

## STUDIES OF THE KIDNEY IN ACUTE INFECTION

### II. OBSERVATIONS WITH THE UREA CLEARANCE TEST IN ACUTE RHEUMATIC INFECTION<sup>1</sup>

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In a previous study (1), we showed by means of the urine sediment count (2), that in acute rheumatic infection there is an abnormal increase in the excretion of formed elements in the urine for varying periods up to ten weeks following the acute stage of the disease. In that study, no instances of diffuse glomerulonephritis occurred.

Changes in renal function in the course of acute infections have been repeatedly investigated (3, 4, 5, 6, 7, 8, 9). These studies show a distinct lack of uniformity in the results obtained, and in their interpretation. This lack of agreement appeared to us to be in part due to the attempt to compare the results of different renal function tests. Those most frequently used were the blood urea nitrogen, phenolsulphonphthalein, and urea excreting power of the kidney. It is quite conceivable that these procedures not only test different functions of the kidney, but that they differ in their sensitivity to changes in renal function. Obviously then, they are not comparable. We felt that in order to obtain significant results in such a study, it would be necessary to select patients with the same infection of about the same degree of severity, and a single test sufficiently sensitive to indicate slight variations from normal. We decided upon the urea clearance test described by Möller, McIntosh and Van Slyke (10) shown to be highly sensitive as an index of the urea excreting activity of the kidney (13).

Acute rheumatic infection was selected as the first disease to be studied. Care was taken in the selection of patients, to obtain as far as

<sup>1</sup> The funds for this study were obtained from the Rheumatic Fever Fund Committee for Encouragement of Medical Research.

possible, uncomplicated acute rheumatic infection. A few had acute fibrinous pericarditis and electrocardiographic evidence of acute myocardial involvement, but none showed evidence of congestive heart failure. In none of our group was there evident arteriosclerosis, hypertension or previous nephritis. Urine specimens for the clearance test were carefully collected by a group of specially trained nurses.<sup>2</sup> Blood and urine urea nitrogen determinations were made by the gasometric method described by Van Slyke (11).

The patients were all confined to bed during the period of investigation, and tests were invariably performed between nine A.M. and twelve noon (12). In all other respects the test was carried out exactly as prescribed by the authors (10). The factor measured by the clearance test is the volume of blood which a definite excretion of urine will clear of urea. When the urine volume is less than 2 cc. per minute the "standard clearance" is employed, being the volume of blood which 1 cc. of urine excreted in 1 minute suffices to clear of urea. When the urine volume is 2 cc. or more per minute "the maximum clearance" is employed, being the volume of blood which one minute's excretion of urine suffices to clear of urea. In the average sized normal adult (surface area 1.73 square meters) the standard clearance varies from 41 cc. to 65 cc. of blood cleared of urea by 1 cc. of urine in one minute, with a mean of 54 cc. For the same individual, the maximum clearance ranges from 64 cc. to 99 cc. of blood cleared of urea in one minute, with a mean of about 75 cc. Multiplying by the factors 1.85 or 1.33, standard or maximum clearance values respectively may be recorded on the basis of 100 per cent of normal renal function.

Table 1 indicates clearance values as determined thirty-four times in seventeen different individuals in whom there was no reason to suspect renal abnormality. The accepted normal range is from 75 per cent to 125 per cent of the average normal renal function, taken as 54 cc. standard, and 75 cc. maximum. Seven of our figures are below this range and one is above. These determinations, however, represent single readings. In each of the five individuals in whom three or more determinations were made, as well as in the entire group, the average results are well within the accepted normal range.

<sup>2</sup> The expense of this special nursing staff was met in part by the Crane Fund and in part by the Rheumatic Fever Fund of the Committee for Encouragement of Medical Research.

TABLE 1  
*Blood urea clearance in normal persons\**

Name	(V) Urine volume	$\sqrt{V_{cor}\dagger}$	(B) Blood urea nitrogen	(U) Urine urea nitrogen	Kidney function per cent of average normal
	<i>cc. per minute</i>	<i>cc. per minute</i>	<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>per cent</i>
G	1.130	1.065	6.16	355.00	115.00
K	0.489	0.699	9.90	500.00	65.28
Mc	0.540	0.735	10.60	798.50	102.36
M	0.563	0.750	10.60	435.00	56.88
L	1.120	1.240	6.85	321.50	107.57
T	0.513	0.753	11.30	787.65	97.09
A	0.690	0.831	13.40	625.35	71.52
J	0.590	0.770	11.20	519.90	66.12
Tw	0.435	0.640	11.10	737.50	78.66
E	0.516	0.738	7.10	584.50	109.40
F	0.473	0.680	6.10	481.45	99.29
	0.324	0.640	13.17	1,167.60	100.90
D	7.100	7.640†	10.90	124.00	115.80†
	10.400	11.350†	8.30	48.40	90.04†
	7.450	6.780†	9.05	172.80	108.00†
C	1.140	1.050	14.60	760.50	102.20
	0.970	0.975	10.35	502.50	85.75
Di	0.623	0.790	8.10	459.70	83.80
	0.815	0.899	12.78	486.00	64.40
	0.669	0.790	17.00	1,021.50	88.30
	0.815	0.915	16.70	1,369.50	136.50
S	0.800	0.905	26.30	1,542.50	98.00
	0.580	0.765	20.00	1,371.50	97.60
	0.584	0.775	25.35	1,567.50	89.00
	0.625	0.895	21.80	1,557.00	107.00
	4.615	5.140†	15.40	258.30	96.90†
Sc	1.060	1.070	12.80	632.50	99.00
	1.000	1.030	10.83	746.00	104.50
	3.370	3.758†	9.85	252.00	125.50†
	0.975	1.935	15.70	842.50	91.00
St	5.140	4.675†	15.90	239.50	86.10†
	4.920	4.475†	11.56	183.75	86.75†
	3.700	3.200†	11.35	187.90	69.10†
	4.810	5.150†	9.57	95.12	66.13†
Average			12.74		93.28

\* Each result tabulated represents the average of two separate hourly determinations.

† Maximum clearance and  $V_{cor}$  instead of  $\sqrt{V_{cor}}$ .

‡ Volume corrected to surface area 1.73 sq. m. (14).

In table 2 are listed the results of the clearance test in sixteen patients with acute rheumatic infection. The test was performed seventy-five times at intervals during the active and convalescent periods.

Of the sixteen patients, eleven showed a distinct elevation of the clearance during the acute period of the disease; three showed normal values, and none showed a depression of the clearance value during the acute stage. The remaining two patients were first observed after the acute stage had passed.

Of the eleven patients who showed an abnormal elevation of the clearance during the acute stage, eight were followed into the convalescent period. In six of these there occurred a moderate to very striking depression of the clearance value during this period. Where it was possible to follow the patient sufficiently long after apparent recovery, the clearance was found to return to normal in from one to eighteen days. During the period of low clearance values, the blood urea nitrogen was normal, and the patients appeared well in every respect. That the urea clearance value may be very low in the presence of normal blood urea nitrogen and creatinine is an indication of its extreme sensitiveness as a test of renal function. It has been shown (13) that blood nonprotein nitrogen is invariably above normal only when the blood urea clearance indicates less than 20 per cent of normal renal function. In one instance, the patient insisted and did leave the hospital feeling perfectly well, although the clearance value showed only 32 per cent of normal kidney function.

Of the patients who showed normal clearance values during the acute stage of the disease, one was observed over a period of nine weeks, during which the clearance fell to 15 per cent of normal kidney function and was found to be normal thirteen days later. The intervals of thirteen and eighteen days represent maximum duration of the low clearance values, since, if more frequent observations had been made, it is quite likely that this period may have been found somewhat shorter.

In no instance was the clearance value found to be unusually low during the acute stage of the disease, and in no instance was it found unusually high except during this period.

The blood urea nitrogen exceeded our highest normal figure only in patient 14. We were unable to obtain further data on this patient.

TABLE 2  
*Urea clearance in acute rheumatic infection\**

Num- ber	Name	Date	Blood urea nitrogen	Urine urea nitrogen	Urine volume corrected†	Per cent of normal function	Temper- ature
			<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>cc. per minute</i>	<i>per cent</i>	<i>°F.</i>
1	T	April 22, 1929 April 30, 1929	13.98 8.50	1,238.30 1,190.00	1.0270 0.6090	165.93 204.96	101.8 99.6
Left hospital A. O. R.							
2	Du	April 23, 1929 May 7, 1929 June 4, 1929 June 10, 1929 June 21, 1929 August 9, 1929	25.50 10.90 10.30 11.30 11.50 9.99	1,152.70 853.50 486.50 265.50 316.00 275.20	0.9840 0.8700 2.2700 2.2990 1.3070 2.4900	82.93 135.01 142.50† 71.54† 58.12 91.24†	102.0 99.6 99.6 99.4 99.6 97.6
3	N	April 24, 1929 May 3, 1929 May 8, 1929 May 17, 1929 July 19, 1929	17.48 11.60 12.00 13.80 17.34	1,397.70 1,273.00 1,392.50 611.50 760.00	0.9950 0.8290 0.5300 0.8660 0.5410	147.19 185.92 156.43 76.62 59.60	104.0 102.2 100.0 99.0 98.6
4	De	April 29, 1929 May 8, 1929	17.68 20.45	987.60 1,030.00	1.1550 0.6760	111.62 75.48	103.6 100.4
5	B	May 1, 1929 May 20, 1929 June 14, 1929	24.70 18.80 10.70	1,231.50 917.00 633.50	0.8606 0.6167 0.5527	85.32 70.35 81.78	104.0 98.8 98.6
6	Tw	May 2, 1929	16.42	1,425.00	0.7879	141.76	102.2
Uncoöperative							
7	C	May 4, 1929 May 13, 1929 May 20, 1929 May 24, 1929 May 28, 1929 June 4, 1929 June 11, 1929 June 21, 1929 June 25, 1929 June 28, 1929 July 10, 1929 July 23, 1929	10.92 10.32 20.35 15.40 15.20 11.90 18.08 10.70 10.62 9.93 5.90 3.35	1,425.00 1,495.50 1,282.50 999.00 822.50 482.00 380.00 151.00 332.00 389.45 139.10 136.96	0.7430 0.7760 0.8863 1.1570 0.8783 0.7267 0.2940 1.0600 0.8890 0.7797 0.6690 0.6610	207.97 235.19 109.76 129.48 93.77 63.91 21.12 26.10 54.44 64.10 35.74 61.62	103.4 101.8 102.4 101.0 103.0 101.4 98.0 99.6 101.0 102.6 100.0 99.0

\* Each result tabulated represents the average of two separate hourly determinations.

† Maximum clearance.

‡ Volume corrected to surface area 1.73 sq. m. (14).

TABLE 2—*Continued*

Num- ber	Name	Date	Blood urea nitrogen	Urine urea nitrogen	Urine volume corrected‡	Per cent of normal function	Temper- ature
Uncoöperative— <i>Concluded</i>							
			<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>cc. per minute</i>	<i>per cent</i>	<i>°F.</i>
8	M	May 16, 1929	16.90	787.50	0.4995	61.12	103.4
		May 22, 1929	18.39	1,119.50	0.8105	100.81	102.2
		June 3, 1929	12.69	382.00	0.4784	38.57	99.6
		June 13, 1929	12.45	306.00	0.2646	23.31	98.6
		June 24, 1929	9.63	317.00	1.1770	66.24	103.4
		July 1, 1929	4.48	210.30	0.5130	61.90	99.8
		July 11, 1929	11.20	112.32	0.7040	15.59	100.0
		July 24, 1929	9.87	462.90	0.7990	77.64	99.6
9	G	May 17, 1929	9.20	1,480.00	0.30195	164.08	104.8
		May 24, 1929	9.94	518.50	1.27200	135.12	103.6
		May 31, 1929	9.10	965.00	0.55440	141.74	104.0
		June 7, 1929	12.50	326.50	0.83320	43.90	102.0
		June 20, 1929	7.34	634.50	0.35255	94.60	100.0
		June 26, 1929	9.55	483.00	0.89210	88.28	99.2
10	A	April 3, 1930	22.55	1,564.50	0.76800	121.40	99.8
		April 10, 1930	26.20	501.00	1.25000	39.45	99.0
		April 11, 1930	16.22	466.00	2.94000	84.70†	99.6
11	C	January 24, 1930	14.12	1,516.00	0.56700	149.40	103.0
A. O. R.							
12	DI	October 29, 1929	4.40	711.00	1.07000	256.07	103.0
		December 6, 1929	7.54	122.40	4.40000	99.75†	102.0
		January 2, 1930	11.05	1,607.00	0.25700	34.67	99.8
		January 20, 1930	7.74	409.00	0.51500	70.60	97.8
		February 11, 1930	19.35	662.00	0.69500	52.25	99.0
		April 7, 1930	7.45	269.00	2.53000	105.25†	98.0
13	K	November 14, 1929	19.10	1,453.00	1.25300	160.40	100.2
		December 4, 1929	13.48	990.55	0.93000	132.40	100.0
		December 30, 1929	14.70	775.00	0.70500	76.50	99.6
		January 23, 1930	11.10	576.75	0.75400	75.30	98.8
		January 31, 1930	17.00	315.50	1.34000	41.00	99.6
		February 7, 1930	14.68	499.50	1.68000	81.20	99.6
		February 17, 1930	12.50	407.00	2.00000	86.70†	99.0
		April 23, 1930	9.68	665.50	1.00000	125.40	98.0

TABLE 2—*Concluded*

Number	Name	Date	Blood urea nitrogen	Urine urea nitrogen	Urine volume corrected†	Per cent of normal function	Temperature
A. O. R.— <i>Concluded</i>							
14	P	February 21, 1930	43.30	1,666.00	0.70500	59.60	99.8
15	R	February 12, 1930	13.65	1,667.00	1.31000	255.00	100.0
		February 20, 1930	16.50	782.00	0.65000	78.80	99.8
		March 10, 1930	18.90	196.50	5.57500	75.90†	99.4
		March 20, 1930	16.67	772.50	1.72200	114.80	98.8
16	S	April 28, 1930	16.30	1,577.00	0.76200	152.30	100.0
		May 6, 1930	9.80	576.50	0.10000	41.15	99.8
		May 7, 1930	18.65	840.00	0.88100	79.92	100.0
		May 8, 1930	9.35	84.10	10.62000	106.25†	100.0
		May 13, 1930	16.65	539.50	1.08500	77.65	99.8
		May 15, 1930	9.80	274.50	2.57000	92.90†	99.6
		May 16, 1930	14.45	893.00	0.69000	95.70	99.6

The urea clearance test has proved itself to be a sensitive index of changes in renal function (urea excreting activity) (13). Under controlled conditions it has a fairly constant normal value (10). Any deviation from this must, we feel, be interpreted as deviation from normal renal function. The normal value is constant in spite of urea feedings (10). It is likewise uninfluenced by the feeding of high or low protein diets.<sup>3</sup> It is evident from our figures that both high and low clearance values are independent of both blood urea nitrogen and urine volumes. The standard urea clearance values vary directly with the urea concentrating power of the kidney  $\left(\frac{U}{B}\right)$ . If we accept the

empirical clearance values determined in normal persons as an indication of average normal renal function, our results in rheumatic infection must be interpreted as indicating a period of renal hyperfunction during the active febrile course of the disease, and renal hypofunction during the afebrile convalescent period. In this sense, renal hyperfunction may be conceived as a compensatory effort to remove from

<sup>3</sup> Unpublished data (author).

the blood and tissues, as rapidly as possible, the urea accumulating as a result of heightened metabolism. Whether the mechanism involved is increased glomerular blood flow or increased glomerular activity, enhancing more rapid urea filtration or more rapid tubular secretion of urea, is not possible to say at this time. In either event, the kidney is responding to some stimulus by a degree of functional activity exceeding the observed normal. Similarly, in the immediate postfebrile period, the kidney loses in varying extent, its capacity for excreting urea. It may be that diminished glomerular flow accounts for this subnormal phase. If, indeed, a structural basis is to be predicated, it may be that the renal functional change noted, is the result of the diffuse cloudy swelling which accompanies febrile states. Whatever the renal damage, it is only temporary, and as our tables show, capable of complete functional restitution. Since the urea clearance test was employed consistently throughout this study, we have been investigating only one particular function of the kidney, namely, its urea excreting activity. The fact that other renal function tests may not show the same results as we have observed would merely mean that either they did not test kidney function with the same degree of sensitiveness as the urea clearance, or that they test some other particular function of the kidney. We feel that the extreme sensitiveness of the urea clearance test renders it invaluable in a study of this nature, where changes in renal function are apt to be slight.

#### CONCLUSIONS

Values for the standard and maximum urea clearance tests have been determined in normal persons.

It has been shown that in the acute febrile stage of rheumatic infection, clearance values are usually higher than the highest observed normal; and during the afebrile convalescent period, the clearance values are usually lower than the lowest observed normal.

These findings have been interpreted as indicating a state of renal hyperfunction during the acute stage as a response to the demand of increased protein catabolism; and a state of renal hypofunction probably as a result of toxic injury to the kidney parenchyma.

In all patients followed, complete restoration of renal function occurred within about two weeks.



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