THE SIGNIFICANCE OF THE URIC ACID, UREA AND CREATININ OF THE BLOOD IN NEPHRITIS*

VICTOR C. MYERS, PH.D., AND MORRIS S. FINE, PH.D

WITH THE COOPERATION OF

WALTER G. LOUGH, M.D.

NEW YORK

In an earlier communication[1] attention was called to the practical value of the estimation of the creatinin of the blood in nephritis. It was pointed out that an appreciable retention of creatinin indicated a grave impairment in the functional condition of the kidney, for the reason that creatinin is normally the most readily eliminated of the three nitrogenous waste products—uric acid, urea and creatinin. In contrast to creatinin, however, uric acid is apparently eliminated by the kidney with difficulty. It is, therefore, not surprising that conditions of moderately decreased kidney permeability should be encountered, in which only the concentration of the uric acid of the blood should be raised. This appears to be the case in gout and early interstitial nephritis. In the present paper it is our intention to lay emphasis on those cases in which the permeability of the kidney is not sufficiently impaired to cause a marked retention of creatinin.

The deductions which Sir A. B. Garrod[2] drew from his work in this connection in 1848 are very interesting, and their general harmony with current views surprising when one considers the methods then available. His conclusions (referring to Bright's disease and the albuminuria following scarlatina) were:

> 1. Uric acid is always present in the blood in albuminuria. The quantity, however, greatly varies: when the functions of the kidneys are much impaired, it exists in quantities almost as great as in gout; in other cases, its amount is small, but it usually exceeds that found in ordinary blood. 2. Urea always exists in large quantities in this blood (a fact which has long since been proved) and no relation is found between the amounts of urea and uric acid. 3. The kidneys are always deficient in their power of throwing off urea; but with regard to uric acid, their excreting function may be impaired or not.

---

*Submitted for publication Feb. 11, 1916.

*From the Laboratory of Pathological Chemistry and the Medical Service of the New York Postgraduate Medical School and Hospital.

1. Myers, V. C., and Lough, W. G.: The Creatinin of the Blood in Nephritis: Its Diagnostic Value. THE ARCHIVES INT. MED., 1915, xvi, 536.

2. Garrod, A. B.: Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease. Medical-Chirurgical Trans., 1848, xxxi, 83.

Garrod's paper apparently aroused considerable discussion, for he appended the following:

> Postscript July 26, 1848. At the discussion which ensued after the reading of the above paper to the society, some remarks were made which implied that I was understood as considering gout to be entirely dependent upon the power of the kidney for the excretion of uric acid; such, however, is not my opinion, and at present I do not wish to advance any hypothesis as to the cause and nature of gout, considering that many further researches should be made on the subject before a theory of the disease could be advanced with safety.

The investigation of von Jaksch[3] in 1896 gave confirmation to the observations of Garrod on the retention of uric acid in nephritis.

Von Noorden[4] gives a most interesting discussion on the uric acid content of the blood in gout and nephritis. He writes:

> The primary cause of the uric acid retention in gout lies in the kidney, according to Garrod. Recently Levison and Luff, and, with certain reservations, also Strauss, have advocated the same view. Levison and Luff showed, in a very large series of postmortems in Denmark and in England, that in cases of interstitial nephritis, uric acid deposits in the articular cartilages are very frequently found, although the condition was not suspected during life. Stripped of all unnecessary detail, this means that the retention of uric acid in the blood and the remaining phenomena of gout are the results of primary disease of the kidney. In certain cases both nephritis and gout are amenable to clinical diagnosis. In other cases, nephritis, and in still others the uric acid diathesis, remain for a long time, perhaps even up to the end of life, clinically free from symptoms and unrecognized. . . .
>
> The figures of Levison and Luff show, in the first place, that nephritis and gout occur in the same individual more frequently than was formerly assumed. They recall to us the facts that harmful influences, especially alcoholism and saturnism, and also heredity, play an acknowledged part in the etiology of both diseases. . . .
>
> . . . It appears that continuous overloading of the blood with uric acid (nephritis) does not necessarily lead to gout, and, moreover, that this overloading is not followed by uric acid deposition without the accession of another still unknown, specific gouty factor.

No noteworthy advance in this connection, however, was made until the advent of Folin's new method.[5] The work of Folin and Denis,[6] and others employing their methods, has been principally to confirm the views advanced by Garrod nearly seventy years ago, although with the quantitative data now available more definite conclusions have been possible. Folin and Denis and the authors[7] have reported cases of uremia with marked retention of uric acid, urea and creatinin. Twelve cases have come under our observation with more than 10 mg. of uric

3. Von Jaksch, R.: Beitrag zur Kenntnis der Uricacidämie der Nephritiker. Zentralbl. f. inn. Med., 1896, xvii, 545.
4. Von Noorden, C.: Metabolism and Practical Medicine, 1907, iii, 669.
5. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, xiii, 469.
6. Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29; 1914, xvii, 487.
7. Myers, V. C., and Fine, M. S.: Jour. Biol. Chem., 1915, xx, 391.

acid per 100 c.c. of blood, in one case 27 mg.; still no gouty symptoms were evident. It is of interest regarding the uric acid that early in the disease the values observed may be somewhat higher (7 to 8 mg.) than at a later stage (5 to 6 mg.), although during the last days of life the amount may very markedly increase, this being coincident with an accumulation of creatin in the blood.

Folin and Denis[8] noted that in the severest cases of uremia there was only a slight increase in the blood ammonia, and that it was likewise only these cases in which a marked retention of creatinin occurred. From this they conclude:

> The figures obtained indicate that the human kidney removes the creatinin from the blood with remarkable ease and certainty. The completeness of the creatinin excretion is, in fact, exceeded only by the still more complete removal of the ammonium salts.

It is possible that other factors, such as acidosis and the formation of urea, may have some relation to the increase in the ammonia of the blood, but the increased blood creatinin is obviously due to one cause, namely, the markedly impaired permeability of the kidneys. Since creatinin is the most readily eliminated of the nitrogenous waste products (creatinin, urea and uric acid) and uric acid the most difficultly eliminated, as indicated above, urea must obviously stand in an intermediate position (see Table 3). That this should be the case seems quite plausible when we consider the ease of excretion of these constituents as determined from a comparative nitrogen partition of normal urine and blood. Uric acid nitrogen forms 2 per cent. of the nonprotein nitrogen of both urine and blood, urea nitrogen about 85 per cent. in urine, but 50 per cent. in blood, and creatinin nitrogen 5 per cent. in urine, but only 2 per cent. in blood. It is quite possible that the physical properties and concentration of these constituents in the blood may play an important rôle in the ease with which the kidney eliminates them.

It has been possible to select from a large series of miscellaneous blood analyses a considerable number of cases with decidedly high figures for uric acid, but with only slightly increased urea concentrations and with creatinin figures scarcely above the normal limits. As was pointed out in a previous communication,[1] a creatinin of over 5 mg. per 100 c.c. of blood appears to indicate an early fatal termination. It was the object of the present study to secure cases of the same type, but at an earlier stage in the disease, when changes in diet and mode of living might be of some aid in withholding for a time the uremia, from which most of these patients ultimately die.

8. Folin and Denis: Jour. Biol. Chem., 1914, xvii, 487.

METHODS EMPLOYED

Before proceeding to a discussion of our data on this subject, it is fitting that a brief description should be given of the methods we have employed for the estimation of uric acid, urea and creatinin in blood. Folin has recently raised certain objections to his own technic[9] for the estimation of uric acid in blood. We have embodied the suggestions of Benedict[10] in our application of the method, and are confident of the reliability of the results. The Duboscq colorimeter has generally been employed for the estimation of the uric acid and creatinin, although in the case of urea, the Hellige instrument has frequently been used. For the estimation about 20 c.c. of oxalated blood are needed. To avoid complications from the influence of food and possible changes in blood volume, the blood has generally been taken in the morning before breakfast.

Uric Acid.—Ten cubic centimeters of the well-mixed blood are pipetted into a casserole of about 375 c.c. capacity and approximately 5 volumes of hundredth-normal acetic acid added. The mixture is heated over a water bath and finally brought to a boil over a free flame, stirring continuously. About 4 c.c. of fairly thick alumina cream[11] are added with continuous stirring for a few minutes. The sides of the dish are washed down from time to time with hot water and the mixture then filtered through a hardened filter paper. The coagulum is returned to the casserole with about 150 c.c. of hot water, heated and filtered through the same paper. The combined filtrates are evaporated to 1 or 2 c.c. (the material should be protein-free) and transferred to a 15 c.c. conical centrifuge tube, washing the casserole with 2 or 3 small portions of hot water but keeping the volume at or below 10 c.c.

About 15 drops of ammoniacal-silver-magnesium mixture[12] are now added, the tube shaken and placed in a cool place (refrigerator) for about 15 minutes to allow for the precipitation of the purins. The tube is centrifuged, the supernatant liquid decanted off and allowed to rest in inverted position for about five minutes. The tip of the tube is then wiped with filter paper and the ammonia allowed to volatilize (may be facilitated with suction).

For the development of the color prepare a 100 c.c. graduated cylinder for the standard and a 50 c.c. cylinder for the unknown. Five c.c. of the uric acid standard[13] (5 c.c. = 1 mg. of uric acid) are pipetted into the 100 c.c. cylinder.

9. Folin, O., and Bell, R. D.: Proc. Am. Soc. Biol. Chem., 1915.

10. Benedict, S. R.: Jour. Biol. Chem., 1915, xx, 629.

11. Prepared by precipitating an 8 per cent. solution of aluminum acetate in acetic acid with sodium bicarbonate, carefully washing with a large volume of distilled water by decantation several times, then filtering.

12. The ammoniacal-silver-magnesium solution is prepared by mixing 70 c.c. of 3 per cent. silver nitrate solution, 30 c.c. of magnesia mixture and 100 c.c. concentrated ammonia. Any turbidity which may develop is filtered off. Magnesia mixture is prepared by dissolving 35 gm. magnesium sulphate and 70 gm. ammonium chlorid in 280 c.c. distilled water and then adding 140 c.c. concentrated ammonium hydroxid.

13. The standard uric acid solution is prepared as follows: Dissolve 9 gm. pure crystallin hydrogen disodium phosphate and 1 gm. dihydrogen sodium phosphate in 200 to 300 c.c. hot water. Filter and make up to about 500 c.c. with hot water. Pour this warm, clear solution on 200 mg. uric acid suspended in a few cubic centimeters of water in a liter volumetric flask. Agitate until *completely* dissolved. Add at once exactly 1.4 c.c. glacial acetic acid. Make up to 1 liter, mix and add 5 c.c. chloroform. Five cubic centimeters of this solution are equivalent to 1 mg. uric acid. The solution should be freshly prepared every two months.

To the standard are added 2 drops of 5 per cent. potassium cyanid, 2 c.c. of Folin-Macallum regent,[14] 20 c.c. of saturated (22 per cent.) sodium carbonate, and, in about one minute, water to the 100 c.c. mark. To the precipitate in the centrifuge tube are added 1 or 2 drops of the potassium cyanid, 2 c.c. of the Folin-Macallum reagent and 15 or 20 c.c. of the saturated sodium carbonate, depending on whether the color is subsequently diluted to 50 or 100 c.c. After forty to sixty seconds dilute with water until the intensity of the color is similar to the standard and then match in the Duboscq colorimeter. The prism of the standard may conveniently be set at the 10 mm. mark.

Urea.—The method is based on the suggestions of Marshall[15] and Van Slyke.[16] Into a test tube (of such size that it will just slip into a 100 c.c. cylinder) are introduced 1 c.c. of 10 per cent. urease solution, or about 0.1 gm. of the dry enzyme,[17] and then 1 to 2 c.c. of water. Two cubic centimeters of blood are now added with an Oswald-Folin pipet and the tube incubated in a beaker of water at 50 C. for about one-half hour. At the end of this time 3 to 4 drops of caprylic alcohol or 1 c.c. of amyl alcohol are added to prevent foaming in subsequent aeration. Into a 100 c.c. graduated cylinder, without lip, are added 15 c.c. of distilled water and 2 drops of 10 per cent. hydrochloric acid. This is now closed with a two-hole stopper having a glass tube passing nearly to the bottom of the graduate. The tube is sealed at the lower end, but contains a number of small holes to aid in the complete absorption of the ammonia (Folin). To the test tube containing the digested blood is carefully added an equal volume of saturated sodium carbonate, or better still, potassium carbonate, the solution being allowed to run underneath the blood. The tube is now immediately inserted in a 100 c.c. (ungraduated) cylinder and a two-hole stopper is used containing one glass tube which passes nearly to the bottom of the tube. This is now connected on one side with a wash bottle containing dilute sulphuric acid and on the other with the graduated cylinder containing the dilute acid for the absorption of the ammonia. The ammonia of the blood is now transferred to the cylinder containing the weak acid, by vigorous aeration for twenty to thirty minutes. At the end of this time the outfit is disconnected and nesslerization (Folin) carried out in the graduated cylinder, dilution being made according to the amount of ammonia present.

Into a volumetric flask of 100 c.c. capacity, if the Duboscq colorimeter is to be used, are pipetted 5 c.c. of ammonium sulphate or ammonium chlorid solution containing 1 mg. of nitrogen.[18] About 50 to 60 c.c. of distilled water are next added. Ten cubic centimeters of modified Nessler's solution[19] are now diluted about five times with distilled water, and of this 20 to 25 c.c. added to the standard solution, which is then made up to the mark with water. At the

14. The reagent, as modified by Prof. S. R. Benedict (private communication), is prepared by boiling 100 gm. sodium tungstate, 20 c.c. concentrated hydrochloric acid and 30 c.c. 85 per cent. phosphoric acid in 750 c.c. distilled water for two hours, preferably under a reflex condenser, and then making up to 1,000 c.c. with water.

15. Marshal, E. K.: Jour. Biol. Chem., 1913, xv, 487.

16. Van Slyke, D. D., and Cullen, G. E.: Jour. Biol. Chem., 1914, xix, 211.

17. Prepared by Dr. I. F. Harris, Bronxville, N. Y.

18. The solution may be prepared by dissolving 0.944 gm. ammonium sulphate or 0.764 gm. ammonium chlorid of the highest purity in distilled water and making up to 1,000 c.c.

19. For the modified Nessler's solution, place 100 gm. mercuric iodid and 50 gm. potassium iodid, both finely powdered, in a liter volumetric flask and add about 400 c.c. water. Now dissolve 200 gm. potassium hydroxid in about 500 c.c. water, cool thoroughly and add with constant shaking to the mixture in the flask; then make up with water to the liter mark. This usually becomes perfectly clear. Keep at body temperature over night, or until the yellowish white precipitate which may settle out is thoroughly dissolved and only a small amount of dark brownish red precipitate remains. The solution is now ready to be siphoned off and used.

same time 7 to 8 c.c. of the freshly diluted Nessler's solution are added to the unknown solution and the volume made up to 25 c.c. in the graduate, unless a high content of urea nitrogen is indicated, in which case more Nessler's solution (up to 25 c.c.) and a dilution to 33⅓, 50, 100 c.c. or even more may be needed to make the color of the unknown of approximately the same intensity as the standard. The colorimetric readings should be made without delay, the standard prism being set at the 10 or 15 mm. mark.

Creatinin.—The technic for the creatinin estimation is briefly[1] as follows: 5 c.c. of the well-mixed blood are treated with 20 c.c. of water (4 volumes) in a 50 c.c. centrifuge tube. After the corpuscles have been laked, about 1 gm. of dry picric acid is added, and the mixture stirred at intervals with a glass rod until it is a light yellow. When the protein precipitation is complete, the tube is centrifuged and the supernatant fluid filtered through a small filter paper. To 10 c.c. of the filtrate is added 0.5 c.c. of 10 per cent. sodium hydroxid, and a similar amount of alkali added to 10 c.c. of standard creatinin in saturated picric acid.[20] It is best to make up simultaneously three standards containing 0.3, 0.5 and 1.0 mg. creatinin to 100 c.c. of picric acid. The tube corresponding most nearly with the unknown is used as standard, the prism of the Duboscq colorimeter being set at either the 10 or 15 mm. mark. Allow ten minutes for the color to develop before comparing.

DISCUSSION

Although considerable attention has recently been given to the urea and nonprotein nitrogen of the blood in nephritis, scant consideration has been accorded the uric acid and creatinin. It is true that the greater part of the waste nitrogen is eliminated in the form of urea, but it does not necessarily follow from this that data on uric acid and creatinin are unimportant and uninteresting. In fact, Folin's[21] classic work of ten years ago on the urine, by way of comparison, would suggest that the reverse might be true. Outside of Folin's laboratory and our own, practically no work has been reported in which estimations of the uric acid, urea and creatinin have been simultaneously carried out on pathological bloods. We do not believe that it is possible to make satisfactory deductions regarding nitrogen retention from the urea or nonprotein nitrogen determinations alone, as many have recently done.

In the most recent paper of Folin and Denis[22] dealing with blood uric acid, these authors point out the importance, from a diagnostic standpoint, of having the uric acid estimation accompanied by that of nonprotein or urea nitrogen. Their data give figures for nonprotein nitrogen and uric acid. It seems unfortunate to us that they did not include figures for urea and creatinin. The determination of the urea concentration of the blood is, we believe, of more value than that of the nonprotein nitrogen, for the reason that it represents the reten-

20. Creatinin may now readily be prepared perfectly pure by the admirable method of Benedict, Jour. Biol. Chem., 1914, xxiii, 183.

21. Folin, O.: Am. Jour. Physiol., 1905, xiii, 45.

22. Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determinations in Blood, THE ARCHIVES INT. MED., 1915, xvi, 33.

TABLE 1.—Blood Analyses in "Early Interstitial Nephritis"

Date 1915-16	Case	Age	Sex*	Blood Analysis			Phthalein 2-Hour Output	Blood Pressure		Urine		Remarks
				Uric Acid, Mg. to 100 c.c.	Urea N, Mg. to 100 c.c.	Creatinin, Mg. to 100 c.c.		Systolic	Diastolic	Albumin	Casts	
8/11	1. J. Ja.	65	♂	9.5	25	2.5	13	185	90	+	+	Apparently early chronic interstitial nephritis.
9/25				8.4	37	2.7		150	85			
1/14				5.0	37	3.9		130	...			
9/21	2. D. D.	52	♂	8.7	20	3.6	20	100	87	+	+	Cirrhosis of liver and chronic interstitial nephritis; severe alcoholism.
9/14	3. L. G.	28	♂	7.2	22	2.1	..	120	95	—	+	Pulmonary tuberculosis.
9/22	4. H. J.	60	♂	7.2	18	2.5	..	...	...	+	—	Prostatic hypertrophy.
6/ 7	5. D. S.	56	♂	7.1	16	2.0	26	185	110	—	+	Apparently early chronic interstitial nephritis.
7/21				6.6	24	3.3						
9/28				6.3	18	2.1	43					
8/13	6. J. Ju.	58	♂	7.0	33	2.6	..	115	80	+	— pus	Chronic constipation; alcoholism.
11/16	7. A. R.	57	♂	6.8	20	1.8	40	140	80	—	+	Carcinoma of stomach; metastases to liver; chronic interstitial nephritis; pneumonia four months previous to admission; painful urination; loss of weight.
11/30				6.3	22	2.5						
6/15	8. M. S.	41	♀	6.7	22	1.5	53	120	75	++	—	Frontal headaches; scarlet fever and diphtheria as a child.
9/14	9. G. P.	27	♂	6.7	14	2.4	62	130	90	+	+	Typhoid fever; headaches.
9/17	10. H. L.	23	♂	6.5	16	2.7	58	130	90	++	+	Pulmonary tuberculosis; tuberculosis of kidney; frequent urination; pain in bladder; headache; dizziness and fainting spells.
8/ 3	11. C. Ma.	54	♂	6.3	31	2.0	45	150	90	—	—	Hypothyroidism; chronic interstitial nephritis; increasing weight; pain in lumbar region.
8/31				4.2	20	1.9						
9/21				6.3	23	2.4						

10/ 8	12. J. Co.	69	♂	6.3	40	1.5	20	130	80	+++	+	Endocarditis; chronic interstitial nephritis (?); cystitis; edema of feet and chest.
9/14	13. M. R.	69	♂	6.3	15	2.5	..	128	84	++	—	Myocarditis; dyspnea; edema of legs; pneumonia two years ago; moderate alcoholism.
9/10	14. Ja. C.	69	♂	6.0	36	2.1	50	...	...	+++	—	Prostatic hypertrophy.
10/18	15. L. J.	59	♂	5.8	45	3.6	Trace	128	85	+	— pus	Tabes dorsalis; pyelitis; impairment of vision.
10/26	16. J. T.	55	♂	5.6	30	1.6	33	118	85	+	+	Diabetes; cataract of right eye; mild chronic interstitial nephritis.
8/10	17. E. H.	41	♂	5.6	13	2.1	45	150	65	—	—	Pericarditis; edema of feet and ankles; moderate alcoholism.
9/21	18. S. S.	47	♂	5.5	25	3.0	..	135	95	++	+	Lobar pneumonia; scarlet fever as a child; periodic drinker.
6/11	19. T. S.	49	♂	5.5	24	3.3	62	150	85	+	+	Carcinoma of larynx; chronic interstitial nephritis; chancre 29 years ago; Wassermann —.
10/12	20. F. D.	45	♂	5.5	12	2.5	37	185	120	—	+	Chronic interstitial nephritis; pain in back, radiating to right thigh; mild grade of optic neuritis.
8/ 3	21. F. S.	20	♀	5.5	11	2.7	40	130	95	++	++	Acute parenchymatous nephritis, following administraton of salvarsan four months previously; generalized edema; frontal headaches; Wassermann ++.
4/15 4/27	22. C. Mo.	54	♂	5.4 3.6	15 16	2.3 2.9	36	212	164	+	+	Chronic diffuse nephritis; myocardial insufficiency; Wassermann ++++; edema of abdomen and chest.
9/ 7	23. S. P.	24	♀	5.2	15	2.5	60	130	92	+	— pus	Syphilis; fainting spells; headaches.
10/26	24. J. A.	32	♂	5.0	21	2.0	28	140	60	+	+	Chronic endocarditis; arthritis; palpitation of heart; dyspnea.
11/ 5	25. F. T.	47	♀	5.0	14	1.4	52	160	90	—	—	Hyperthyroidism; general weakness; loss of weight; bronzing of skin; scarlet fever as a child; typhoid fever.
11/19 12/ 8	26. K. W.	49	♀	5.0 4.2	22 19	2.5 1.6	28 37	225	140	++	+	Chronic endocarditis; chronic interstitial nephritis; decreased urinary output; dyspnea; scarlet fever as child.

* ♂ signifies male; ♀ signifies female.

tion of a definite compound, and, further, is more easily and more accurately determined. Where possible, however, both determinations are desirable. Folin and Denis divide their cases into the four mathematically possible groups, namely, cases with the uric acid and nonprotein nitrogen of the blood, both normal; cases with normal uric acid and high nonprotein nitrogen; cases with high uric acid and normal nonprotein nitrogen (gout); and cases with high figures for both uric acid and nonprotein nitrogen (nephritis). The classification they have employed is obviously valuable, although we believe the "staircase effect" of the retention of uric acid, urea and creatinin, brought out in our Table 3 is even more valuable, particularly as regards the so-called uric acid bloods. In agreement with Folin and Denis, we have likewise observed cases with moderately high figures for nonprotein and urea nitrogen but with normal figures for uric acid. These cases belong to quite a different group (some of them are cases of parenchymatous nephritis), and will not be discussed at present.

It will be evident from the present paper that there are many cases which have only a slight or moderate retention of urea, but in which there is a very marked retention of uric acid (Table 3, Groups I and II). We might refer to other cases in which there was present, in addition, a marked retention of urea, but in which the creatinin retention was comparatively slight (Table 3, Group III). In the cases of the latter group the prognosis from the urea alone would have been far different from that made in the light of the blood creatinin. Still other cases might be mentioned in which a greater retention of creatinin was present and proved the more valuable diagnostic sign.[1] The determination of uric acid, urea and creatinin obviously gives a survey of the character of nitrogenous retention that would not be possible from the urea alone. Other tests may, of course, prove of value. Thus, in many cases of severe nephritis, the acidosis may be a factor of greater moment than the nitrogen retention, as we have recently observed with the aid of Van Slyke's apparatus for determining the carbon dioxid combining power of the blood.

It may be well at this point to recall that the normal range of these nonprotein nitrogenous blood constituents is, for uric acid, 2 to 3 mg., for urea nitrogen, 12 to 15 mg., and for creatinin, 1 to 2.5 mg. per 100 c.c. of blood. An inspection of Tables 1 and 2 shows uric acid figures between 5 and 10 mg. In most instances the figures for urea nitrogen are likewise increased, the majority of observations being between 20 and 30 mg. per 100 c.c. of blood. The urea retention is, however, nothing like that encountered in more advanced cases of interstitial nephritis, as shown in Table 3. The figures for creatinin, on the other hand, are nearly all very close to, or only slightly above, the normal limits.

The data of Table 1 give the results of a series of twenty-six cases[23] in which the concentration of the blood uric acid is decidedly increased without a corresponding increase in the urea or creatinin. Some of these cases show symptoms which, in general, are characteristic of "early interstitial nephritis." In other cases, although the nephritis was not the predominant clinical condition, it would appear that the systemic disturbances resulting from, or associated with, a variety of conditions, such as tuberculosis, typhoid fever, pneumonia,

TABLE 2.—EVIDENCE OF "INTERSTITIAL NEPHRITIS" IN FOUR CASES OF DIABETES (THREE FATAL) AS SHOWN BY THE EXAMINATION OF THE BLOOD[24]

Date 1915-16	Case	Age	Sex	Sugar of Blood, Per Cent.	Sugar of Urine, Per Cent.	Uric Acid, Mg. per 100 c.c. of Blood	Urea N, Mg. per 100 c.c. of Blood	Creatinin, Mg. per 100 c.c. of Blood	CO_2* Combining Power of Plasma, c.c. per 100 c.c.
10/29	L. F.[1]	52	♀	0.80	2.2	10.5	55	2.1	37
10/30				1.10	0.5	...	..	...	31
4/10	M. W.[2]	53	♂	0.37	1.7	6.0	18	2.0	..
4/17				0.98	1.6	...	..	...	..
2/ 4	M. S.[3]	38	♀	0.53	1.3	5.0	44	2.3	49
8/26	B. S.[4]	46	♀	0.42	3.6	7.6	28	4.7	12

* Corrected values.

1. Duration of disease, several years; no coma until day of death, October 30; small amount of albumin in urine of October 26; 2.7 per cent. of sugar; only faint trace of acetone in urine.

2. Gangrene of toes at times during the last five years; glucosuria very severe early in the disease but later improved; systolic blood pressure 150 to 165 mm.; phthalein output 44 per cent.; moderate amount of albumin in urine of April 10; at death (April 18) urine showed only small amount of acetone; uremic symptoms thirty hours before death and about six hours previous to last blood analysis.

3. Shortness of breath; vomiting; increased frequency of urination; cloudy urine; history of scarlet fever; blood pressure 125 to 85; urine showed from faint trace to small amount of albumin; sugar, 1.0 to 1.5 per cent.; trace of acetone; no casts found; phthalein output 13 per cent.

4. Patient entered hospital in coma and died several hours later; urine contained very large amounts of albumin, acetone and diacetic acid, and many granular casts.

carcinoma, cardiac disorders, chronic alcoholism, etc., exerted the same influence on the kidney. It is not improbable that similar factors are at work in gout and the apparently uncomplicated cases of interstitial nephritis.

The data recorded in Table 2 are likewise of interest in this connection, since they clearly demonstrate a similar state of affairs in four

23. For the opportunity of studying the majority of these cases we are under obligations to the director of the Medical Department, Dr. Edward Quintard. We are also indebted to Drs. Samuel Lloyd, J. Bentley Squier, Arthur F. Chace and Robert H. Halsey for a number of interesting cases which they have brought to our attention.

TABLE 3.—Uric Acid, Urea N and Creatinin of Blood in Gout and Various Stages of Nephritis

Date 1915-16	Case	Age	Sex*	Diagnosis	Present Condition	Uric Acid, Mg. to 100 c.c. of Blood	Urea N, Mg. to 100 c.c. of Blood	Creatinin, Mg. to 100 c.c. of Blood	Phthalein Output 2 Hrs.	Systolic Blood Pressure	Urine	
											Albumin	Casts
9/ 3	M. K.	49	♀	I Typical case of gout	Unchanged	9.5	13	1.1	48	230	+	—
10/ 5	T. B.	57	♂			8.4	12	2.2	35	164	—	+
10/ 6	L. J.	43	♂			7.2	17	2.4	..	200	—	—
10/ 6	C. P.	..	♂			6.8	14	1.7	..	...	..	..
8/11	J. Ja.	65	♂	II Apparently early cases of chronic interstitial nephritis	Unchanged	9.5	25	2.5	..	185	+	+
9/25						8.0	37	2.7	13	150		
1/14						5.0	37	3.9	..	130		
6/ 7	D. S.	56	♂			7.1	16	2.0	..	...	—	+
7/21						6.6	24	3.3	26	185		
9/28						6.3	18	2.1	43	...		
9/21	D. D.	52	♂			8.7	20	3.6	20	100	+	+
8/13	J. Ju.	58	♂			7.0	33	2.6	..	175	+	—
8/ 3	C. M.	54	♂			6.3	31	2.1	23	150	—	—
1/ 6	L. P.	57	♂			8.0	80	4.8	0	240	++	++
3/ 1						4.9	17	2.9	10	170		

4/23	J. P.	34	♂	III Moderately severe cases of chronic interstitial and chronic diffuse nephritis	Improved	8.3	72	3.2	25	238	+++	++
5/21						5.3	21	1.9	43	145		
1/15	W. C.	49	♂			9.5	44	3.5	38	210	++	++
1/28						2.5	19	1.9	52	120		
8/ 6	L. B.	32	♀			7.7	67	3.1	..	165	++	+
10/ 1						6.7	17	1.6				
8/ 7	L. H.	39	♀			8.3	39	2.9	10	200	+++	++
8/24						6.5	24	3.0				
4/11	E. C.	50	♀	IV Typical terminal cases of chronic interstitial nephritis with uremia	Died	22.4	236	16.7	0	210	++	Pus
3/23	T. D.	34	♂			15.0	240	20.5	2-3	225	++	+
1/25	S. H.	37	♂			14.3	263	22.2	0	220	++	+
5/28	M. O.	8	♀			13.0	90	11.1	0	265	+++	+
4/15	J. W.	34	♂			8.7	144	11.0	Trace	225	+	+

* ♂ signifies male; ♀ signifies female.

The cases in Group I require no further comment here, while for Group II reference may be made to the same cases in Table 1.

The following remarks may be made concerning the cases in Group III:

L. P.—Chronic interstitial nephritis with uremia; marked edema of feet and ankles previous to admission; thickening of arterial walls; left hospital improved.

J. P.—Chronic diffuse nephritis; Wassermann ++++; generalized edema; left hospital improved.

W. C.—Chronic diffuse nephritis; chronic alcoholism; severe headache; mild generalized edema; probable edema of brain; severe acidosis on admission as shown by carbon dioxid combining power of blood (Van Slyke); improving.

L. B.—Acute parenchymatous nephritis; pulmonary tuberculosis; pericarditis; edema of feet, ankles and face; left hospital improved.

L. H.—Chronic interstitial nephritis; mitral regurgitation; dyspnea; occipital headaches; left hospital improved.

The cases in Group IV need no comment. The blood analyses reported were those made shortly preceding death.

advanced cases of diabetes.[24] In the first case it will be noted that the uric acid reached 10.5 mg. and the urea 55 mg. per 100 c.c. of blood, although the creatinin figure was quite normal.

The results collected in Table 3 summarize observations illustrative of those on which our views on this subject have been based. Typical cases of gout show, as a rule, blood uric acid values from two to five times the normal (Group I). The amounts of urea and creatinin are normal, or in the case of urea only slightly above normal. Many early cases of nephritis, probably of the interstitial type, give blood pictures which differ little from those of gout[25] (Group II). The uric acid findings are quite as high and the urea content varies from only slightly above to more than double the normal amount. The creatinin is only slightly increased. As the condition of the cases of this type becomes more severe, the retention of urea increases, until we have high values for urea as well as for uric acid (Group III). If improvement takes place, the concentration of urea gradually falls until the picture is that of the preceding group. If, on the other hand, the case goes on to a fatal termination, the retention of uric acid and urea is followed by that of creatinin, the concentration of which may reach twenty times the normal (Group IV).

SUMMARY

A series of thirty cases are recorded with high values for the uric acid of the blood, but without a corresponding retention of urea and creatinin. These cases were apparently suffering from "early interstitial nephritis," probably secondary in many instances to other systemic disturbances. Since the blood urea was not markedly increased or the phthalein output markedly decreased (in certain cases), it is believed that the uric acid was of considerable value as an early diagnostic test. The possibility is further suggested that a retention of uric acid may be earlier evidence of renal impairment of an interstitial type than the classical tests of albuminuria and cylinduria.

The blood pictures in early interstitial nephritis and gout are strikingly similar, particularly as regards the increase in uric acid. In view of the other clinical signs in common, it would seem that this similarity must be more than accidental.

---

24. Some of these cases have already received attention in another connection (blood sugar); Cf. Myers, V. C., and Bailey, C. V.: Jour. Biol. Chem., 1916, xxiv, 147.

25. The relation of uric acid to gout will be made the topic of a future communication from this laboratory by one of us (M. S. F.) and Dr. C. V. Bailey.

From the data in Table 3 it is evident that as the permeability of the kidney is lowered in the type of cases studied, it becomes apparent, first, by a retention of uric acid, later by that of urea, and lastly, by creatinin, producing a "staircase effect."