STUDIES OF UREA EXCRETION. III.

The Influence of Body Size on Urea Output

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(Received for publication August 21, 1928)

In the absence of data on subjects differing greatly in size, Austin, Stillman, and Van Slyke (1) adopted, as the simplest premise, the assumption that blood urea clearance, urine volume, and augmentation limit vary directly as the body weight.

However, Addis (8) has found that his "urea excretion ratio," which is the "maximum clearance," defined in our preceding paper (6), parallels more exactly the body surface area than it does the weight. Such a relation might be anticipated, if one considers that the rate of general metabolism, and hence probably the outputs of urea and water, parallel the body surface, and that Dreyer (3) has shown that the blood volume also parallels the surface area. The kidney weights, furthermore, were shown by Taylor, Drury, and Addis (8), to vary in rabbits in proportion to the body surface rather than to the total body weights. The clearance values observed in the animals examined before autopsy paralleled the kidney weights and skin areas. Hence these authors were led to correct their urea excretion ratios observed in patients by multiplying the observed ratios by the factor

$$\frac{\text{average normal surface area}}{\text{area of subject}}.$$

Our experience confirms that of Addis and his colleagues. More constant normal values are obtained if one substitutes A (= surface area) in place of W in the clearance formulae. We have found it convenient to use as a unit the surface area 1.73 square meters, which is the mean of the areas of men and women of 25, estimated from the adjusted medico-actuarial tables of Baldwin and Wood published by Fiske and Crawford (5).

When corrected for body size, the formulae for standard blood urea clearance C_s, and maximum blood urea clearance C_m, defined in the preceding paper (6), are accordingly written as

$$C_s = \frac{U}{B}\sqrt{V \times \frac{1.73}{A}} = \frac{U}{B}\sqrt{V_{\text{cor.}}}$$

$$C_m = \frac{U}{B} \times V \times \frac{1.73}{A} = \frac{U \times V_{\text{cor.}}}{B}$$

The corrected urine volume, $V_{\text{cor.}}$, is the observed volume of urine in cubic centimeter per minute multiplied by the factor $\frac{1.73}{A}$, A being the body area in square meters that is normal for the subject's height and age. The clearance formulae, written with $V_{\text{cor.}}$ in place of V, indicate the cubic centimeters of blood per *unit surface area* cleared of urea per minute, the unit of surface urea being 1.73 square meters. In the case of the C_s formula, with $V_{\text{cor.}}$, the value calculated indicates the cubic centimeters blood clearance per unit surface area when the per minute urine volume is 1 cc. per unit surface area. Blood clearance, urine volume, and hence augmentation limit are thus all based on surface area. (See derivation of original formula on page 102 of Austin, Stillman and Van Slyke (1)).

The *correction for body size* is applied as follows. The age and height of the subject having been ascertained, the value of the correction factor $\frac{1.73}{A}$ is read from the line chart in figure 1. The observed value of V, in cubic centimeters of urine per minute, is multiplied by this factor. The corrected V thus obtained is used in the standard clearance formula, $C_s = \frac{U\sqrt{V_{\text{cor.}}}}{B}$, or the maximum clearance formula, $C_m = \frac{UV_{\text{cor.}}}{B}$, for the calculations outlined in the preceding paper (6).

In the correction factor $\frac{1.73}{A}$, A represents in square meters the mean surface area of normal persons of the subject's height and age. Surface area is thus used as the nearest available parallel to the mass of functioning renal tissue (8) present in a normal subject. Because of the likelihood that the subjects examined will be obese, edematous, or

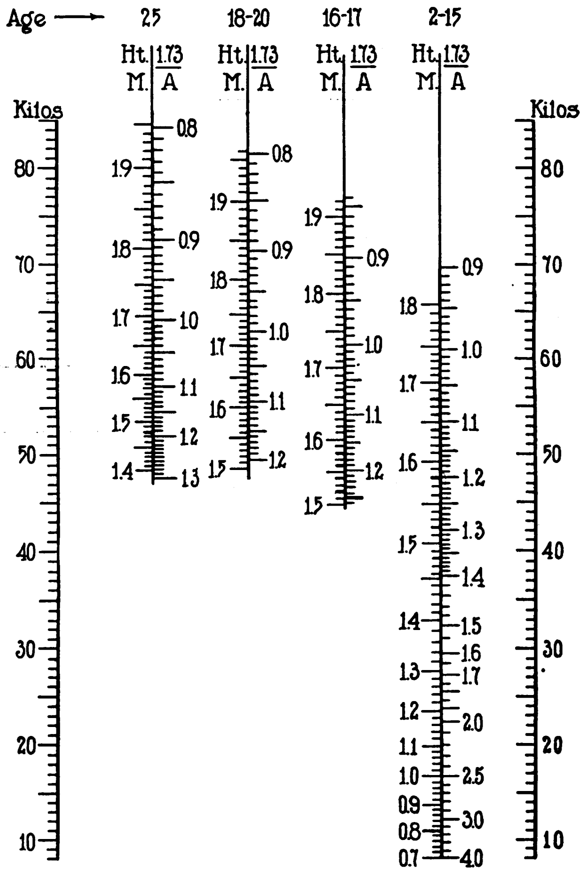

FIG. 1. CHART FOR ESTIMATING VALUES OF THE CORRECTION FACTORS, $\frac{1.73}{A}$, FROM HEIGHT AND AGE, AND FOR COMPARING OBSERVED WEIGHTS WITH WEIGHTS NORMAL FOR THE SUBJECTS EXAMINED

The value of $\frac{1.73}{A}$ is read off opposite the height of the subject in meters, on the scale for subjects of his age, or of 25 if he is mature. A horizontal line from the same point to the weight scale on either side cuts the latter at a point indicating the ideal weight of the subject.[1]

[1] The ideal weight is not used in calculation of the clearance corrections, but we have added the "ideal weight" scales to Fig. 1 because we have found them of convenience for comparison with the observed weights of edematous, obese, or emaciated patients.

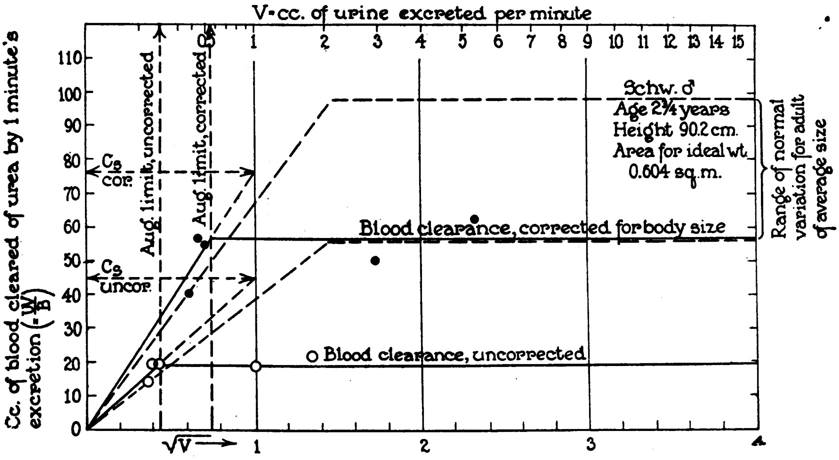

FIG. 2. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 13.6 KGM. IDEAL WEIGHT

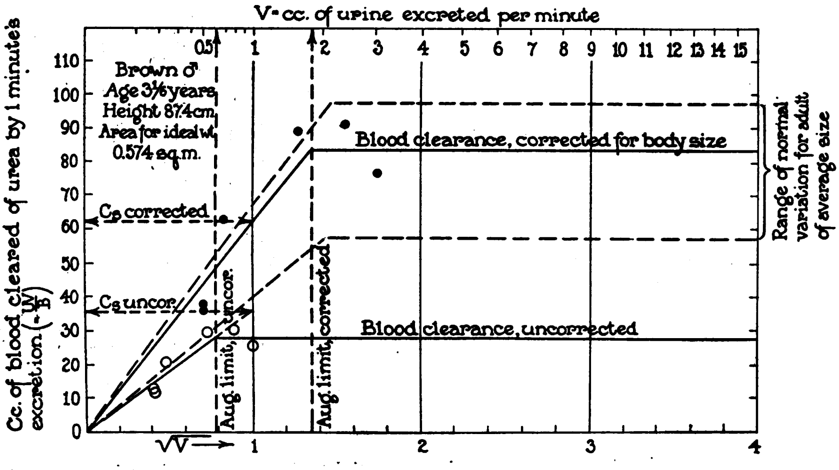

FIG. 3. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 12.6 KGM. IDEAL WEIGHT

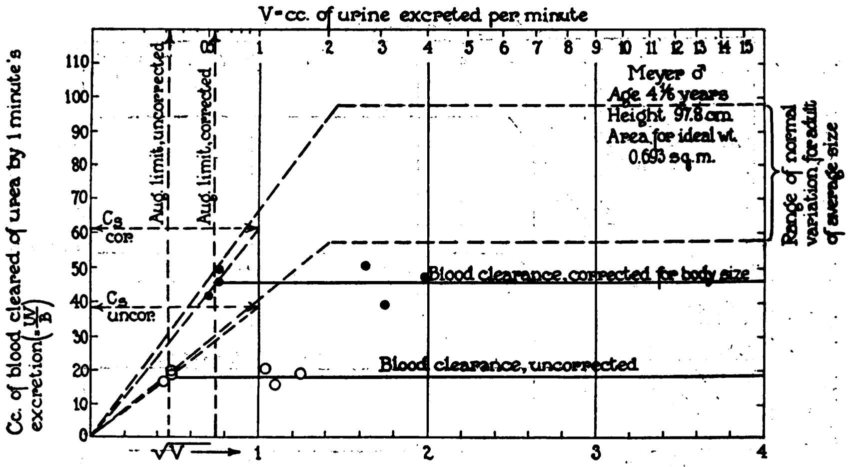

FIG. 4. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 15.4 KGM. IDEAL WEIGHT

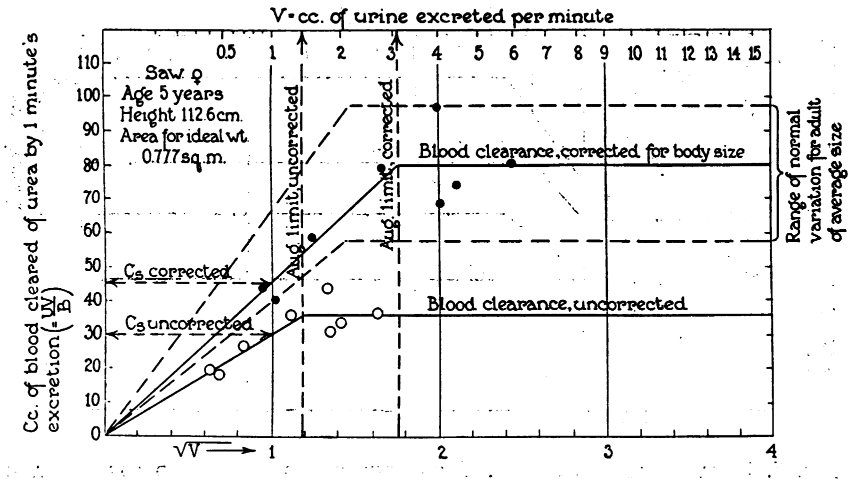

FIG. 5. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 19.3 KGM. IDEAL WEIGHT

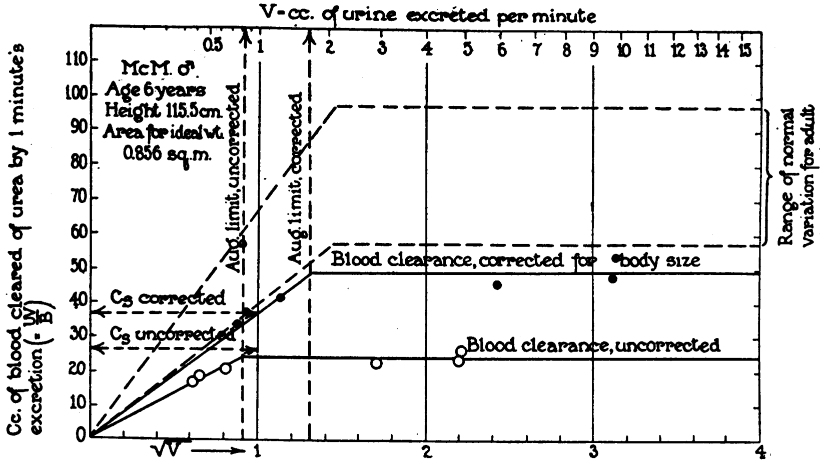

FIG. 6. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 21.1 KGM. IDEAL WEIGHT

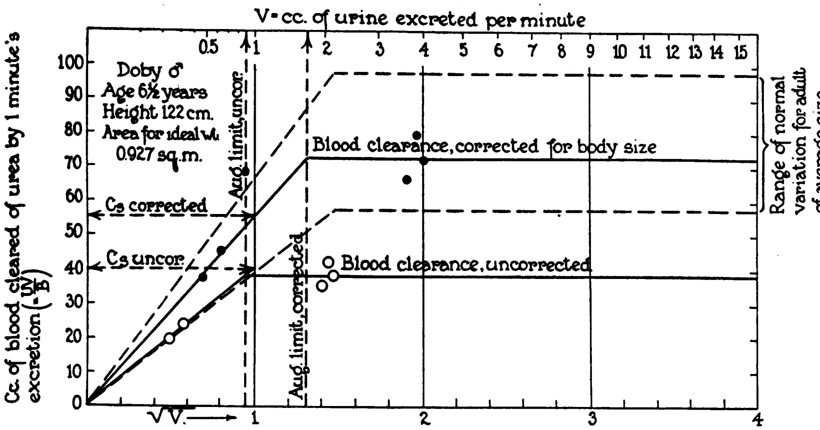

FIG. 7. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 23.8 KGM. IDEAL WEIGHT

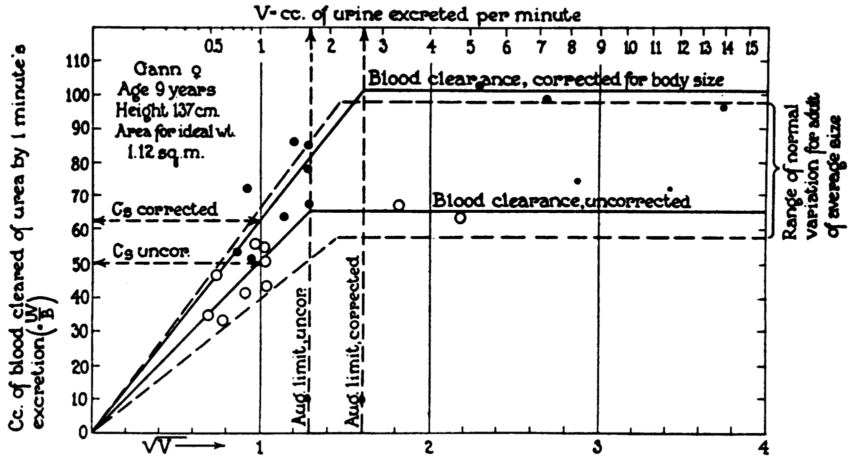

FIG. 8. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 31.8 KGM. IDEAL WEIGHT

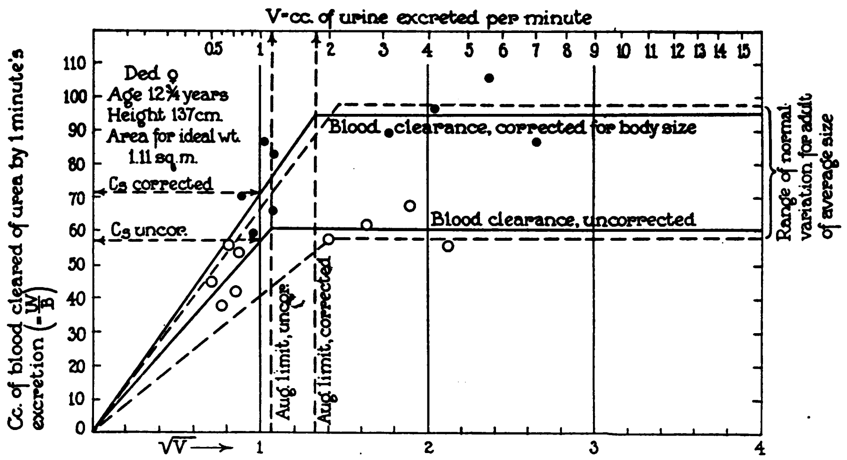

FIG. 9. UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 31.5 KGM. IDEAL WEIGHT

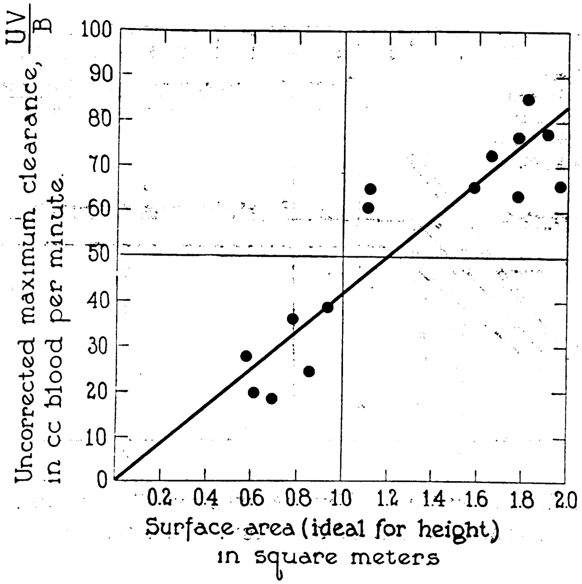

FIG. 10. RELATIONSHIP OF SURFACE AREA TO UNCORRECTED MAXIMUM CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

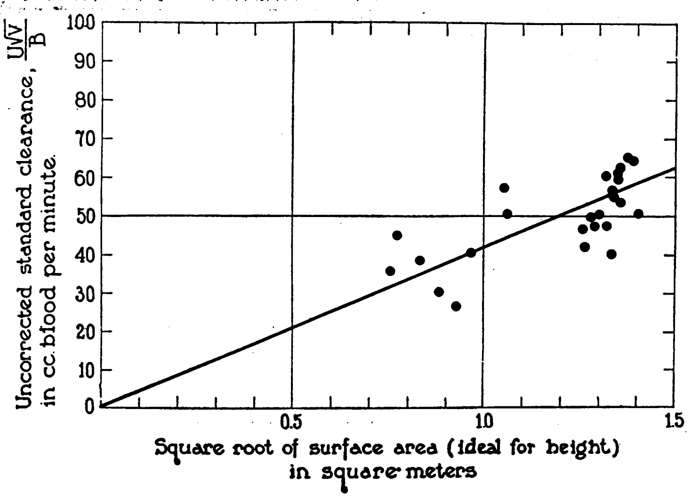

FIG. 11. RELATIONSHIP OF SURFACE AREA TO UNCORRECTED STANDARD CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

emaciated, it appears more exact, for correction of the clearance values, to use the body surface estimated from the weight which is ideal for a subject of that height and age, rather than the actual surface estimated from the height and the observed weight at the moment of observation. For adults over 25 years of age we use as A the surface area of the average normal person of 25 and the subject's height.

Figure 1 has been constructed as follows. From the tables of Baldwin and Wood (5) curves were constructed, with weight and height as the coördinates, for males and females of different ages from 5 to 25. From 5 to 15 the height-weight relationship could be expressed by a single curve, but the increasing weight-height ratio during adolescence necessitated 2 additional curves for the age interval 16–25. From the height-weight values of these curves, surface areas were calculated by Du Bois' (4) height-weight formula, and a second set of curves was constructed representing mean normal height-surface area relationships for the ages covered. From these two sets of curves the scales of figure 1 were constructed, down to those for the height 1.4 meter (age about 12 years). Below this body size we have employed the data of Benedict and Talbot (2) as given in their figures 7, 8, 10, and 13, which give height-weight and height-area relationships down nearly to birth. In constructing the scales of figure 1 we have used the means of the height-weight and height-area relationships of males and females. The sexes differ too little to justify, for our purpose, separate scales for each.

The standard clearance is affected by a given deviation from ordinary body size only in proportion to the deviation of $\frac{\sqrt{1.73}}{A}$ from unity, since the V value by which the factor is multiplied is under the square root sign in the formula $C_s = \frac{U}{B}\sqrt{V}$. Hence a variation of ± 10 per cent in surface area affects the C_s by only approximately ± 5 per cent. Such a variation corresponds to a height range in adults between 157 and 181 cm., or 62 and 71 inches. In determining the standard clearance for clinical diagnosis a factor of less than 5 per cent can be neglected; and the correction factor need be applied only to patients outside the above limits of body size.

TABLE 1

Data concerning urea excretion

Subject	U Urine urea nitrogen	B Blood urea nitrogen	V Urine volume	$V \times \frac{1.73}{\text{Area}}$ Urine volume corrected for body size	Uncorrected clearances: $\frac{UV}{B}$ Observed clearance*	Uncorrected clearances: $\frac{U\sqrt{V}}{B}$ Standard clearance calculated for $V = 1$ from observations below augmentation limit	Clearances corrected for body size: $\frac{U\left(V \times \frac{1.73}{A}\right)}{B}$ Observed clearance*	Clearances corrected for body size: $\frac{U\sqrt{V \times \frac{1.73}{A}}}{B}$ Standard clearance calculated for $V \times \frac{1.73}{A} = 1$ from observations below augmentation limit
	mgm. per 100 cc.	*mgm. per 100 cc.*	*cc. per minute*	*cc. per minute*	*cc. blood per minute*	*cc. blood per minute*	*cc. blood per minute*	*cc. blood per minute*
Schw. ♂	1,121	(10.5)	0.132	0.370	14.1	38.8	39.5	64.9
2 $\frac{9}{12}$ years.	1,346	10.5	0.154	0.431	19.8	50.4	55.3	84.2
15.9 kgm.	1,147	10.5	0.176	0.493	19.2	45.8	53.8	76.5
90.2 cm. height	260	15.1	1.03	0.287	17.7*		49.4*	
0.620 sq. m. surface area ideal for height.	175	(15.0)	1.88	0.529	21.9*		61.7*	
$\frac{1.73}{\text{Area}} = 2.80$	Average clearance.				19.8*	45.0	55.5*	75.2
Brown. ♂	832	11.0	0.167	0.486	12.6	30.9	36.7	52.6
3 $\frac{2}{12}$ years.	756	(10.6)	0.167	0.486	11.9	29.2	34.7	49.7
14.6 kgm.	912	10.2	0.233	0.677	20.8	43.2	60.6	73.5
87.4 cm. height.	527	9.5	0.534	1.55	29.5	40.4	86.0	69.0
0.595 sq. m. surface area ideal for height	337	8.9	0.793	2.4	30.2*		90.8*	
	235	(9.20)	1.000	2.91	25.5*		74.4*	
$\frac{1.73}{\text{Area}} = 2.91$	Average clearance.				27.9*	35.9	82.6*	61.2

Meyer. ♂	1,067	12.7	0.197	0.498	16.6	37.3	41.8	59.1
$4\frac{2}{12}$ years.	1,088	13.1	0.233	0.59	19.7	40.7	49.0	63.7
17.9 kgm.	1,033	13.1	0.233	0.59	18.4	38.1	46.5	60.5
97.8 cm. height.	286	15.2	1.08	2.73	20.3*		51.4*	
0.675 sq. m. surface area	194	15.1	1.22	3.09	15.7*		39.7*	
ideal for height	184	(15.2)	1.57	3.97	19.0*		48.1*	
$\frac{1.73}{\text{Area}} = 2.53$	Average clearance......................				18.3*	38.7	46.4*	61.1
Saw. ♀	562	11.4	0.400	0.848	19.7	31.2	41.8	45.4
5 years.	433	11.3	0.472	1.00	18.1	26.3	38.3	38.3
24.8 kgm.	406	10.7	0.693	1.47	26.3	31.6	55.8	46.0
112.6 cm. height.	294	(10.2)	1.23	2.61	35.5	31.9	78.2	48.4
0.815 sq. m. surface area	262	10.7	1.78	3.77	43.5*		92.3*	
ideal for height	169	10.0	1.82	3.86	30.8*		65.2*	
$\frac{1.73}{\text{Area}} = 2.12$	171	(10.3)	2.00	4.24	33.3*		70.4*	
	152	11.2	2.67	5.66	36.2*		76.8*	
	Average clearance......................				36.0*	30.3	76.2*	44.5
McM. ♂	636	14.5	0.383	0.781	16.8	27.2	34.3	38.8
6 years.	612	14.3	0.433	0.883	18.5	28.2	37.8	40.5
17.5 kgm.	452	14.4	0.650	1.327	20.4	25.3	41.6	36.1
115.5 cm. height.	124	16.0	2.92	5.96	22.6*		46.2*	
0.850 sq. m. surface area	83.9	17.2	4.83	9.86	23.6*		47.8*	
ideal for height	88.7	16.3	4.88	9.96	26.5*		54.2*	
$\frac{1.73}{\text{Area}} = 2.04$	Average clearance......................				24.2*	26.9	49.4*	38.5

TABLE 1—*Continued*

Subject	U Urine urea nitrogen	B Blood urea nitrogen	V Urine volume	$V \times \frac{1.73}{\text{Area}}$ Urine volume corrected for body size	Uncorrected clearances: $\frac{UV}{B}$ Observed clearance*	Uncorrected clearances: $\frac{U\sqrt{V}}{B}$ Standard clearance calculated for $V = 1$ from observations below augmentation limit	Clearances corrected for body size: $\frac{U\left(V \times \frac{1.73}{A}\right)}{B}$ Observed clearance*	Clearances corrected for body size: $\frac{U\sqrt{V \times \frac{1.73}{A}}}{B}$ Standard clearance calculated for $V \times \frac{1.73}{A} = 1$ from observations below augmentation limit
	mgm. per 100 cc.	*mgm. per 100 cc.*	*cc. per minute*	*cc. per minute*	*cc. blood per minute*	*cc. blood per minute*	*cc. blood per minute*	*cc. blood per minute*
Doty. ♂	1,435	18.0	0.250	0.467	19.9	39.9	37.2	54.5
6 $\frac{6}{12}$ years.	1,270	17.9	0.343	0.640	24.3	41.6	45.4	56.8
21.3 kgm.	307	17.0	1.97	3.68	35.6*		66.5*	
122.0 cm. height.	281	13.8	2.08	3.88	42.4*		79.2*	
0.927 sq. m. surface area ideal for height	303	17.0	2.17	4.05	38.7*		72.3*	
$\frac{1.73}{\text{Area}} = 1.87$	Average clearance......................				38.9*	40.8	72.7*	55.7
Gann. ♀	937	(13.2)	0.486	0.751	34.5	49.5	53.3	61.6
9 years.	1,115	13.2	0.548	0.846	46.3	62.6	71.5	77.8
26.8 kgm.	653	11.7	0.594	0.918	33.2	43.0	51.3	53.5
137 cm. height.	466	9.4	0.833	1.29	41.3	45.2	63.8	56.2
1.12 sq. m. surface area ideal for height	488	8.2	0.933	1.44	55.5	57.5	85.8	71.5
$\frac{1.73}{\text{Area}} = 1.55$	453	8.8	1.07	1.65	54.9	53.2	84.8	66.2
	435	9.2	1.07	1.65	50.4	48.9	77.8	60.8
	479	11.9	1.08	1.67	43.6	41.8	67.4	52.0
	273	14.0	3.40	5.25	66.3*		102.5*	
	197	14.5	4.69	7.24	63.8*		98.6*	
	Average clearance......................				65.1*	50.2	100.6*	62.5

Ded. ♀	1,013	11.3	0.500	0.775	44.9	63.4	69.6	79.0
12 $\frac{9}{12}$ years.	739	11.4	0.583	0.904	37.8	49.5	58.6	61.5
32.5 kgm.	866	10.4	0.667	1.034	55.6	62.1	86.0	83.4
137 cm. height.	556	9.7	0.733	1.136	42.0	49.1	65.2	61.1
1.12 sq. m. surface area	760	10.7	0.750	1.163	53.2	61.5	82.6	76.5
ideal for height	274	9.6	2.00	3.10	57.2*		88.5*	
$\frac{1.73}{\text{Area}} = 1.55$	248	10.7	2.67	3.98	62.0*		92.3*	
	189	(10.0)	3.58	5.55	67.7*		105.0*	
	122	9.9	4.50	6.97	55.8*		85.9*	
	Average clearance				60.7*	57.1	92.9*	72.3

* Figures marked * represent maximum clearance values, observed when V was above the augmentation limit for the subject.

In estimating the maximum blood urea clearance, however, by the formula $C_m = \frac{UV}{B}$, a 10 per cent correction to V causes a 10 per cent correction to the C_m value calculated. Hence, to avoid an error greater than ±5 per cent, we can neglect body size in estimating the maximum clearance only in adults between 164 and 176 cm., or 65 and 69 inches, in height.

EXPERIMENTAL

In order to measure satisfactorily the influence of body size on urea excretion rate it is necessary to compare children with adults. With ordinary adults variation in size, as a factor in influencing the volume of blood, the urea content of which is excreted per minute, is less important than other, unknown factors, which may be summarized as "individual constitution." These may cause the standard or maximum clearance of an individual, of average size and normal to all appearances, to vary by as much as 25 per cent from the mean normal clearance. The effect of body size is so obscured by the greater effects of individual constitution that the size effect in adults can be measured only by statistical methods. In order to make it an outstanding factor it is necessary to study subjects with a greater size range than can be obtained in the adults usually available for observation.

We have accordingly, by the technique described in the preceding paper (6), determined the urea excretion curves on a number of children. The numerical data are given in table 1, and the curves in figures 2 to 9. The correction for body size is made, as previously described, by multiplying the observed V value by the factor $\frac{1.73}{A}$.

DISCUSSION OF RESULTS

It is obvious from figures 2, 3, 4, 5, 6, 7, 8, and 9, that correcting the blood urea clearances, by multiplying the observed values of V in cc. urine excreted per minute by the factor $\frac{\text{average adult surface area}}{\text{surface area of subject}} = \frac{1.73}{A}$, causes data from children, at least down to 3 years of age, to fall within the same range as the data of adults in respect to maximum blood urea clearance and standard blood urea clearance. This manner of correcting for body size therefore makes it possible to put on a common basis for comparison, with regard to urea excreting ability, subjects of the widest range of body size that is likely to be encountered in this type of examination.

The figures for the augmentation limit, corrected for body size, show an average of 1.7 cc. per minute. This is somewhat lower than the corresponding figure for normal adults (2.1 cc.), but within the limit of variation for adults. The augmentation limit values, show a greater inidvidual variation for children than for adults. This may be due to the fact, that, with the small urine volumes often found in determinations of the standard clearance in children, failure to empty the bladder completely, and consequent errors in measuring the urine volume, become of increased importance. For routine determinations of the urea excreting function in small children it may therefore prove advantageous when possible to give sufficient fluids to cause free diuresis, and determine the maximum instead of the standard clearance.

In a recent paper (7) Rabinowitch and Breitman have given for a number of children data from which the standard clearance (corrected for surface area calculated from the observed weight) can be calculated. The experimental procedure of these authors is such that their results can not be very accurately compared with ours. First, they give a large amount of urea just before the test, which causes the blood urea to vary irregularly. Second, they use as the blood urea value the mean of the two figures obtained one hour before, and shortly after the 1-hour period from which the urine urea is determined. Third, they determine the urea output during only a single 1-hour period on each child. However, if their data are recalculated in such a way that the second blood urea value only is used, and the results are plotted into our figure 11, the axis of their group falls near to that for our 25 individuals. That the dispersion for their results is greater than for ours is probably due to the factors mentioned above.

It does not seem necessary to present comparative calculations to show that the area correction is more exact than the weight correction. Such calculations may readily be made from the data in table 1. They show that the weight formulae, $\frac{U}{B}\sqrt{\frac{V}{W}}$ and $\frac{UV}{BW}$ yield in the children values for the standard and maximum clearance respectively which are quite above the range for adults: urea excretion rates in small subjects do not decrease so rapidly as body weights. They decrease rather as the surface area, or the 2/3 power of the weight.

The degree of exactness with which the maximum clearance, $\frac{UV}{B}$, varies in proportion to surface area in different subjects is indicated by figure 10 in which we have plotted against surface area the mean maximum clearance for each of the 7 adults reported from this laboratory in the preceding paper (6), and each of the children reported in the present paper. In figure 11 the uncorrected standard clearance, $\frac{U\sqrt{V}}{B}$, is similarly plotted against the square root of surface area for each of the 17 adults reported in the preceding paper, and each of the children in the present one.

SUMMARY

The calculated maximum and standard blood urea clearances, previously defined (6), may be corrected for variations in body size by means of a factor based on the assumption, introduced by Addis (8), that excretion varies directly as surface area. Thus corrected, data from small children yield the same normal values as adults for the maximum and standard clearances, and also for the augmentation limit of urine volume, at which maximum excretory efficiency is attained.

The nature of the standard clearance formula is such that correction for body size in persons between 62 and 71 inches in height does not exceed 5 per cent, and in tests of renal function may be neglected.

For the maximum clearance the range of height with less than 5 per cent correction is 65 to 69 inches.

BIBLIOGRAPHY

1. Austin, J. H., Stillman, E., and Van Slyke, D. D., J. Biol. Chem., 1921, xlvi, 91. Factors Governing the Excretion Rate of Urea.
2. Benedict, F. G., and Talbot, F. B., Publications of Carnegie Institute of Washington, 1921, No. 302. Metabolism and Growth from Birth to Puberty.
3. Dreyer, G., Ray, W., and Walker, E. W. A., Skand. Arch., 1913, xxviii, 299. The Blood Volume of Warm Blooded Animals; Together with an Inquiry into the Value of Some Results Obtained by the Carbon Monoxide Method in Health and Disease.

4. Du Bois, D., and Du Bois, E. F., Arch. Int. Med., 1916, xvii, 863. Clinical Colorimetry. X. A Formula to Estimate the Approximate Surface Area if Height and Weight be Known.
5. Fisk, E. L., and Crawford, J. R.: How to Make the Periodic Health Examination. New York, 1927, page 345.
6. Möller, E., McIntosh, J. F., and Van Slyke, D. D., J. Clin. Invest., 1928, vi, 485. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults.
7. Rabinowitch, I. M., and Breitman, R., Am. J. Dis. Child., 1927, xxxiv, 1000. The Estimation of Renal Efficiency of Children.
8. Taylor, F. B., Drury, D. R., and Addis, T., Am. J. Physiol., 1923, lxv, 55. The Regulation of Renal Activity. VIII. The Relation Between the Rate of Urea Excretion and the Size of the Kidneys.