THE RATE OF EXCRETION OF URINE IN SUBJECTS WITH DIFFERENT AMOUNTS OF RENAL TISSUE

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THE RATE OF EXCRETION OF URINE IN SUBJECTS WITH DIFFERENT AMOUNTS OF RENAL TISSUE[1]

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In the vast literature on renal function, there is to be found only one method proposed as an indirect means of measuring the mass of functioning kidney tissue, namely, the Addis Ratio (1) $\left(\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 cc. of blood}},\right.$ under certain special conditions of diuresis and high blood urea concentration). That this method is an accurate index of functioning renal tissue has been shown by several considerations, summarized by MacKay (2). In each of three species (rat, rabbit, and dog) the value of the Ratio bears a direct linear relationship to the actual weight of the kidneys. In man, a similar relationship has been demonstrated between the Ratio and body surface, while body surface and kidney weight are in turn in straight-line association.

The purpose of this paper is to study in man the relation between the amount of functioning renal tissue (as measured by the Ratio) and the volume of urine per unit of time under conditions designed to induce "minimum" and "maximum" rates of excretion.[2] MacKay and MacKay (3) have already demonstrated the relation between the blood urea concentration and the amount of functioning renal tissue (similarly measured).

LITERATURE

Under stringent conditions of (*a*) urea and water administration and (*b*) withdrawal of dietary fluids, Addis (4) found in man a relationship between the amount of kidney tissue and the rates of urine excretion. He suggested that the disturbing influence of extra-renal factors on the excretion rates might be diminished by using a "volume quotient" (the quotient obtained by dividing the "maximum" volume per hour by the "minimum" volume per hour) with which to predict kidney mass.

Experimentally, the amount of renal tissue has been altered by subtotal nephrectomy, ligation of renal artery branches, and ligation of

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[2] It must be emphasized that no true "minimum" or "maximum" rate of urine excretion is attained. These terms are used throughout this paper for brevity, and signify that the conditions are such as to induce a slow or rapid rate.

kidney poles. Bradford (5) found in dogs a "considerable and practically permanent increase in the amount of urine passed" after about two-thirds of the total kidney mass had been excised; after the excision of three-fourths of the kidney mass, the polyuria was more marked. Mark (6), also in dogs, found that there was a reduction in the "maximum" rate of urine excretion when only small amounts of kidney remained, while the "minimum" rate of excretion increased. Chanutin and Ferris (7) observed the rate of urine excretion when water intake was restricted in rats after kidney pole ligation. Table 1 shows the mean values derived from their protocols.

TABLE 1

"Minimum" rate of urine excretion in rats from which portions of the kidneys had been removed by pole ligation. (After Chanutin and Ferris (7).)

Kidney weight per cent of normal	"Concentration test"	
	Cc. per 24 hours	Specific gravity
100.0	2.4	1.058
75.6	10.8	1.024
66.6	15.0	1.017
31.2	15.6	1.014

As yet, no data have appeared showing in statistical terms how the rate of urine excretion is related to the mass of kidney tissue. Obviously, it would be very useful clinically if one could predict renal mass merely by measuring the volume of urine excreted in a given time. It was to determine whether this could be done that the present study was undertaken.

METHODS

Five hundred and twenty-four sets of observations, collected in this laboratory during the past 10 years, were analysed by standard statistical methods (8, 9). In each set the data included the (*a*) Addis Ratio as per cent of normal, (*b*) maximum rate of urine excretion as induced by water and urea administration, and (*c*) minimum rate of urine excretion as induced by withdrawing liquids from the diet.

Subjects. The subjects were, for the most part, ambulatory patients with Bright's disease of varying type, severity, and duration. (Some were normal as judged by the Ratio, urinary sediment, and absence of proteinuria.) Age varied from 9 to 63 years. Body surface varied from 0.83 to 2.50 square meters, with a mean of 1.72 sq. m. The majority were males. Many subjects were studied more than once.

Diet. The diet varied with the type of the disease being treated. Most subjects were taking a diet low in salt and adequate in protein and calories.

Edema. A few subjects were seen when edematous and again in edema-free periods. All observations were included in the analysis.

Conditions. Each subject received a copy of the following printed directions:

DIRECTIONS

1. After breakfast take no fluids of any sort until next morning.

This means no coffee, tea, soup, milk, etc., as well as no water.

2. At 9:00 P.M. that evening void urine and throw it away.

Do not void for some hours before 9:00 P.M. so that you may have no difficulty in emptying the bladder completely.

After 9:00 P.M. if possible do not void urine again until next morning, but if it is necessary pass the urine directly into the special bottle which is provided.

3. At 6:00 A.M. next morning pass urine directly into the special bottle.

4. At 6:02 A.M., i.e. immediately after collecting the night urine in the special bottle, drink a large glass of water in which the urea in the box has been dissolved. Then during the next half hour slowly drink three other large glasses of water. The water may be taken hot if desired.

5. At 7 A.M. void and throw away urine. Drink two glasses of water slowly.

6. At 8 A.M. void and throw away urine. Drink two glasses of water slowly.

7. At 8:50 A.M. be in the laboratory.

8. Take no breakfast.

After the subject came to the laboratory, his urine was collected and measured for three consecutive hours and blood specimens were withdrawn at the middle of each collection period. The rate of urea excretion (mgm. in one hour's urine) and the concentration of urea in the blood (mgm. in 100 cc.) were determined; from this data the Ratio was calculated and expressed as per cent of normal for the subject's body surface (1).

Minimum volume. The volume of urine excreted during the restriction of dietary fluids was divided by the elapsed time to obtain the rate of excretion as cubic centimeters per hour. This rate was adjusted to the mean body surface of the group (1.72 sq. m.) before statistical analysis.

Specific gravity of the "concentration test." The specific gravity of the urine obtained during restriction of fluids was measured by a hydrometer at room temperature. No correction was made for proteinuria.

Maximum volume. The maximum rate of excretion of urine in any one of the three hour-periods during the execution of the Ratio was selected and expressed as cubic centimeters per hour. Before statistical analysis, this rate was corrected to a body surface of 1.72 sq. m. The specific gravity of this urine was not recorded.

Volume quotient. This variable $\frac{\text{maximum volume}}{\text{minimum volume}}$ was calculated in each of the 524 sets of observations; there was no need to correct it for surface area.

Statistical terms. A few terms should be explained briefly for those not familiar with statistical methods (8, 9).

a. *Correlation coefficient* (r) is a measure of the correlation of two variables when the means of the arrays fall upon a straight line, within the errors of sampling. (An array is a row or a column of a correlation table.)

b. *Correlation ratio* (η) is a measure of the correlation of two variables without regard to the linearity of the means of the arrays. The value of η given here is corrected in each case to allow for the influence of the number of the arrays (18). When $\zeta/P.E._\zeta$ is greater than 3, η is significantly greater than r, and may be used in place of r. ($\zeta = \eta^2 - r^2$.)

c. *Standard deviation* (σ) is a measure of dispersion or variation.

d. *Regression lines* are lines formed by plotting the means of the arrays. In this study curves have been fitted to them, when possible, by the method of least-squares. In every correlation of two variables, there are two regression lines (one the means of the rows, the other the means of the columns): when they are at right angles, correlation is nil; when they coincide, correlation is unity. It is important to bear in mind that the regression of x on y allows x to be predicted when y is known; the regression of y on x allows y to be predicted when x is known.

RESULTS

The results of the statistical analyses are presented in Table 2, Correlation Tables 3–6, Regression Tables 7–10, and in Figures 1–5.

DISCUSSION

General considerations. The regressions were curvilinear ($\zeta/P.E._\zeta > 3$) in the correlations of the Ratio with minimum volume, specific gravity of the concentration test, and volume quotient. The only linear regression ($\zeta/P.E._\zeta < 3$) was found in the case of the maximum volume, which also showed the highest correlation with the Ratio.

On theoretical grounds one expects that, of two tests of function having the same correlation ratios (η) with the mass of functioning kidney tissue, the test which has the more linear regression with renal weight would be the better test clinically. Thus, the correlation ratio (η) of blood urea concentration with the Addis Ratio is $-$ 0.90 ($\zeta/P.E._\zeta = 4.3$), but a study of the scatter diagram drawn by the MacKays (3), from which η was calculated, shows that the mass of kidney tissue may decrease to as little as 50 per cent of normal before the blood urea changes appreciably in concentration. Despite the high correlation ratio, the fact that the curve of the plotted observations is far from linear signifies that the blood urea concentration is an insensitive test of kidney mass. The MacKays' curve, in fact, approaches the shape of a rectangular hyperbola; any variable which actually formed the latter curve when plotted against kidney weight would plainly be useless as a clinical test, even though the correlation approached unity.

Therefore, the maximum rate of urine excretion, because it happens to have a linear regression and a comparatively high correlation with the Ratio, is the best measure of kidney mass of those variables studied in this paper.

TABLE 2

Statistical characteristics of the Addis Ratio (per cent of normal) with minimum volume, specific gravity of concentration test, maximum volume, and volume quotient. The Addis Ratio is denoted by x in each instance, the other variable by y.

Characteristic	Minimum volume	Specific gravity concentration test	Maximum volume	Volume quotient
r	-0.354 ± 0.026	$+0.530 \pm 0.021$	$+0.697 \pm 0.015$	$+0.568 \pm 0.020$
η_{xy}	-0.351	$+0.577$	$+0.710$	$+0.683$
$\zeta/\text{P.E.}_\zeta$		4.00	2.39	7.44
η_{yx}	-0.399	$+0.554$	$+0.705$	
$\zeta/\text{P.E.}_\zeta$	3.23	2.77	1.84	
M_x	62.53 ± 0.77	62.53 ± 0.77	62.53 ± 0.77	62.53 ± 0.77
M_y	31.88 ± 0.54	1.0255 ± 0.0002	437.3 ± 5.73	17.95 ± 0.36
σ_x	26.01 ± 0.52	26.01 ± 0.52	26.01 ± 0.52	26.01 ± 0.52
σ_y	18.22 ± 0.38	0.0072 ± 0.0001	194.4 ± 4.05	12.29 ± 0.25
N	524	520	524	524

Regression of Addis Ratio (per cent of normal) on minimum volume:

$$x = 78.628 - 0.505y.$$

Regression of Addis Ratio (per cent of normal) on specific gravity of concentration test:

$$x = 1909y - 1896.$$

Regression of Addis Ratio (per cent of normal) on maximum volume:

$$x = 0.0933y + 21.728.$$

Regression of Addis Ratio (per cent of normal) on volume quotient:

$$x = 75.3 + 0.1243y - 60.89e^{-0.1202y}.$$

Prediction of the amount of kidney tissue. Figure 1 shows in line-chart form the most probable predictions of the amount of functioning kidney tissue (expressed as per cent of the normal Ratio) from a given rate of urine excretion under the conditions outlined above. Each line in the chart represents the calculated regression line of the Ratio on the appropriate variable.

In 50 cases, the Ratio was predicted (by means of Figure 1) from the maximum volume, minimum volume, specific gravity of the concentration test, and volume quotient; the predictions were compared with the actual Ratios and the root-mean-square deviations (8) of the errors calculated. The deviations were 29.8 for the minimum volume, 19.9 for the maximum volume, and 22.1 for both the volume quotient and the

TABLE 3

Correlation table. Addis Ratio (per cent of normal) and minimum volume (cubic centimeters/hour/1.72 sq. m.)

Minimum volume—cc./hour	Addis Ratio—per cent of normal																								Totals
	0–4.9	5–9.9	10–14.9	15–19.9	20–24.9	25–29.9	30–34.9	35–39.9	40–44.9	45–49.9	50–54.9	55–59.9	60–64.9	65–69.9	70–74.9	75–79.9	80–84.9	85–89.9	90–94.9	95–99.9	100–104.9	105–109.9	110–114.9	115–119.9	
140–149.9			1																						1
130–139.9						1																			1
120–129.9																									0
110–119.9					1																				1
100–109.9																									0
90– 99.9		1			1	1						1				1									5
80– 89.9																									0
70– 79.9				1	1	1	2	1	2	1		1			2										12
60– 69.9	1	1	1		2	1	4	1		1	1	2	1	2		1	1								20
50– 59.9			2	2	1	2	4	3	2	3	2	3	1		1			3	2	1	2	1			35
40– 49.9		1	3	1	1	3	11	3	2	2	3	2		3		4	1	4	3		1				48
30– 39.9		3	3	4	2	9	4	5	2	3	8	9	8	6	5	6	7	5	4	4	1	2	1		101
20– 29.9	1	1	2	3		2	6	3	6	11	10	11	10	14	7	13	15	14	11	7	7	4	2	1	161
10– 19.9	1	1	1			2	3	1	2	4	4	14	11	11	7	20	10	10	11	5	4	4	2	1	129
0– 9.9			1						1	1	1	2	2	1	1										10
Totals	3	8	14	11	9	22	34	17	17	26	29	45	33	37	23	45	34	36	31	17	15	11	5	2	524

TABLE 4

Correlation table. Addis Ratio (per cent of normal) and specific gravity of concentration test

Specific gravity—concentration test	Addis Ratio—per cent of normal																								Totals
	0–4.9	5–9.9	10–14.9	15–19.9	20–24.9	25–29.9	30–34.9	35–39.9	40–44.9	45–49.9	50–54.9	55–59.9	60–64.9	65–69.9	70–74.9	75–79.9	80–84.9	85–89.9	90–94.9	95–99.9	100–104.9	105–109.9	110–114.9	115–119.9	
1.046–1.047......											1														1
1.044–1.045......												1													1
1.042–1.043......											1			1											2
1.040–1.041......												1				1									2
1.038–1.039......													1		1	1	1		2	1	2	1			10
1.036–1.037......												2	3			2	3	2				1			13
1.034–1.035......							2			1		3	1	4	1	5	4	3	3	1	2	2	1		33
1.032–1.033......						1						5	1	6		6	7	4	5	4	2	1	1	1	44
1.030–1.031......							2		2	3	3	7	4	4	3	6	3	7	5	1	3		2	1	56
1.028–1.029......						1	1	1		6	3	7	2	3	4	8	4	5	5	4		2	1		57
1.026–1.027......			1		1		3	1	2	4	4	5	4	7	3	5	4	5	2	1	2	2			56
1.024–1.025......	1	1				1	4		4	3	5	3	8	5	4	1	1	4	3	4					52
1.022–1.023......				1		4		5	1	3	6	4	4	2	3	2	4	3	2		2				46
1.020–1.021......			3			2	5	1	2	3	3	2	3	4		4		1			1	1			35
1.018–1.019......			3			7	4	3	1		1	3	1	1	2				2						28
1.016–1.017......		2	2	8	2	2	5	1	1	2						2	1	1	1	1	1				32
1.014–1.015......		2	3	2	1	2	4	3	1	1	2	1	1		1										24
1.012–1.013......	2	3	2		5	1	3	1	3			2				1						1			24
1.010–1.011......							1	1									1								3
1.008–1.009......																									
1.006–1.007......						1																			1
1.004–1.005......																									
Totals........	3	8	14	11	9	22	34	17	17	26	29	46	33	37	22	44	33	35	30	17	15	11	5	2	520

TABLE 5

Correlation table. Addis Ratio (per cent of normal) and maximum volume (cubic centimeters/hour/1.72 sq. m.)

Maximum volume—cc./hour	Addis Ratio—per cent of normal																							Totals
	0–4.9	5–9.9	10–14.9	15–19.9	20–24.9	25–29.9	30–34.9	35–39.9	40–44.9	45–49.9	50–54.9	55–59.9	60–64.9	65–69.9	70–74.9	75–79.9	80–84.9	85–89.9	90–94.9	95–99.9	100–104.9	105–109.9	110–114.9	115–119.9	
960–999																						1			1
920–959															1										1
880–919																			2						2
840–879								1									1			1	1	1			5
800–839																			1						1
760–799														1		3		3	1	2	1	1			12
720–759												1	1			1	5	3	3	1	3	2			20
680–719														1		4	2	3	5	2	1				18
640–679												1	1	2	2	4	3	3	2	2	2	1			23
600–639									1	1	1	1	1	3	2	6	6	3	2				1		28
560–599			1						3	3	1	2	3	3	3	5	2	2	2	3		1	1	1	36
520–559											1	3	4	5	3	3	2	3	3	2	4		1		34
480–519							2	1		1	4	3	4	5	3	3	5	4	3	1		1			40
440–479							1	1	2	3	1	10	3	2	1	5	3	6	1	1	2	1	1		44
400–439							3		1	3	2	6	6	3	1	4	1	2	3	2		2		1	40
360–399							3	4	3	3	6	5	4	5	4	1		3	3						44
320–359						4	2	1		5	4	5	4	2		2	1	1							31
280–319					1	5	4	2		2	1	2				2									19
240–279					1	4	5	2	1	1	1	2	2	4	2	1	1				1				28
200–239		1	3		3	5	5	2	2	1	1	1		1											25
160–199		1	4	5		3	2	1	1	1	2					1	1						1		23
120–159		1	3	3	1	1	4	2	1		1				1										18
80–119	1	2	1	2	2		1			2	2	2													16
40– 79		3	1	1	1		1		1		1	1													10
0– 39	2		1				1		1																5
Totals	3	8	14	11	9	22	34	17	17	26	29	45	33	37	23	45	34	36	31	17	15	11	5	2	524

TABLE 6

Correlation table. Addis Ratio (per cent of normal) and volume quotient

Volume quotient	Addis Ratio—per cent of normal: 0–4.9	5–9.9	10–14.9	15–19.9	20–24.9	25–29.9	30–34.9	35–39.9	40–44.9	45–49.9	50–54.9	55–59.9	60–64.9	65–69.9	70–74.9	75–79.9	80–84.9	85–89.9	90–94.9	95–99.9	100–104.9	105–109.9	110–114.9	115–119.9	Totals
69–71.9													1												1
66–68.9																			1						1
63–65.9																						1			1
60–62.9																									0
57–59.9																	1								1
54–56.9												2				1			1						4
51–53.9															1	1		1							3
48–50.9									1											1	1				3
45–47.9																1		1	1						3
42–44.9														1	1	1				1		2			6
39–41.9											1		1		1	1	2		2		2				10
36–38.9												1	1		1	1	1	1	2				1		9
33–35.9										1		1				4		4	1		1			1	13
30–32.9										1		6	2			2	3	1	3	4	1	1			24
27–29.9												2	5	2	4	3	3	3	1	2	1	1			27
24–26.9									2	1	2		5	5	2	10	3	4	2	1	3				40
21–23.9							1		1	2		2		8	2	2	5	3	7	3	1	1		1	39
18–20.9						1			2	6	5	5	4	3		3	7	3	1		1	1	1		43
15–17.9			1				1		1	2	6	5	5	5	2	3	4	5	3	2	1	3	2		51
12–14.9			1			2	2		2	3	1	3	3	6	3	6	2	6	4	2	2				48
9–11.9						4	8	4	2	2	4	7	4	2	2	2	1	4	1	1	1	1	1		51
6– 8.9		1	1	2	1	5	8	10	2	4	4	5	2	3	4	4	1		1						58
3– 5.9		2	7	7	4	9	10	3	1	3	3	5		2			1								57
0– 2.9	3	5	4	2	4	1	4		3	1	3	1													31
Totals	3	8	14	11	9	22	34	17	17	26	29	45	33	37	23	45	34	36	31	17	15	11	5	2	524

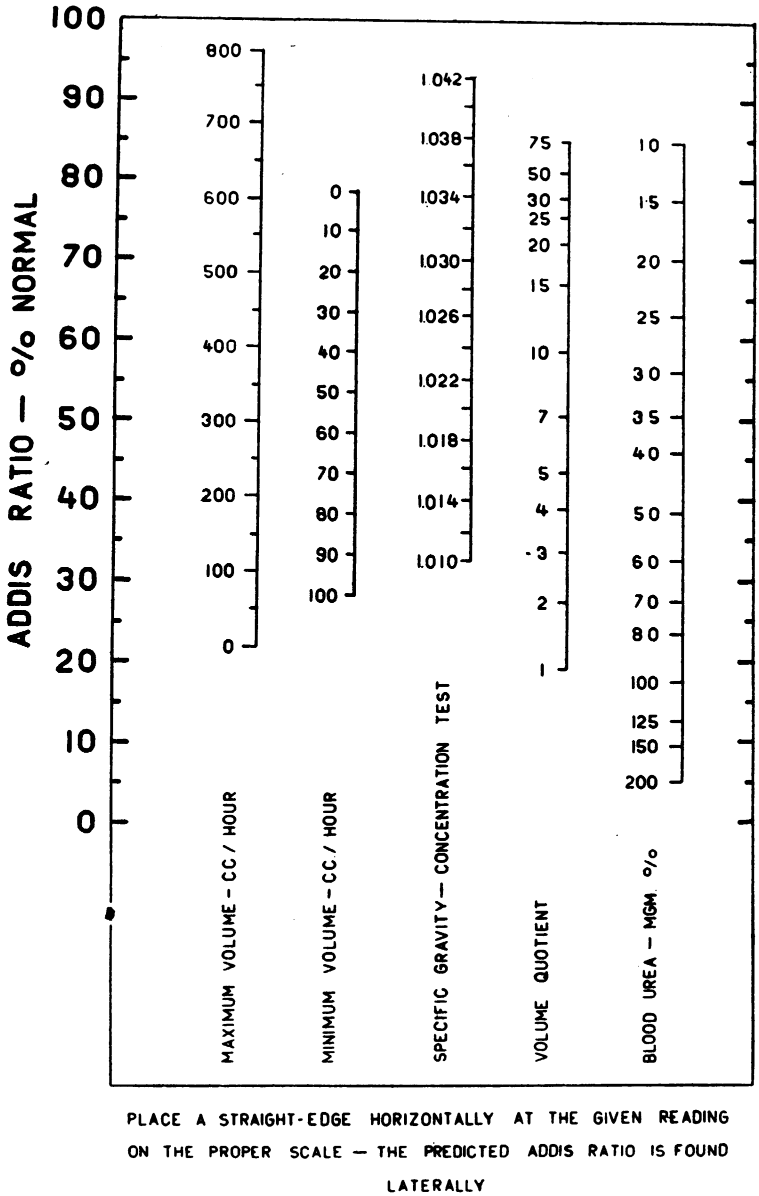

FIG. 1. LINE CHART FOR PREDICTING ADDIS RATIO FROM MINIMUM VOLUME (CC./HR./1.72 SQ. M.), MAXIMUM VOLUME (CC./HR./1.72 SQ. M.), SPECIFIC GRAVITY OF CONCENTRATION TEST, VOLUME QUOTIENT, AND BLOOD UREA (MGM./100 CC.). (BLOOD UREA LINE CALCULATED FROM DATA OF MACKAY AND MACKAY (3).)

specific gravity. These results mean roughly that the odds are 2 to 1 in favor of a prediction being within ± 30 per cent [3] of the true value when the minimum volume is used, and within ± 20 per cent when any of the other variables are used to estimate renal mass.

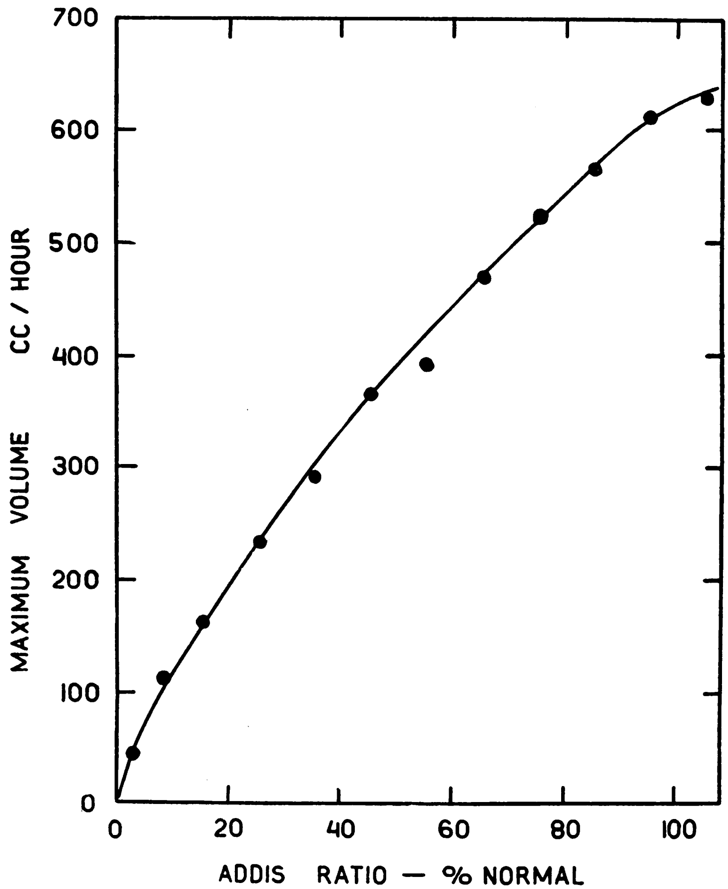

FIG. 2. THE REGRESSION LINE OF MAXIMUM VOLUME (CUBIC CENTIMETERS /HOUR/1.72 SQ. M.) ON THE ADDIS RATIO (PER CENT OF NORMAL).

Regression lines of the studied variables on the Addis Ratio. The regression line of the maximum rate of urine excretion on the Ratio is shown in Figure 2. The means fall quite smoothly along a parabola, which when extended meets the origin. The maximum rate begins to decrease almost as soon as kidney tissue becomes less than normal in amount: the slight lag in response may be an artefact due to the small

[3] In per cent of the normal, not of the actual Ratio in any specific instance.

number of observations at 105 per cent of normal, or may mean that the stimulus is insufficient to provoke a maximal renal response.

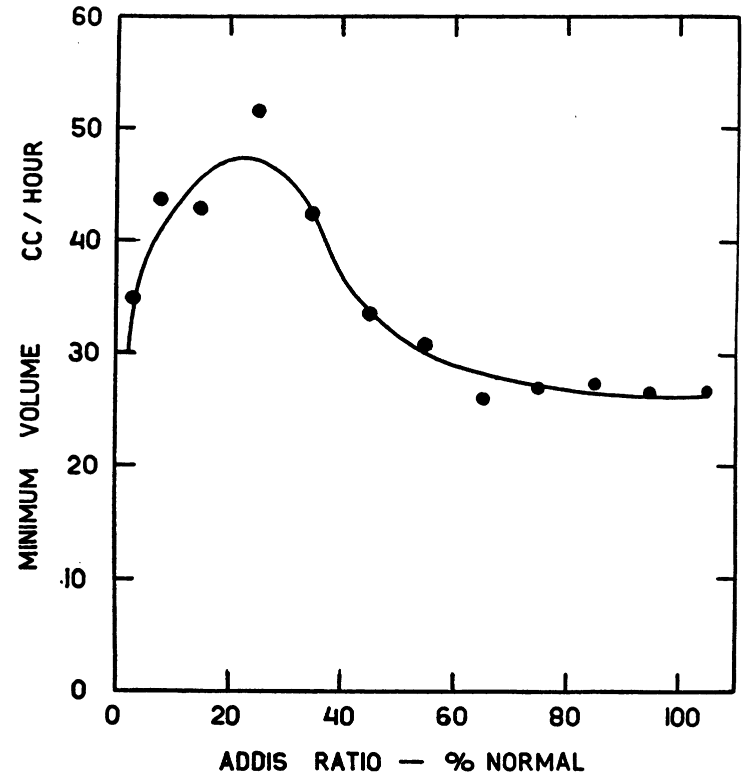

FIG. 3. THE REGRESSION LINE OF MINIMUM VOLUME (CUBIC CENTIMETERS /HOUR/1.72 SQ. M.) ON THE ADDIS RATIO (PER CENT OF NORMAL).

The behavior of the minimum rate of excretion of urine is shown in Figure 3. The curve is not so smooth, and is of a more unusual shape. The capacity of the kidney to produce urine at a slow rate is not involved until about 40 per cent of renal tissue is removed; a polyuria then follows, reaches its height when only 25 per cent of tissue remains, and declines rapidly toward anuria as the mass of kidney disappears.

The regression line of specific gravity of the "concentration test" on the Ratio is given in Figure 4. As kidney substance is removed, the kidney is able to produce urine of high specific gravity until about 20 per cent of the tissue is gone; the urine's specific gravity then rapidly decreases at a rate which does not slacken until only 30 per cent of the original kidney weight remains.

The volume quotient may be looked upon as a measure of the adaptability of the kidney to diametrically opposite stimuli (to excrete urine at a "maximum" and at a "minimum" rate). Figure 5 shows that this

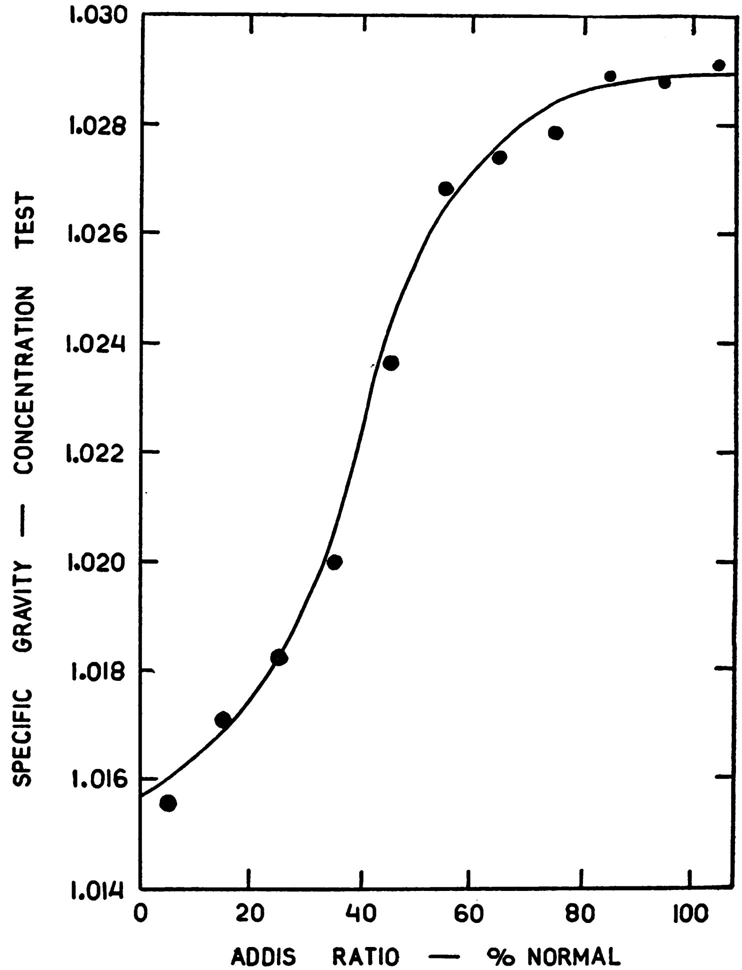

FIG. 4. THE REGRESSION LINE OF THE SPECIFIC GRAVITY OF THE CONCENTRATION TEST ON THE ADDIS RATIO (PER CENT OF NORMAL).

adaptability is affected almost as soon as tissue is removed, and decreases in a straight line until the kidney is able to excrete urine at only one rate regardless of the stimulus.

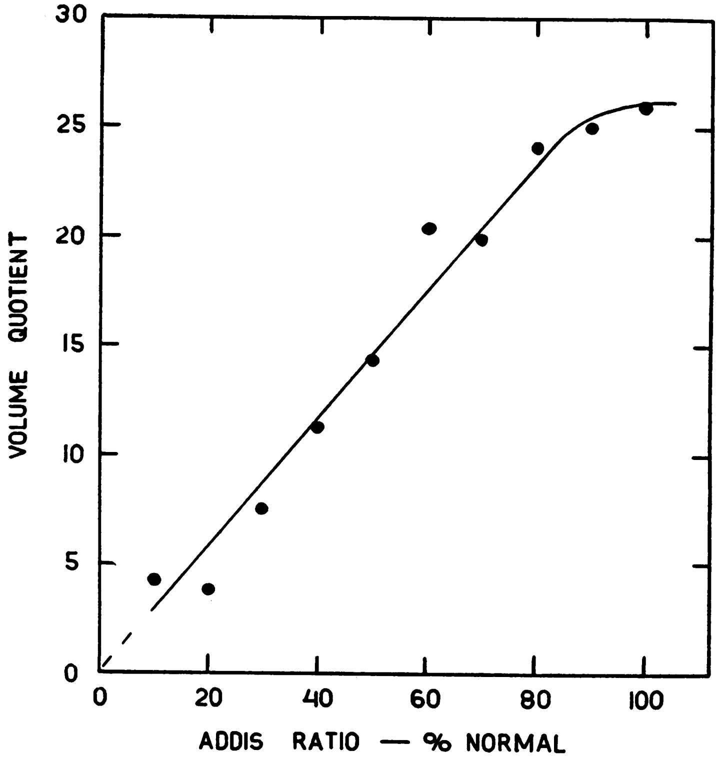

FIG. 5. THE REGRESSION LINE OF THE VOLUME QUOTIENT ON THE ADDIS RATIO (PER CENT OF NORMAL)

The data for the four related regression lines are given in Tables 7 to 10.

TABLE 7

Regression line of Addis Ratio (per cent of normal) on maximum volume (cubic centimeters/hour/1.72 sq. m.)

Maximum volume	Addis Ratio	Number of observations
40	23.5	15
120	31.2	34
200	39.9	48
280	47.1	47
360	57.0	75
440	69.7	84
520	74.4	74
600	73.9	64
680	84.8	41
760	88.5	42
		524

TABLE 8

Regression line of Addis Ratio (per cent of normal) on minimum volume (cubic centimeters/hour/1.72 sq. m.)

Minimum volume	Addis Ratio	Number of observations
5	53.5	10
15	72.7	129
25	69.1	161
35	57.8	101
45	50.3	48
55	53.6	35
65	41.7	20
75	42.0	12
85		0
95	38.5	5
105		0
115	22.5	1
125		0
135	27.5	1
145	12.5	1
		524

TABLE 9

Regression line of Addis Ratio (per cent of normal) on specific gravity of the concentration test

Specific gravity	Addis Ratio	Number of observations
1.0055	27.5	1
1.0095	50.8	3
1.0135	32.1	48
1.0175	40.6	60
1.0215	57.3	81
1.0255	64.4	108
1.0295	73.0	113
1.0335	79.9	77
1.0375	81.6	23
1.0415	63.8	4
1.0455	55.0	2
		520

TABLE 10

Regression line of Addis Ratio (per cent of normal) on volume quotient

Volume quotient	Addis Ratio	Number of observations
3	29.7	88
9	52.0	109
15	69.5	99
21	72.9	82
27	75.8	67
33	80.0	37
39	82.0	19
45	87.5	9
51	80.0	6
57	73.5	5
63		0
69	87.5	2
		524

SUMMARY AND CONCLUSIONS

A statistical analysis was attempted in correlating the Addis Ratio (as a measure of the amount of functioning renal tissue) with the rates of excretion of urine under specified conditions designed to induce minimum and maximum rates of excretion.

Tests of function are discussed from the view-point of the shape of their regressions with the amount of functioning tissue which they are designed to measure. The shape of the regression is at least as important as the correlation in determining the clinical value of the test.

The odds are 2 to 1 that the Ratio may be predicted within a range of ± 20 per cent by means of urine excretion rates.

The behavior of the rates of excretion of urine with different amounts of kidney tissue as measured by the Ratio is described. No explanation for the shape of the curves is given.

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