JCI The Journal of Clinical Investigation

THE UREA CLEARANCE TEST IN TOXEMIAS OF PREGNANCY

David Hurwitz, W. Richard Ohler

J Clin Invest. 1932;11(6):1119-1128. https://doi.org/10.1172/JCI100468.

Research Article

THE UREA CLEARANCE TEST IN TOXEMIAS OF PREGNANCY

(A Preliminary Report)

By DAVID HURWITZ and W. RICHARD OHLER

(From the Department of Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital, Boston)

(Received for publication June 2, 1932)

At present there is no adequate study of the value of measuring renal function or the changes in blood chemistry in order to differentiate the toxemias of pregnancy from chronic nephritis or demonstrate the return of function of kidneys acutely damaged by severe toxemia or eclampsia. It appears from work previously done that the urea clearance test of Van Slyke and his associates offers a much more accurate method of study of renal function than other tests in common usage. For example, it has been shown that the blood urea clearance must usually fall below fifty per cent of its normal value before significant changes occur in blood creatinin, blood urea nitrogen, blood uric acid, or phenolsulphonephthalein values, and that only after the urea clearance falls below twenty per cent of normal is there usually a change in all of the above values (1, 2).

Consequently, it seemed worth while to apply the urea clearance test to a series of patients entering the Boston Lying-in Hospital with a diagnosis of toxemia or nephritis and to a similar group followed in the out-patient toxemia clinic of the Hospital. It also appeared advisable to make a comparative study between data obtained from the urea clearance test and those obtained from other more common methods for studying kidney function. In this report, such comparative data have been limited to the blood nonprotein nitrogen, blood uric acid, blood urea nitrogen, one-hour water test for dilution and concentration, and the phenolsulphonephthalein test.

The patients were classified into toxemic, chronic nephritic and eclamptic groups and a normal pregnant control group. The dividing line between toxemia and chronic nephritis was frequently indefinite, but an attempt was made to include under chronic nephritis the following patients: those who had a definite history of nephritis just before becoming pregnant; those who had a high blood pressure and albuminuria in the early months of pregnancy (up to the fifth month); and those who continued with high blood pressure (over 160 mm. Hg systolic) for some months after delivery. A few of the last mentioned are probably not true nephritics at the present time, but for the purpose of this report are considered thus until proved otherwise. Patients were classified as

toxemics when they had blood pressures over 140 mm. systolic and showed albumin in a catheter specimen. A few of the toxemics were severe enough to be called pre-eclamptic. The toxemics were all in the latter part of pregnancy (after the seventh month). The eclamptics all had hypertension, one or more convulsions, diminished urine output, and albuminuria.

METHODS AND NORMAL VALUES

1. Nonprotein nitrogen was determined by the method of Folin (16). The normal limits are 25 to 40 mgm. per cent, although it is normally lower in pregnancy.

2. Uric acid was determined by the method of Folin and Benedict (15). The normal limits are 2.5 to 5.0 mgm. per cent.

3. Blood urea nitrogen was obtained by the gasometric method of Van Slyke (3). Although the upper limit of normal is 23 mgm. per cent, it is lower in pregnancy. Folin gives 5 to 9 mgm. per cent as the normal range in pregnancy. We have taken 12.5 mgm. per cent as the upper limit of the blood urea nitrogen in normal pregnancy.

4. The one-hour test was carried out as follows: breakfast is omitted and 1000 cc. of water is given at 8:00 A.M.; specimens are collected hourly until lunch, which is dry, and then at 4 P.M. and 6 P.M. Normally, a patient should dilute to 1.003 or less, concentrate to 1.024 or more and excrete the liter of water in the first four hours. The normal pregnant patients and a few patients in the other groups were given concentration tests, i.e. four urine samples were collected hourly in the morning after abstaining from fluids for twelve hours. Normally, a patient should concentrate to 1.025.

5. The phenolsulphonephthalein test was done as follows: after the patient has voided, the dye is given intramuscularly. A glass of water is then given and repeated in one hour. Two hours and ten minutes after the injection, the urine is collected, made alkaline and compared with standards (17). Normally, at least 55 per cent of the dye is excreted.

6. The urea clearance test was done as follows: the patient is given nothing to eat or drink after midnight before the test. Breakfast is omitted. At 7:45 A.M. she is given 200 cc. of water. At 8:00 A.M. the patient voids and is immediately catheterized for residual urine. If the residual urine is over 30 cc. she is catheterized two hours after the first catheterization, otherwise she is allowed to void at 10 A.M. A blood sample is taken one hour after the first voiding. The urea in blood and urine was determined by the method of Van Slyke (3). The patient is kept in bed during the test. The height and weight is obtained. The clearance may be expressed in "the number of cc. of blood cleared of urea per minute," or in per cent of normal clearance, which we have used because it is easier thus to compare the standard with the maximum clearance. For derivation of formulae, see papers of Van Slyke and associates (4, 5, 7, 8). Correction for body surface was applied (6). The lower limit of normal is about 80 per cent.

RESULTS OF BLOOD CHEMICAL STUDIES AND FUNCTIONAL TESTS

In Tables I, II, III and IV, we have summarized the results of the entire study. In instances where more than one test has been done, we have simply indicated the range of values without regard to sequence. Inasmuch as we are interested primarily in the comparison between the

urea clearance values and the values found in other tests, we have separated, wherever possible, the data in these tables into two sub-groups, one containing those cases in which the urea clearance was normal and the other, those cases in which the urea clearance was abnormal.

TABLE 1

Toxemia group

21 cases	Non-protein nitrogen	Blood urea nitrogen	Uric acid	One-hour test		Phenol-sulphone-phthalein	Urea clearance
				Low specific gravity	High specific gravity		
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*			*per cent*	*per cent of normal*
Sub-Group I (Normal Urea Clearance)							
II		4.8					178
III	26–29	6.2	3.5–3.4				157
IV	28–31	6.7	5.1	1.002	1.010	40	108
V	20–25	4.6	2.7–3.7	1.007	1.018		144
VIII	30–39	10.6	3.1–4.0	1.003–05	1.012–15	50	90–109
IX	30–31	4.5	3.0–5.2	1.007	1.018		130
X	22–34	5.6–10.3	3.3–3.4	1.002	1.026	40	80–123
XI	22	4.6	3.9	1.008	1.021		107
XII	25	3.6	8.3				116
XVI	25	4.8–5.2	3.8	1.002	1.025	75	112–125
XVIII	33–40	12.2	3.7–5.7	1.005	1.022		161
XX	24–43	4.1–5.8	3.3–6.2				101–160
XXI	27–30	2.8	3.4–3.7	1.008	1.026	40	173
Sub-Group II (Low Urea Clearance)							
I		7.9					79
VI	31–41	7.9–12	3.9–4.6	1.006–07	1.010–26		36–93
VII	33–41	8.0–8.6	3.0–6.1	1.009	1.016	60	58–86
XIII	27–28	6.7–8.6	3.8–4.4	1.003	1.025		60–97
XIV	30–39	6.3–9.2	4.0–4.1	1.002–05	1.010–13		66–99
XV	27–31	11.9	4.2–5.8	1.002	1.020	55	66
XVII	35–40	6.2	3.3–3.7	1.005	1.022	50	79
XIX	24–31	5.6	3.5	1.005	1.016		70–90
Averages for entire group 30		6.9	4.3	1.005	1.019	51	111
Per cent abnormal findings 0		0	11	82		63	14

Toxemia group

In the sub-group in which the urea clearance tests are within normal limits, abnormalities appear in the other tests, particularly in the uric acid and one-hour test. In like manner, in the sub-group in which the

urea clearance values are low, normal values appear in the other tests, including the one-hour test. In other words, the urea clearance values do not agree with the values for the other tests, nor do the findings among the other tests agree with each other. It is apparent, therefore, that the values for the urea clearance test are independent of values found among

TABLE II

Chronic nephritic group

17 cases	Non-protein nitrogen	Blood urea nitrogen	Uric acid	One-hour test		Phenol-sulphone-phthalein	Urea clearance
				Low specific gravity	High specific gravity		
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*			*per cent*	*per cent of normal*
Sub-Group I (Normal Urea Clearance)							
XXII	20	6.2	3.0				84
XXXI	29	3.8	4.2				84
XXXVII	26	7.2	6.5	1.006	1.020	50–55	111
Sub-Group II (Low Urea Clearance)							
XXIII	30–37	5.1–10.8	3.1–4.6	1.003–07	1.011–18	20–80	66–76
XXIV	29–31	7.2–9.6	4.6–5.4	1.005	1.013–20		51–72
XXV	29–57	12.7	6.5–8.0				26
XXVI	35–41	4.6–6.6	2.9–5.0	1.008	1.017	50	54–85
XXVII	21	8.8	2.8	1.003	1.023		31
XXVIII	39–46	6.7–10.1	4.6–5.4	1.002–05	1.013–15	15–60	57–75
XXIX	24–28	8.5	4.0–4.4	1.005	1.020–30	40	59
XXX	38–39	8.6–22.0	4.2–4.7	1.010	1.020	40	32–50
XXXII		8.5		1.004	1.017		71
XXXIII	27–29	9.0–9.2	3.6–5.0	1.002	1.014–24		79–81
XXXIV	28–38	9.4–12.1	4.1–5.2	1.006–20	1.022–24	45	76–121
XXXV	22–30	16.9		1.003–07	1.020–25		41
XXXVI	28–39	14.2–15.1	4.7–5.7	1.006	1.034		41–78
XXXVIII	37–39	13.8	4.9–5.1	1.000	1.017		28
Averages for entire group 32		9.8	4.6	1.005	1.020	45	64
Per cent abnormal findings 12		29	20	79		100	67

the other tests employed. It also appears that in the toxemia group a large percentage of the urea clearances (87 per cent) are within normal limits. Furthermore, we have data, not included in the table, on a group of sixteen patients with a previous history of toxemia, eleven of whom are now pregnant again. In this group we have found normal urea clearances throughout.

Chronic nephritic group

In the sub-group of normal urea clearances, we have recorded only three cases. It is possible, however, that the urea clearance values in Cases XXXIII and XXXIV might well be considered within normal limits. It will be noted that the highest values for the urea clearance in the chronic nephritic group are to be found in Case XXXIV and Case XXXVII. It so happens that there is some question concerning the clinical diagnosis of nephritis in these two cases, discussion of which will be found later in the text. In the remaining two cases in Sub-group I (XXII and XXXI), the urea clearance values are only slightly above

TABLE III

Eclamptic group

5 cases	Non-protein nitrogen	Blood urea nitrogen	Uric acid	One-hour test		Phenol-sulphone-phthalein	Urea clearance
				Low specific gravity	High specific gravity		
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*			*per cent*	*per cent of normal*
(Low Urea Clearance) *							
XXXIX.....	32–42	4.9–8.5	3.0–6.3				55–80
XL.....	36	15.9	5.8				8
XLI.....	26–43	5.3–11.5	3.2–7.8	1.009	1.022	70	70–82
XLII.....	32–33	11.1–19.0	4.2–5.8	1.005	1.020	40	16–82
XLIII.....	37	4.5–9.8	4.2–4.6	1.004	1.019	80	57–150
Averages for entire group..... 36		10.7	5.2	1.006	1.020	63	61
Per cent abnormal findings..... 0		40	60	100		67	60

* All eclamptics had at least one abnormal urea clearance.

the lower limit of normal. Apart from the above five cases, the urea clearance findings for the group stand out as definitely abnormal. Furthermore, a comparison of the urea clearance values with values for the other tests reveals the same lack of agreement as was noted in the toxemia group. In the clinical material under consideration, we are dealing with cases in which nephritis, if present at all, is present to only a slight or moderate degree. In other words, we are seeking a method of detecting early kidney damage. As a result of our studies, we are forced to conclude that tests other than the urea clearance test do not give information sufficiently reliable or consistent to be of value in the problem of differential diagnosis here presented. It is true that our clinical group is a small one, but it is also true that our conclusions are in agreement

with the findings at the Boston Lying-in Hospital where the above mentioned tests have been done as a routine for a period of years. Whether or not the urea clearance findings are of value as an aid in the ultimate diagnosis, we can not say until the clinical material has been observed over a period of time. We can say this much, however, that in the group here presented, the urea clearance findings compare favorably with clinical impressions.

TABLE IV

Normal pregnancy group

5 cases	Non-protein nitrogen	Blood urea nitrogen	Uric acid	One-hour test		Phenol-sulphone-phthalein	Urea clearance
				Low specific gravity	High specific gravity		
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*			*per cent*	*per cent of normal*
(Normal Urea Clearance) *							
XLIV.....		8.0			1.032		93
XLV.....		7.0			1.019		83–97
XLVI.....		4.8–6.8			1.021		136–154
XLVII.....		7.1–9.8			1.032		129–161
XLVIII.....		5.0			1.024		115–153
Averages for entire group...		6.9			1.026		127
Per cent abnormal findings..		0			40		0

* There were no abnormal urea clearances in the normal pregnancy group.

Eclamptic group

In this small group of eclamptics, each patient had at least one abnormal uric acid determination and one abnormal urea clearance. A more detailed discussion of the individual cases follows.

Normal pregnancy group

Three of the patients in this group showed a lack of ability to concentrate urine to 1.025 whereas none of them showed any abnormalities in the urea clearance test.

GENERAL DISCUSSION OF THE UREA CLEARANCE FINDINGS

In our study there were one hundred three urea clearance tests done on sixty-four patients. In the toxemia group, the average urea clearance was 111 per cent, which is well above normal. In eight cases the urea clearance was slightly low during the acute stage; the five that could be repeated became normal. In general, our results in the toxemia group

differ from those of Spalding, Shevky and Addis (11), who found low Addis ratios in toxemia. Their cases, however, included eclamptics and chronic nephritics. Stander's (12) results are similar to ours. In patients with a previous toxemia, the average of the tests done on those pregnant again without toxemia was 126 per cent. One in the series was low but was normal a few weeks later. A non-pregnant group with a history of previous toxemia all were normal (average 91 per cent).

The urea clearance in the chronic nephritic group averaged 64 per cent (about one-half the average normal pregnant value). One patient (XXXIV) had normal urea clearances the first two times (121 and 104 per cent). She was a thirty-eight year old multipara who had a high blood pressure and a cloud of albumin in the fifth month, with a history of similar trouble in her last two pregnancies. Her third urea clearance was slightly low (76 per cent). After a hysterectomy, she had continued to have hypertension, but the albumin cleared up in a week. Two other patients (XXXIII and XXXVII) had hypertension, 160 to 170 systolic, but no albumin since delivery,—one was two to three months postpartum, the other about a year. The urea clearances of the first averaged 79 per cent (borderline) while that of the second was 111 per cent. These patients had hypertension but were not definite nephritics. Repeated tests on them would be interesting. We do not believe it fair to make a diagnosis of nephritis on the basis of an increased blood pressure alone.

The urea clearance in the eclamptic group averaged 61 per cent. The group is small and the results scattered because of the marked differences in the general and renal condition of the patient. The first patient was a very sick eclamptic who ran a high blood pressure (190 systolic, 85 diastolic) for thirteen days and then had a drop to 130 systolic, 100 diastolic and had albumin for eleven days after delivery. Her last test was 55 per cent, which was lower than her earlier tests. We have not seen her since her discharge and it is too early to say much about persistent renal impairment. The next case with 8 per cent was almost anuric during the test and died the next day. The fourth case in the eclampsia group showed a steady rise in urea clearance—the first, 16 per cent, was during her sickest period when urine was scanty; the second, 48 per cent, was done two weeks later, and the third, 82 per cent, about two months after leaving the hospital when she felt perfectly well, had no elevation of blood pressure or albumin in the urine. This rise in urea clearance with the patient's recovery is very striking. We hope to extend our observations to other cases of this sort. Apparently in eclampsia, the urea clearance is low not only because of the decreased volume output, but also because of a low urea concentration factor. In our small series, there was either a striking return to normal clearance, or there was a persistently low clearance value as in the first eclamptic. Possibly the latter will go on to chronic nephritis as is known to occur so

often after eclampsia (13). Further application of this test to the eclamptic group is desirable and may give very important information.

In the normal pregnancy group the average of the urea clearances is 127 per cent, which is higher than the average non-pregnant normal. Spalding, Shevky and Addis also obtained high results in the Addis ratio in normal pregnancy (11). Possibly this explains the low blood urea nitrogen found in normal pregnancy (10). The normals were first obtained at about the fifth month of pregnancy and are being followed throughout pregnancy.

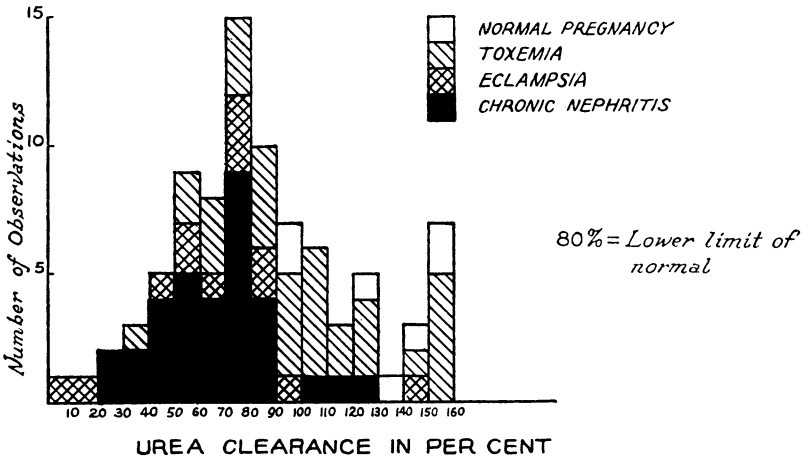

FIG. 1. DISTRIBUTION OF UREA CLEARANCE TESTS IN NORMAL PREGNANCY, TOXEMIA, ECLAMPSIA AND CHRONIC NEPHRITIS

Figure 1 illustrates the distribution of individual urea clearance tests in toxemia, eclampsia and chronic nephritis. It is noteworthy that below 75 per cent (lower limit of normal) all but six tests were in nephritics and eclamptics. Of these, four were repeated soon after and found to be normal, the other two have not returned to the clinic. There are seven normal clearances in the nephritic group on six patients, of whom three had other low tests and two were questionable nephritics impossible to diagnose at the present time. It may be seen that the preponderance of tests done in the chronic nephritic group was below 80 per cent, while that of the toxemic group was above 80 per cent. The tests done in the eclamptic group were scattered for reasons mentioned above.

Van Slyke and Cope (14) have recently described a simplified method of determining the urea clearance, which, while it is not quite as accurate as the method used above, saves time when several determinations are made at once.

We wish to acknowledge the interest and aid of Dr. F. C. Irving, Dr. Saul Berman, and Dr. M. V. Kappius. Mr. James Quinn made the routine chemical analyses.

SUMMARY AND CONCLUSIONS

1. Blood chemistry tests, phenolsulphonephthalein and one-hour tests did not help in the differentiation between chronic nephritis and acute toxemias.

2. One hundred three urea clearance tests were done on 64 patients falling in groups of normal pregnant, toxemics, eclamptics, patients who had toxemia in a previous pregnancy, and chronic nephritics.

3. The urea clearance checked up well with the clinical diagnoses with only a few exceptions. It was found to be higher than the usual normal limits in normal pregnancy, normal in toxemias, decreased in the acute stage of eclampsia (with tendency to rapid return to normal in one case) and low with a high degree of consistency in chronic nephritis.

4. The data suggest a correlation between the high urea clearance and the low blood urea nitrogen in normal pregnancy.

BIBLIOGRAPHY

1. Van Slyke, D. D., McIntosh, J. F., Möller, E., Hannon, R. R. and Johnston. C., J. Clin. Invest., 1930, viii, 357. Studies of Urea Excretion. VI, Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function.
2. Johnston, C., J. Clin. Invest., 1931, ix, 55. The Relationship of Blood Uric Acid Content to the State of Renal Function in Nephritis.
3. Van Slyke, D. D., J. Biol. Chem., 1927, lxxiii, 695. Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease.
4. Austin, J. H., Stillman, E. and Van Slyke, D. D., J. Biol. Chem., 1921, xlvi, 91. Factors Governing the Excretion Rate of Urea.
5. Möller, E., McIntosh, J. F. and Van Slyke, D. D., J. Clin. Invest., 1928, vi, 427. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults.
6. McIntosh, J. F., Möller, E., and Van Slyke, D. D., J. Clin. Invest., 1928, vi, 467. Studies of Urea Excretion. III. The Influence of Body Size on Urea Output.
7. Möller, E., McIntosh, J. F., and Van Slyke, D. D., J. Clin. Invest., 1928, vi, 485. Studies of Urea Excretion. IV. Relationship Between Urine Volume and Rate of Urea Excretion by Patients with Bright's Disease.
8. MacKay, E. M., J. Clin. Invest., 1928, vi, 445. Studies of Urea Excretion. V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease.
9. Folin, O., J. Am. Med. Assoc., 1917, lxix, 1209. Recent Biochemical Investigations on Blood and Urine.
10. Harding, V. J., Physiol. Rev., 1925, v, 279. Metabolism in Pregnancy.
11. Spalding, A. B., Shevky, M. C. and Addis, T., Am. J. Obst. and Gynec., 1922, iv, 350. The Extent of the Renal Region in the Toxemias of Pregnancy.
12. Stander, H. J., Ashton, P. and Cadden, J. F., Am. J. Obst. and Gynec., 1932, xxiii, 461. The Value of the Various Kidney Function Tests in the Differentiation of the Toxemias of Pregnancy.

13. Peckham, C. H., Bull. Johns Hopkins Hosp., 1929, xlv, 176. Chronic Nephritis Following Eclampsia.
14. Peters, J. P. and Van Slyke, D. D., Quantitative Clinical Chemistry. Volume 2. Methods. Williams and Wilkins, 1932, pp. 935–939.
15. Benedict, S. R., J. Biol. Chem., 1922, li, 187. The Determination of Uric Acid in Blood.
Folin, O., J. Biol. Chem., 1922, liv, 153. A System of Blood Analysis. Supplement IV. A Revision of the Method for Determining Uric Acid.
16. Folin, O. and Wu, H., J. Biol. Chem., 1919, xxxviii, 81. A System of Blood Analysis.
17. Rowntree, L. G. and Geraghty, J. T., Arch. Int. Med., 1912, ix, 284. The Phthalein Test. An Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease.