	104
each time	2–3	8.58	193	21.9	75.7*		101*
Experiment Number 3	9–10	1.67	1068	25.8	69.2	53.5	99
A. H.	10–11	1.42	1034	25.5	57.5	48.3	89
7 a.m., 15 grams urea. 11	11–12	3.67	593	32.3	67.3*		90*
a.m., 20 grams urea and	12–1	7.87	264	40.0	52.2*		70*
200 cc. of water. 1:30	1–2	2.08	1095	34.2	67.0	46.2	85
p.m., lunch and 200 cc. of water	2–3	2.42	901	31.7	68.8*		92*
Experiment Number 25	9–10	0.57	679	13.5	28.5	37.9	70
A. H.	10–11	0.57	747	13.2	32.0	42.7	79
8:30, breakfast. 12 noon,	11–12	0.63	800	12.6	40.2	50.4	93
lunch and 1000 cc. of	12–1	1.63	495	13.3	60.8	47.5	88
water. 1 p.m., 500 cc. of	1–2	10.83	87.3	13.6	77.5*		103*
water	2–3	9.07	88.8	13.1	61.5*		82*
Experiment Number 5	10–11	0.60	1074	15.6	41.3	53.3	99
W. N.							
7 a.m., breakfast and 15 grams urea in 75 cc. of water. Could not void on time							

TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_S = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_S = 54$, $C_m = 75$
		cc. per minute	*mg. per 100 cc.*	*mg. per 100 cc.*	*cc. blood per minute*	*cc. blood per minute*	*per cent*
Experiment Number 12	9–10	1.55	940	21.9	66.5	53.4	99
W. N.	10–11	1.13	864	32.5	30.2	28.3	52
7:15 a.m., 15 grams urea and 50 cc. of water. 8 a.m., breakfast and 100 cc. of water							
Experiment Number 26	10–11	7.07	142	14.1	70.2*		94*
W. N.	11–12	8.67	90	14.6	53.5*		71*
8 a.m. breakfast and 1000	12–1	3.73	272	15.8	64.3		86*
cc. of water. 10 a.m.,	1–2	12.50	85.3	15.0	70.8*		95*
500 cc. of water. 12 noon,	2–3	8.70	93	14.0	57.6*		77*
lunch and 1000 cc. of water							
Experiment Number 32	9–10	0.73	1010	16.0	46.4	53.9	100
W. N.	10–11	0.37	1070	15.4	25.5	42.3	78
8 a.m., breakfast. 12 noon,	11–12	0.77	974	14.7	50.8	58.2	108
lunch with 200 cc. of	12–1	1.12	936	15.0	69.7	66.0	122
water. 1:30 p.m., 250	1–2	2.80	390	14.9	73.2*		98*
cc. of water	2–3	1.70	601	14.5	70.5*		94*
Experiment Number 9	10–11	2.42	725	30.5	57.3	37.0	69
J. C. B.	11–12	2.03	834	29.6	57.5	43.8	81
7 a.m., 15 grams urea in 50	12–1	1.23	916	22.6	50.0	45.0	83
cc. of water. 8 a.m.,	1–2	3.10	516	22.0	72.6*		97*
breakfast. 1 p.m., lunch and 250 cc. of water. 1:45 p.m., 250 cc. of water							
Experiment Number 15	9–10	1.80	808	24.2	60.2	44.8	83
J. C. B.	10–11	1.27	746	24.9	38.0	33.8	63
7 a.m., breakfast. 7:30	11–12	1.75	775	24.6	55.3	41.8	78
a.m., 15 grams urea and	12–2	8.73	Lost	20.7			
50 cc. of water. 12:05	2–3	12.47	109	20.1	67.6*		90*
p.m., lunch and 1000 cc. of	3–4	3.75	302	17.3	65.3*		87*
water. 1:05 p.m., 500 cc. of water							

TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_S = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_S = 54$, $C_m = 75$
		cc. per minute	*mg. per 100 cc.*	*mg. per 100 cc.*	*cc. blood per minute*	*cc. per blood minute*	*per cent*
Experiment Number 28	9–10	0.97	781	19.4	38.8	39.6	73
J. C. B	10–11	1.00	731	19.2	38.1	38.1	71
7:30 a.m., breakfast. 12	11–12	1.25	656	18.9	43.3	38.8	72
noon, lunch	12–1	1.02	642	16.6	39.3	39.1	72
	1–2	0.80	746	17.2	34.7	38.8	72
Experiment Number 31	9–10	7.33	119.4	14.7	59.6*		79*
J. C. B.	10–11	7.58	103.3	12.5	62.6*		83*
7:30 a.m., breakfast and 500	11–12	8.75	83.4	12.3	59.3*		79*
cc. of water. 8:40, 10, 11	12–1	6.67	113.7	11.3	67.2*		90*
a.m., and 12 noon, 500	1–2	12.33	54.2	11.2	59.6*		79*
cc. of water each time. 12	2–3	11.67	52.2	10.5	58.0*		77*
noon, lunch. 1 p.m., 300							
cc. and 2 p.m., 200 cc. of							
water							
Experiment Number 33	10–11	0.80	765	13.7	44.6	49.8	92
D. V. S., 1927	11–12	1.33	640	11.6	73.6	63.6	118
8:30, breakfast. 12:45	12–1	1.07	619	12.7	52.0	50.3	93
p.m., lunch. No fluids.	1–2	0.73	775	11.2	50.7	59.2	110
Cutaneous blood	2–3	0.50	906	10.3	44.0	62.2	115
	3–4	0.70	806	9.4	60.0	71.7	133
	4–5	0.60	808	(9.4)	51.6	66.5	123
Experiment Number 34	9–10	6.41	153	13.1	74.8*		100*
D. V. S. 1927	10–11	16.25	58.6	12.3	77.4*		103*
8:30 a.m., breakfast with	11–12	13.25	86.0	12.3	92.6*		123*
800 cc. of water. 8:50	12–1	6.37	137	10.3	84.8*		113*
and 9:15 a.m. 200 cc.,	1–2	5.26	173	9.6 (1–2 and 2–3)	94.8*		126*
9:20 400 cc., 9:35 10 cc.,	2–3	1.32	438		60.2	52.4	97
and 10:40 200 cc., 10:45	3–4	2.77	281	(9.0)	86.4*		115*
400 cc. of water. 12:30							
p.m., lunch with 200 cc.							
of water. Venous blood							

TABLE 3

Standard blood clearances in 9 other subjects

Initials	Height	Weight	Body surface	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	Standard clearance $\frac{U\sqrt{V}}{B}$	Per cent of average normal clearance, taken as $C_S = 54$
	cm.	*kgm.*	*square meter*	*cc. per minute*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*cc. blood per minute*	*per cent*
F. C.	166.3	67.1	1.75	0.32	1,671	25.2	37.3	69
				0.55	872	12.7	51.0	95
				0.83	822	15.9	46.4	86
				0.93	642	9.4	65.8	122
				1.03	947	16.8	52.1	96
Average							50.5	93
E. V.	160	58.1	1.60	0.25	1,282	20.2	31.7	59
				0.73	1,114	22.1	43.1	80
				1.57	605	14.8	51.0	95
Average							42.0	78
C. A.	178	64.4	1.80	0.48	939	9.8	66.5	123
				0.53	1,253	14.0	65.4	121
				0.63	854	10.7	63.1	117
Average							65.0	121
G. S.	173.5	61.2	1.72	0.46	1,433	18.8	51.6	96
				0.60	1,208	12.9	72.6	134
Average							61.1	113
J. S.	168.9	61.2	1.70	0.48	1,104	16.0	48.0	89
				1.03	777	16.9	46.7	86
Average							47.4	88
H. C.	173.8	58.9	1.70	0.52	1,414	15.1	67.2	124
				0.79	1,078	17.8	53.8	100
Average							60.5	112
C. D.	175.2	72.1	1.87	0.62	973	12.6	60.6	112
				0.67	1,205	21.0	46.8	87
Average							53.7	99
J. P.	181	82.3	2.03	0.67	946	13.0	59.3	110
				0.70	1,132	13.5	69.5	129
Average							64.4	119
W. G.	177.7	61.7	1.78	0.29	1,432	16.3	47.5	88
				0.69	876	11.7	62.2	115
Average							54.9	102

TABLE 4

Summary of augmentation limit and standard clearance in normal adults

Subject	Body size: Weight	Body size: Height	Body size: Surface area	Augmentation limit Urine per minute	Standard clearance $C_S = \frac{U\sqrt{V}}{B}$ (from points below augmentation limit): Number of observations	Mean C_S of individual	Probable deviation of a determination from mean C_S of the individual		Mean C_S corrected for body area	Per cent of average normal clearance, taken as $C_S = 54$, $C_m = 75$
	kgm.	*cm.*	*square meters*	*cc.*		*cc. blood per minute*	*cc. blood per minute*	*per cent of mean C_S*	*cc. blood per minute*	*per cent*
Austin	66	179.5	1.83	2.40	14	49.8	±2.92	±5.86	48.6	90
Van Slyke (1921)*	72	174	1.86	(3.97)	14	(54.1)	±3.91	±7.23	(52.1)	96
Van Slyke (1927)	72	174	1.86	2.05	8	59.5	±5.08	±8.54	57.3	106
J. F. M.	60.3	164	1.65	2.35	7	47.2	±4.45	±9.42	48.3	89
L. L.	58.3	171	1.68	1.98	6	56.9	±6.12	±10.75	57.1	106
W. M.	72.2	182	1.43	1.67	7	50.8	±8.20	±16.15	48.2	89
J. C. B.	57.3	171	1.67	2.55	11	40.1	±2.34	±5.84	40.9	76
A. H.	52.7	159.5	1.53	1.98	7	46.6	±3.49	±7.49	49.5	92
Rehberg	80.0		1.95†	2.45	11	68.3	±5.11	±7.48	(64.3)†	119
McLean	70.0	175	1.85		14	62.4	±5.13	±9.20	(60.4)	112
F. C.	67.1	166	1.75		5	50.5	±6.75	±13.30	50.3	93
E. V.	58.1	160	1.68		3	42.0			42.6	79
C. A.	64.4	178	1.72		3	65.0			65.3	121
G. S.	61.2	173.5	1.72		2	61.1			61.4	114
J. S.	61.2	169	1.70		2	47.4			47.9	89
H. C.	58.9	174	1.70		2	60.5			61.1	113
C. D.	72.1	175	1.87		2	53.7			51.8	96
J. P.	82.3	181	2.03		2	64.4			59.4	110
W. G.	61.7	177.7	1.78		2	54.9			54.1	100
Mean	65.2					54.5	±4.9	±9.2	53.8	100
Maximum	82.3					68.3	±8.2	±13.3	65.3	121
Minimum	52.7					40.1	±2.3	±5.8	40.9	76
Probable deviation of an individual mean from the mean of the group						±5.7			±5.0	±9.2
Maximum observed deviation of an individual mean from mean of the group						+13.8 −14.4			+11.5 −12.9	+21.3 −23.9

* Excluded from average. See text.

† Calculated for an estimated height of 175 mm.

TABLE 5

Summary of data on maximum clearance in normal adults

Reference to source of data	Subject	Maximum clearance $C_m = \frac{UV}{B}$					
		Number of observations	Mean C_m of individual	Probable deviation of a determination from mean C_m of individual		Mean C_m corrected for surface area	Surface area
			cc. blood per minute	*cc. blood per minute*	*per cent of mean C_m*	*cc. blood per minute*	*square meters*
(6)	Austin	6	77.2	±3.89	±5.04	73.2	1.83
Present paper*	Van Slyke (1927)	6	85.1	±5.39	±8.48	79.2	1.86
	J. F. M.	5	72.5	±2.17	±2.99	76.2	1.65
	L. L.	6	76.6	±6.14	±8.02	79.1	1.68
	W. N.	7	65.7	±6.32	±9.62	59.1	1.93
	J. C. B.	9	63.6	±5.10	±7.76	66.1	1.67
	A. H.	5	65.5	±3.34	±5.26	74.0	1.53
Rehberg (15)	Rehberg	4	103.8	±9.92	±9.55	94.7	(1.90)
Mean of above data			76.3	±5.3*	±7.0	75.2	1.753
Maximum			103.8	±9.9	±9.6	94.7	1.93
Minimum			65.5	±2.2	±5.0	59.1	1.53
Probable deviation of an individual mean from mean of group			±9.0			±6.5	
Addis (2)	Dru.	33	93.0	±2.98	±3.20		
	Col.	4	74.4	±2.94	±3.95		
	Sci.	6	86.3	±4.97	±5.76		
	Add.	21	76.5	±3.66	±4.79		
	Jen.	4	83.4	±3.71	±4.45		
	Nor.	4	97.3	±5.44	±5.59		
	Ges.	4	68.2	±2.52	±3.70		
	Jac.	4	99.1	±3.44	±3.47		
	New.	7	64.4	±1.51	±2.34		
	Pis.	6	83.7	±7.02	±8.39		
	Kol.	7	96.5	±2.94	±3.05		
	Nye.	6	73.1	±4.65	±6.36		
	Nak.	4	76.3	±2.49	±3.26		
Mean of Addis data			82.3	±3.7	±4.5		
Maximum of Addis data			99.1	±7.0	±8.4		
Minimum of Addis data			64.4	±1.5	±2.3		
Probable deviation of an individual mean from mean of average			±7.7				

* For data from this laboratory (excluding Rehberg) mean probable deviation is ±4.6.

The results of these calculations are given in table 4.

In addition to the above experiments, in which the complete excretion curves were obtained over the maximum urine volume range, observations with ordinary urine volumes, below the augmentation limit, were made on 9 other normal subjects, and are reported, with the resulting standard clearance values, in table 3. The subjects were young men engaged in such activity as involves ordinary laboratory work.

The augmentation limit. It is seen from table 4, that the augmentation limit in the 8 normal subjects observed occurs at between 1.67 and 2.55 cc. per minute, if the observation made on Van Slyke in 1921 is excluded. The higher augmentation limit in this case, due to a very high average maximum clearance, falls statistically outside the group, since it differs by more than four times the mean error[3] from the average. There were only 4 determinations with high urine volumes in this case (data of Austin, Stillman, and Van Slyke) and they were made while the subject was about the laboratory, and not under the conditons of rest imposed on the subjects used for the analyses reported n this paper. Accordingly additional experiments on the same subject have been performed with the present series of observations, during which the subject was sitting quietly at his desk. The augmentation limit and clearances thus obtained fall within the limits of the rest of our observations. In the calculation of the average augmentation limit and maximum clearance, and the variation for the group of normal subjects, given in tables 3 and 4, only the present figures are used for this subject.

NORMAL VALUES AND VARIATIONS OF THE STANDARD AND MAXIMUM BLOOD UREA CLEARANCES

In table 4 are summarized the mean standard clearances of the normal subjects reported in detail in tables 2 and 3, and in addition the standard clearances calculated from previous data of Austin, Stillman and Van Slyke (1921). Similarly in table 5 are summarized

[3] The mean error calculated as the standard deviation, $\pm \sqrt{\frac{\Sigma - a^2}{n-1}}$, divided by the square root of the number of observations (fig. 9).

the maximum clearances of the same subjects, and in addition those on the 13 normal subjects reported by Addis (1922) with 4 or more observations on each.

For each subject, in tables 4 and 5, on whom 4 or more C_s or C_m values are available, the probable deviation of a given determination from the average in each subject, and of the mean value of each subject from the mean of all 9 subjects, have been calculated by the formula $0.675 \sqrt{\frac{\Sigma d^2}{n - 1}}$ where Σd^2 represents the sum of the squares of the deviations of individual determinations from the mean, and n represents the number of determinations. According to the theory of statistics, if the probable deviation is correctly determined half the results obtained are likely to show less deviation while half of them show greater deviations. Our number of determinations, n, is in fact too small in each individual to permit a really accurate estimate of the probable deviation of the standard or maximum clearance in his case; and likewise the number of subjects is too small to permit an accurate estimate of the probable individual deviation from the mean of the group. However, the data given, comprising 120 standard clearance determinations on 18 normal subjects and 158 maximum clearances on 20 normal subjects, appear sufficient, taken together, to yield an approximate idea of the degree of constancy to be expected in the standard and maximum clearance values in a normal individual, and of the range of these values in different normal subjects.

The "percentage probable deviation" values in tables 4 and 5 indicate that the variability among different determinations on a given subject is somewhat less for the maximum clearance than for the standard clearance. This is perhaps what could be expected, since with the smaller urine volumes, with which the standard clearance is determined, failure to empty the bladder completely must be of greater importance. We do not believe, however, that the data are sufficiently numerous to justify any comparative conclusions save that both clearances show variations of the same general order of magnitude.

The maximum clearance values calculated from Addis' 13 subjects average 82 cc. of blood cleared of urea per minute, while the values calculated from our 7 subjects and Rehberg average 75 cc. It appears possible that the difference may be due partly to greater body size in Addis' subjects. He employs 1.82 square meters as the mean surface area (private communication through MacKay), and if the subjects

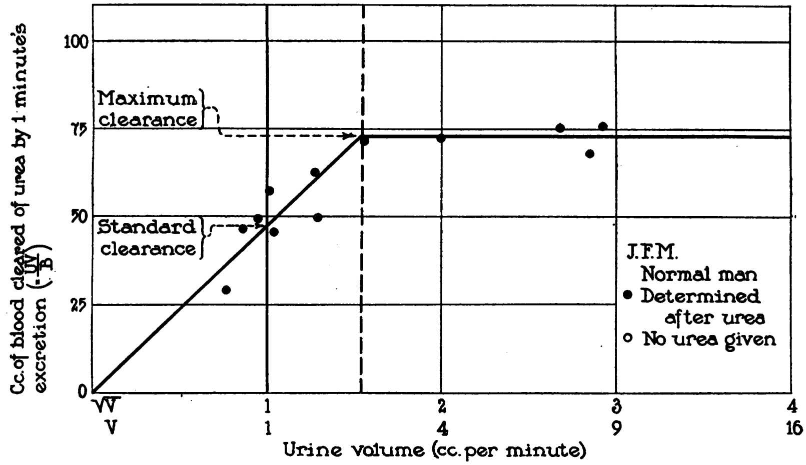

FIG. 3. UREA EXCRETION CURVE FROM NORMAL SUBJECT

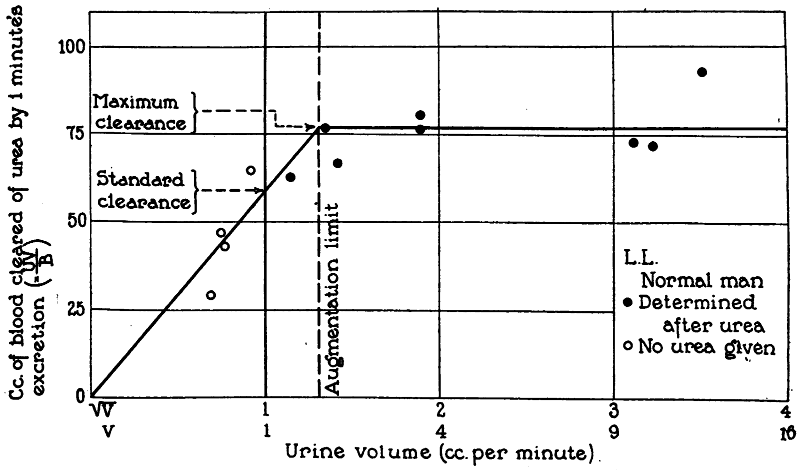

FIG. 4. UREA EXCRETION CURVE FROM NORMAL SUBJECT

he reports average as large as this, his mean C_s of 82 would correspond to one of 78 for subjects of 1.73 square meters area. As the exact heights and weights of Addis' subjects are not obtainable, we have used our own value, $C_m = 75$, as the normal mean, per 1.73 square meters body area (see following paper).

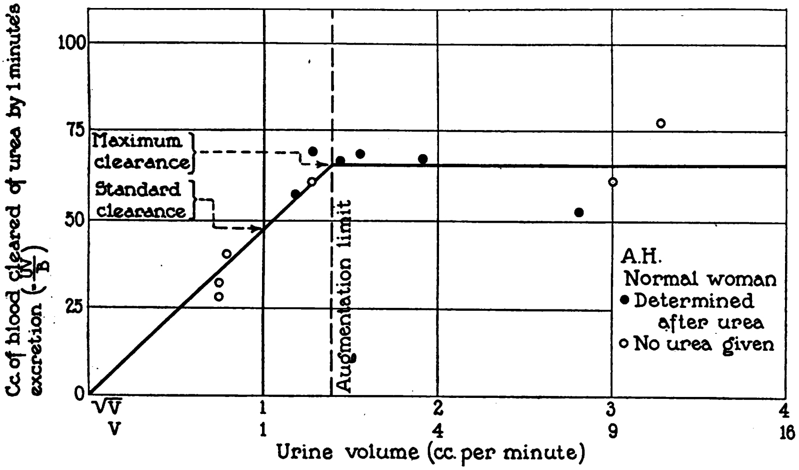

FIG. 5. UREA EXCRETION CURVE FROM NORMAL SUBJECT

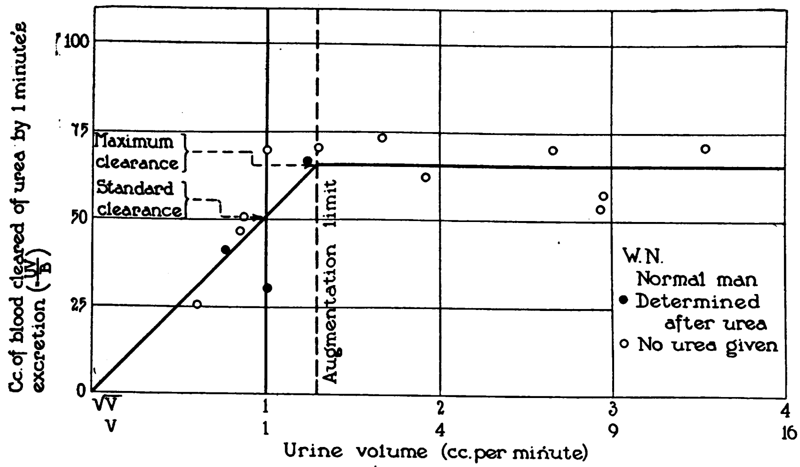

FIG. 6. UREA EXCRETION CURVE FROM NORMAL SUBJECT

The range of variation in the urea excretion curves of figures 3 to 9 covers the range of variation of the results observed in all the subjects in tables 2 and 3. The combined curves given in figures 10, 11, and 12 therefore cover the area which, in all probability, represents the extreme variation ordinarily to be expected in normal subjects.

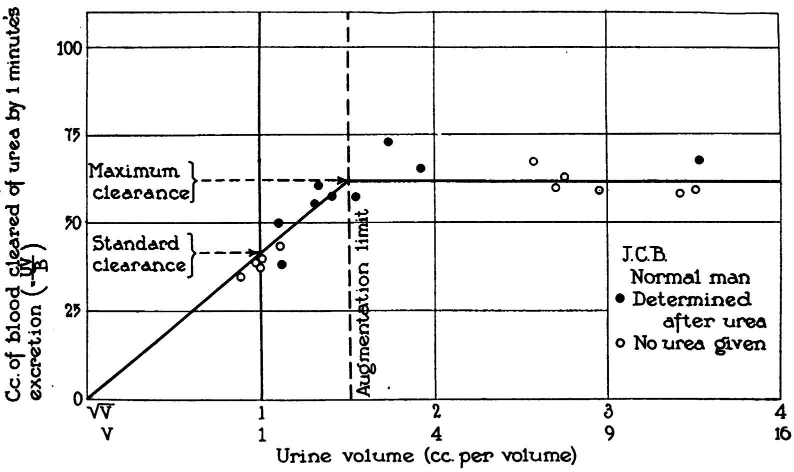

FIG. 7. UREA EXCRETION CURVE FROM NORMAL SUBJECT

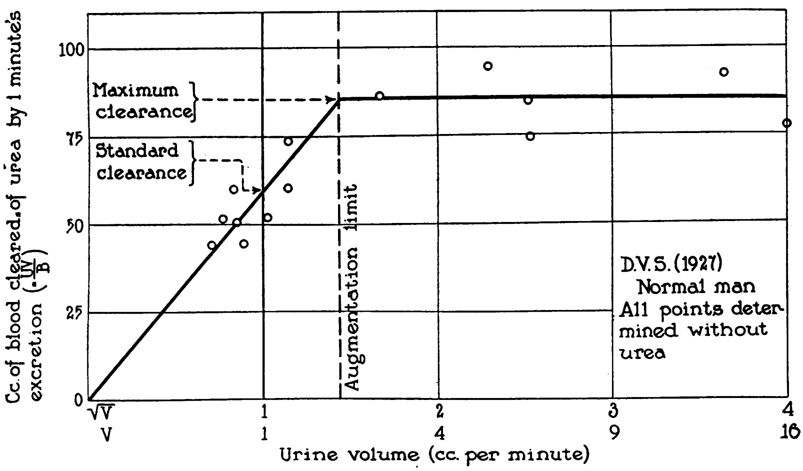

FIG. 8. UREA EXCRETION CURVE FROM NORMAL SUBJECT

The results of our experiments, plotted in figures 3 to 8, and those calculated from the data of Rehberg, plotted in figure 9, confirm the conclusions of Austin, Stillman, and Van Slyke. There is a distinct

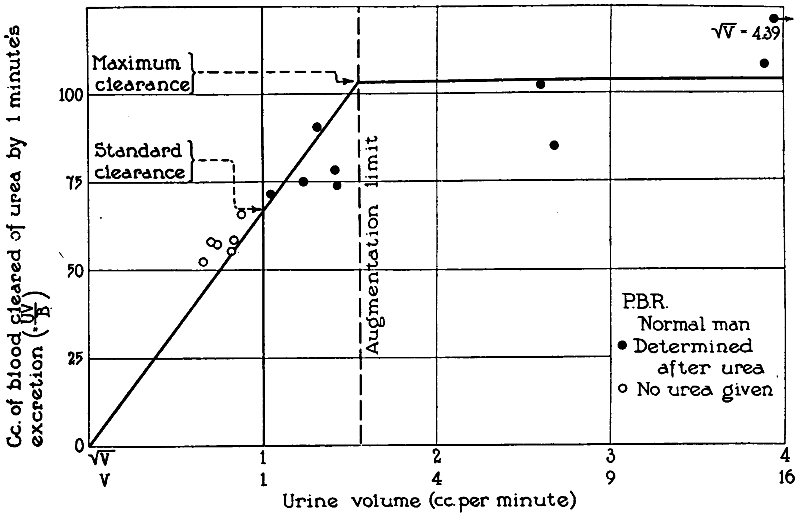

FIG. 9. UREA EXCRETION CURVE FROM NORMAL SUBJECT

Calculated from data given by Rehberg (Biochem. J., 1926, xx, 447)

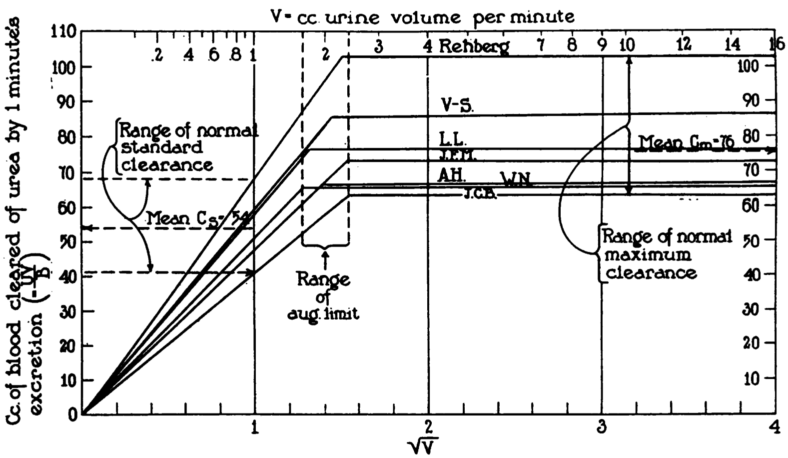

FIG. 10. RANGE OF UREA EXCRETION CURVES FOR NORMAL SUBJECTS

Only the curves shown in figures 3 to 9 are repeated, but the area enclosed by them covers also the other C_s and C_m values tabulated in tables 3 and 4. The data are uncorrected for variations in body size.

augmentation limit. Below it the clearance increases with increasing urine volume, while above it the clearance is independant of urine volume. The grouping of points about the slanting portion of the curve indicates that the square-root rule which this portion represents expresses the average effect of urine volume changes. No other line or curve could follow the experimental points more closely. The deviations of the points are frequently considerable, since other, unknown factors, besides urine volume influence the rate of urea excretion (Addis and Drury, 1923). It is obvious, however, that the

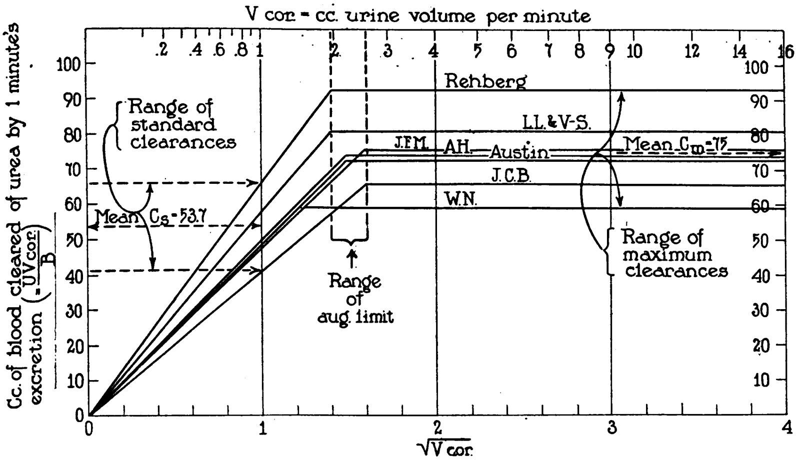

FIG. 11

Same curves as in Figure 10, but corrected for body size by multiplying V values by the correction factor $\frac{1.73}{\text{square meters surface area}}$.

square-root rule is followed with sufficient constancy to make interpretations of urea excretion rates with ordinary urine volumes (below the augmentation limit) much more exact when corrected for the volume effect than they would be if urine volume as a factor were neglected. In fact, the deviations of the experimental points from the slanting line representing this rule are not significantly greater than the deviations from the horizontal part of the curves covering ranges in which urine volume changes do not influence output. The square-root rule affords as satisfactory a correction for urine volume effect, or the hydration factor of the blood which controls this effect, below the augmentation limit as appears to be obtainable.

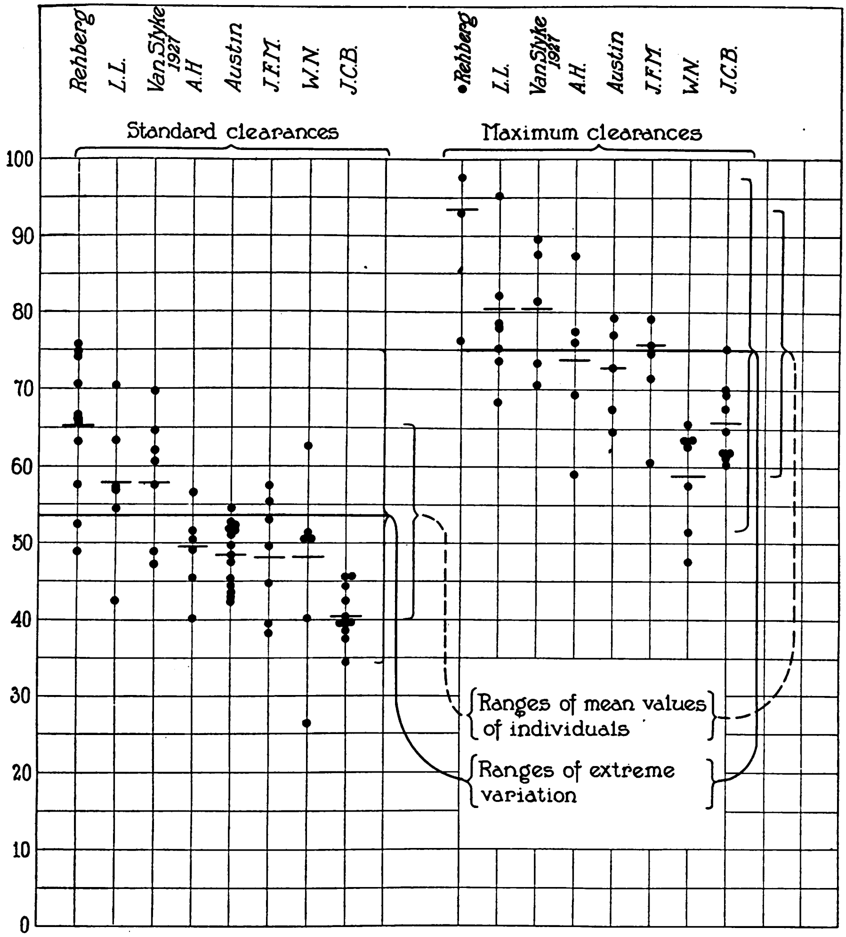

FIG. 12. VARIATIONS IN STANDARD AND MAXIMUM CLEARANCE VALUES IN NORMAL SUBJECTS

The points ● marked indicate the results of separate clearance determinations. The mean of the clearances for each subject is indicated by ——.

For the increase in urea excretion rate which accompanies increase in water excretion rate up to the augmentation limit two hypothetical explanations may be offered.

1. Increase in urine volume diminishes the amount of work the kidney has to do against osmotic pressure in compressing each gram of urea from the volume it occupies in the blood to the smaller volume it occupies in the urine. Less work is required to compress the urea of 100 cc. of blood into 2 cc. of urine than to compress it further into 1 cc. of urine. The kidneys, because they work more easily with increased urine volume, may work faster, and excrete more urea per minute. From this view point, the increase in urea excretion rate which accompanies accelerated water output is a direct cause of the latter. (For quantitative calculation according to the laws of thermodynamics of the mechanical work done by the kidney per gram molecule of substance excreted see pages 93 to 96 of Barcroft (1914)).

2. The other hypothesis is that increase of renal circulation, or stimulus of the secretory activity of the renal cells, may accelerate excretion of both urea and water. The accelerated water output in this case would not be the cause of the accelerated urea output. Both would be due to a common stimulus acting on the kidney. Even dilution of the blood by water drinking might be such a cause, either inducing larger proportions of renal capillaries to open up (*vide* Richards (1920–21)) or, making the secretory cells become more active.

For the purpose of estimating from urea excretion the work which the kidneys will do under standard conditions it is, however, a matter of indifference whether the acceleration of urea output that comes with increased urine volume is caused by the latter, or merely accompanies it as the result of a renal stimulus that affects both. Whether, in introducing $\sqrt{V}$ as a factor in the standard blood urea clearance calculation, we are dealing with the direct cause of fluctuations of clearance with urine volume, or are using urine volume as a fairly consistent indicator of such cause, does not greatly matter when we are concerned merely with measurement of renal ability.

SUMMARY

1. The relationship between urine volume and urea excretion has been studied in 6 more normal adults.

2. The observations of Austin, Stillman, and Van Slyke have been confirmed, that with urine volumes below a certain point (the augmentation limit) the urea output increases in direct proportion to the

square root of the urine volume, and that when the urine volume reaches this limit urea excretion attains its maximum, unaffected by further increase in urine volume.

3. The augmentation limit has been calculated for 8 normal subjects (our 6 and 2 others on whom the necessary data are found in the literature). It has been found to average 2.13 cc. of urine per minute, with a probable deviation of ±0.24 cc.

4. When the urine volume exceeded the augmentation limit, the urea excretion was found to equal the urea content of a volume of blood which was constant for an individual within a probable variation of ±6 per cent. This volume of blood, which a minute's excretion with urine volumes above the augmentation limit suffices to clear of urea, is termed the "*maximum clearance.*" Data from this and Addis' laboratory on 20 normal adults show mean maximum clearances ranging from 64 to 99 cc. of blood per minute. For the person of average adult size (surface area = 1.73 square meters) the mean maximum clearance is about 75 cc. of blood per minute.

5. When the urine output was below the augmentation limit the square root formula of Austin, Stillman, and Van Slyke was used to estimate the urea that would be excreted with a urine volume of 1 cc. per minute, which is approximately the average output of a normal adult under ordinary conditions. The volume of blood, which 1 cc. of urine exereted in 1 minute suffices to clear of urea, is termed the "*standard clearance,*" since it is estimated for a standard urine volume output. The standard clearance was found to be constant for an individual within a probable variation of ±10 per cent. In 18 different normal adults the mean standard clearance varied from 40 to 68 cc. of blood per minute. Estimated per 1.73 square meters of surface area, the range was 41 to 65 cc., with a mean of 54 cc.

6. Line charts (figures 1 and 2) are given for graphic estimation of the maximum and standard blood urea clearances, and for comparison of the results on a percentage basis with the mean normal values.

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