IK-21

Uremia

Etiology, Types and Diagnosis

L. G. ROWNTREE, M.D.
Minneapolis, Minn.

Reprinted from
THE JOURNAL OF THE IOWA STATE MEDICAL SOCIETY
January Issue, 1917

Uremia

Etiology, Types and Diagnosis

L. G. ROWNTREE, M.D.,
Minneapolis, Minn.

Reprinted from
THE JOURNAL OF THE IOWA STATE MEDICAL SOCIETY
January Issue, 1917

UREMIA*

Etiology, Types and Diagnosis

L. G. Rowntree, M.D.
Professor of Medicine, the University of Minnesota

Nature shields her secrets: yields them grudgingly. The human mind is inquisitive but speculative. Theories are readily advanced: disposed of with difficulty. Theories are important because theories control therapy. Utilizing method as a fulcrum, facts are occasionally pried from nature. New facts are usually anticipated or at least ante-dated by theories. New facts must needs be considered in relation to old theories. Uremia is not lacking in either facts or theories.

Theories Relative to the Cause of Uremia—1. Retention of products of normal metabolism. Babington[1], working with Bright eighty years ago, by crude methods determined that urea was present in the blood in abnormally large quantities. Bright believed urea toxic and accepted it as the cause of the clinical syndrome which he was encountering in nephritis, and he called the condition uremia or urea poisoning. Subsequent work showed urea to be relatively non-toxic, consequently it was abandoned as the cause of uremia.

The development of studies of renal function has recently revived interest in this old subject since the fact has been established that the large majority of the cases of uremia are associated with marked increase in the blood urea. New

*Read before the Rock Island meeting of the Iowa and Illinois District Medical Association, August, 1916.

1. Babington—Bright's article on Cases and Observations Illustrative of Renal Disease. Guys Hosp. Rep., Vol. i, 1836, p. 360.

light was thrown upon the subject by the work of Marshall and Davis[2] which showed that urea was found in practically all the tissues of the body (bone, skin and fat excluded) in the same concentration as exists in the blood, which indicates that the total urea content of the body is probably eight to ten times that of the blood.

Hewlett[3] has made an important contribution within the current year. In order to determine the toxic effects of urea in man, 100 grams of urea were taken by mouth within a few hours. "When the concentration of urea in the blood exceeded 70 mgm. per 100 cc. of blood the subject usually complained of headache, dizziness, drowiness, mental apathy, inability to concentrate attention, muscular weakness and fatigue, and slight muscular tremor." Hewlett believes that in the asthenic type of uremia the above symptoms can be justly attributed to the high concentration of urea.

Dr. Grave and I have repeated this experiment with somewhat similar results. Chart I reveals the findings in one of these experiments indicating the level of blood urea nitrogen, the output of urine and of urea, Ambard's constant and the duration and intensity of symptoms. The urea (100 grams) was taken between 10 A. M. and 11:30 A. M. Nausea was felt at 10:30, regurgitation occurred between 11 and 11:30 A. M. Headache with a dazed sensation, chilliness and inability to concentrate mentally appeared at 11:30 and persisted until 1 P. M. Headache was more severe in the upright posture. Between

2. Marshall & Davis—Urea, Its Distribution in and Elimination From the Body. Jour. Biol. Chem., Balt., 1914, Vol. xviii, p. 53.

3. Hewlett—Abstract of Discussion. Jour. A. M. A., Vol. lxvii, No. 13, p. 939.

10:45 A. M. and 1 P. M. four fluid stools were passed Thirst and diuresis persisted throughout the day. The most marked symptoms were encountered while the urea N of the blood exceeded 30 mgm. per 100 cc.

Chart II gives the typical results of similar experiments on dogs. Urea was fed in large quantities for a period of eleven days. At the end of four days the dogs became subdued and quiet. The following day the blood urea nitrogen was found to be 36 mgm. per 100 cc. The symptoms continued for five days and disappeared when the urea N fell below the level of 25 mgm. per 100 cc. Diarrhœa appeared in one animal. Nausea and vomiting were rather marked features.

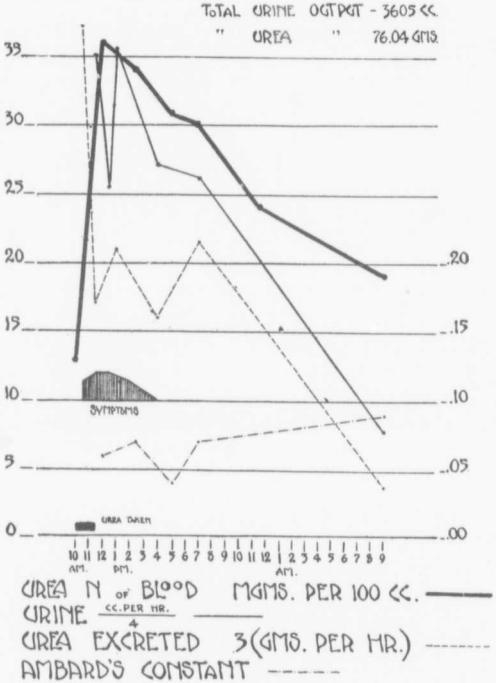
These findings are borne out in clinical experience. Personally I have repeatedly seen acute exacerbations of uremia manifestations follow the administration of high protein diet in chronic nephritis, while on the other hand I have seen chronic uremia disappear on low protein diet.

Urinary Poisoning—Clinical or experimental cases of anuria due to bilateral nephrectomy, tying off of ureter, impacted urinary calculi or mercurial poisoning yield a pure type of anuria. Anorexia, progressive asthenia and terminal stupor are, as a rule, the only symptoms observed under these conditions. Ascoli[4] calls this condition "urinary poisoning." He differentiates it from uremia, and in this Foster[5] concurs. In origin this differs from most instances of uremia from the point of view of its sudden and acute onset with the complete retention of water and simultaneously of all other constituents of urine.

4. Ascoli—Vorlesungen uber Uremie, Jena, 1903.
5. Foster—Uremia: A Differentiation of Types. Jour. A. M. A., Vol. lxvii, No. 13, p. 927.

I.

UREA FEEDING. MAN.



WCS.

In the majority of cases of uremia a selective retention is possible, the time element and different threshholds of excretion for various urinary constituents playing a role.

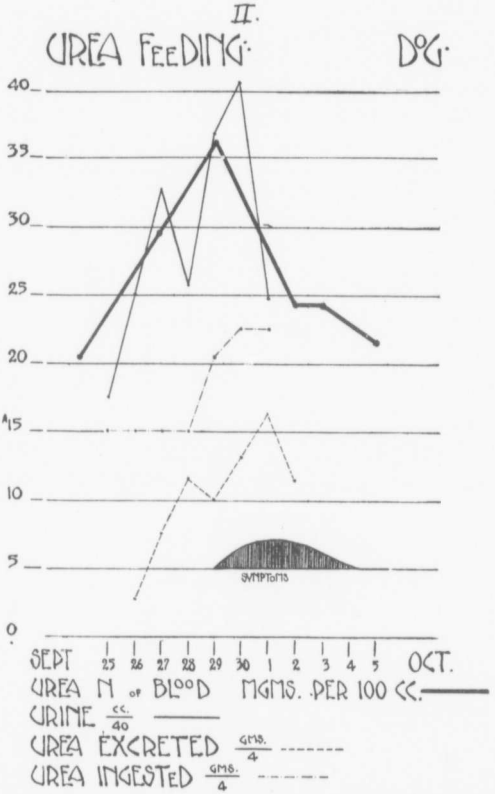
As the cause of uremia other urinary constituents have come under suspicion from time to time. Ammonia, creatinine, uric acid, trimethylamine, and the salts of potassium have all been considered possibilities. Recently abundant proof has been established as to the simultaneous accumulation of urea, creatinine and uric acid. The proof of casual relationship is still lacking. Dr. Grave and I are at present attempting experimentally to secure and maintain in the blood a level in these substances corresponding to that found clinically in uremia.

Hartman[6] has recently isolated from the urine a substance which he calls urinod—a bright yellow oil which gives the reactions of a cyclic ketone, to which he has ascribed the empirical formula C6H8O. Urinod has the odor of urine. Normally it is conjugated in the urine. In its free state it is extremely toxic. Hartman on injecting himself with a small quantity of this substance, developed intense nausea, extreme headache, loss of appetite, restlessness, insomnia and increased frequency of urination. If this can be confirmed it will have an important bearing on the subject of uremia.

2. Products of abnormal metabolism. The possibilities of an abnormal metabolism, or of the accumulation of products of an abnormal catabolism, must also be considered. That tissue breakdown does occur in uremia at times is proved beyond question. This, as a rule, appears shortly ante-mortem and may be observed in conditions other than diseases of the kidney.

Foster holds abnormal metabolism responsible

6. Hartman—The Symptoms of Urinod Poisoning. Arch. Int. Med., 1915, Vol. xvi, p. 98.



for at least one form of uremia. He has isolated a highly toxic crystalline substance from the blood in a series of cases of convulsive uremia.

The symptoms following the injection of animals with this substance are fecal discharges, convul-

sions, muscular twitchings and coma. The substance is isolated by a purely empirical method. Its constitution and nature being entirely unknown.

3. Edema of the brain, local or general. This theory is an old one introduced by Rees, and championed by Traube. Of late years it is gaining many new adherents. Fischer considers it the underlying cause in most cases of uremia. Widal and Straus are inclined to hold it responsible for at least the eclamptic type. Foster has reported three cases of uremia with practically normal renal function which, at autopsy, exhibited edema of the brain in addition to renal changes. For some years past I have felt that cerebral edema probably played an etiologic role in cases of uremia developing in so-called parenchymatous nephritis in which condition renal function approximates normal except in relation to the excretion of salt and water.

4. Acidosis. Acidosis has been held responsible. Von Jaksch[7] suggested this as long ago as 1888. Straub & Schlayer[8] and Fischer[9] particularly have recently championed this idea.

Interested in both acidosis and uremia, I have studied many cases and attempted to see a causal relationship. Taking as criteria of acidosis a diminished alkaline reserve of the blood, a decreased carbon dioxid tension of alveolar air, and an increase in hydrogen ion concentration of the blood, it must be admitted that acidosis does oc-

7. Von Jaksch—Ueber die Alkalescenz des Blutes bei Krankheiten.. Zeit. f. klin. Med., 1887, Vol. xiii, p. 350.

8. Straub & Schlayer—Die Uramie eine Saurevergiftung? Munch. med. Wochen,, 1912, lix, p. 569.

9. Fischer, Martin H.—The Treatment of Nephritis and Allied Conditions. Jour. A. M. A., May 13, 1913, Vol. lx, p. 1682.

Date	Alv. CO_2 mm. Hg.	pH Blood	CO_2 cap. of plasma. cc. of CO_2	Urea N.	T. n-p. N. mgm. per 100 cc. bl.	Creatinine	Phthalein & Ambard's	Remarks
4—17	29.72	7.2		97	171	—	Phth. 7%	$NaHCO_3$ 15 gms. daily
4—19	26.15	7.3	30.4	181	206	24	Trace / Am. C. 1.02	600 cc. 4% $NaHCO_3$ I.V.
4—20	25.67	7.5	37.57	158	203	19	— / 1.09	
Before 4—22	—	—	24.59	91	171	—	—	600 cc. 4% $NaHCO_3$ I.V.
After	—	7.6	26.45					
4—24	30.4	7.45	—	87	162	—	— / 0.41	
Before 4—25	39.4	7.3	31.7	84.5	—	—	—	Transfusion
After		7.45	31.94	67.	—	—	—	

cur in many cases of uremia. On the other hand death from uremia may occur without any suggestion of acidosis. As a result of personal studies, I am thoroughly convinced that the acidosis is not responsible for the uremia. Table I presents the results of one of these studies. The acidosis can be corrected without the disappearance of uremia and death from uremia may still occur. Except in acute uremia I have yet to see anything but temporary relief from the correction of the acidosis.

5. Inasmuch as the existence of an internal secretion in the kidney has not been proven, and since we know practically nothing positive in nature concerning nephrolysins, theories concerning them will not be discussed.

It is interesting that we are returning to the views of Bright. We may be nearer the truth as to the cause of uremia than were he and his coworkers. We have more theories: certainly we are no more definite.

Diagnosis of Uremia—Uremia is a term used to designate a symptom-complex, the manifestations of a toxemia resulting from renal insufficiency from any cause. Accepting this as the definition of uremia, the diagnosis becomes extremely simple. In the presence of this symptom complex it is only necessary to establish renal insufficiency. The clinical manifestations of uremia are too familiar to warrant discussion before this Society.

Renal insufficiency is characterized by definite functional changes which are easily ascertained.

The phenolsulphonephthalein excretion[10] is markedly reduced—usually to a trace, often to zero: the total non-protein nitrogen[11] of the blood is increased usually to more than 50 mgms. per 100 cc. of blood: the urea nitrogen [12] being chiefly responsible constituting from 75 per cent. to 85 per cent. of the total non-protein nitrogen: the uric acid and creatinine content are simultaneously augmented [13]: the freezing point of the serum is depressed below 0.60: Ambard's[14] constant, which indicates the ability of the kidney to excrete compared with that of a normal kidney with the same level of urea in the blood, is also increased.

In establishing renal insufficiency it is not necessary to apply all these tests. The phthalein output, together with the urea content of the blood usually yield all the information necessary for practical purposes.

Since the symptom-complex, *i. e.*, clinical uremia, is sometimes encountered in diseases of the kidney while functionally evidence of marked renal insufficiency is wanting, it becomes necessary to face the question as to what we must diagnose such conditions.

Types of Uremia—The differentiation of types

10. Rowntree & Geraghty—The Phthalein Test. Arch. Int. Med., March, 1912, Vol. ix, p. 284. For literature see Symposium—On the Study of Renal Function, by Christian, Janeway and Rowntree. Trans. of Cong. Amer. Physicians and Surgeons, 1912, Vol. ix, p. 1. Also Symposium on Uremia: Jour. A. M. A., Vol. lxvii, No. 13.

11. Folin & Denis—New Methods for the Determination of Total Non-Protein Nitrogen Urea and Ammonia in Blood. Jour. Biol. Chem., 1912, Vol. xi, p. 527.

12. Marshall—A New Method for the Determination of Urea in Blood. Jour. Biol. Chem., 1913-14, Vol. xv, p. 487.

13. Myers & Fine—The Significance of Uric Acid, Urea and Creatinine of the Blood in Nephritis. Arch. Int. Med., April, 1916, p. 570.

14. Ambard & Hallion—Relation Entre la Temperature do corps et l'activite Renale. Comptes. Rend. Soc. d. Biol., 1912, Vol. lxxii, p. 931. Ibid, 1912, Vol. lxxiii, p. 435.

is not exactly easy since many factors must be considered. Many bases of classification can be entertained, among which the following may be considered.

1. On the basis of symptoms. Emil Riess[15] has recently divided uremia into the following types:

1. Asthenic.
2. Psychic.
3. Convulsive.
4. Mixed.

He states that marked increased urea content and increased molecular concentration of the blood characterize groups one and four, but that these phenomena are usually lacking in the psychic and convulsive form. Foster, on the other hand, believes that the cases of the convulsive type "all show periods of clear-cut nitrogen retention." In addition they show an increase in the undetermined nitrogen. It is from this group that he has isolated the crystalline compound already referred to. My experience coincides largely with that of Foster but I have seen at least one case with convulsions which was considered by excellent observers as an eclamptic type of uremia in which there was no retention of nitrogen and in which renal function was practically normal. Inasmuch as arterio-sclerosis existed cerebral arterio-sclerosis could not be excluded At autopsy this was found to be the basis for the convulsions. Unquestionably many such cases have been considered uremia and perhaps they account to some extent for confusion in the literature in regard to the convulsive type.

15. Reiss, Emil—Zur Klinik und Einteilung der Uraemie. Zeit. f. klin. Med., 1914, lxxx, p. 97. Ibid., 1914, lxxx, p. 424.

2. On an etiologic basis Foster[16] has differentiated the following types:

A. Retention, urinary poisoning of ascoli.
B. Cerebral edema type.
C. Toxic type, or epileptiform uremia.

I find it difficult to accept this clinical differentiation between types one and three as I am convinced that convulsions occur in the ordinary retention type. The basis of classification is not constant since symptoms are brought into consideration in the last type.

3. On the basis of renal functional studies. Personally I would differentiate uremia into two types from the functional viewpoint.

First—Uremia associated with renal insufficiency, due in all probability to the accumulation of products of normal and abnormal metabolism.

Second—Uremia without renal insufficiency, in which group we have cases with disturbance of salt and water metabolism, the uremia being due to cerebral edema. This is a rare type of uremia. Certain other cases in which vascular changes are marked are frequently brought forward as uremia. Cerebral vascular changes are often responsible.

It is possible that in time we will only recognize the first group as true uremia and that physico-chemical studies will demonstrate that cerebral edema is dependent largely upon extra-renal factors.

4. According to the course of the disease.

A. Latent uremia. This is renal insufficiency in which the clinical manifestations have not yet made their appearance. The importance of its

16. Foster—Loc. Cit. (5).

recognition is obvious. It can be exemplified by the following case:

L. G., age twelve, admitted March 27, 1911, as an interesting case of diabetes insipidus. The past history contained nothing of importance except the passing of large quantities of urine and marked thirst. He was well nourished, not ænemic, apparently a normal-looking boy. His blood-pressure ranged around 100 mm. Hg. Some slight thickening of the radial arteries was noted: no definite eye changes. The urine on admission was large in amount, from 2,000 to 2,500 cc., clear, specific gravity 1005-1010. No albumin, no casts. At this time no suspicion of nephritis was entertained, although a trace of albumin had been noted once previous to admission. The phthalein test, performed March 28th, showed an output of only 7 per cent. for two hours. Three days later only 3 per cent. was excreted. With the exception of the phthalein findings absolutely no evidences of nephritis were present at this date. A week later he developed headaches, and a trace of albumin in the urine appeared. He rapidly became uremic and died April 9, 1911.

Autopsy: A most intense grade of chronic interstitial nephritis was present, with almost complete disappearance of the cortex. A slight grade of acute nephritis was superimposed.

B. Acute uremia

L. J. Johnson, colored girl, age twelve, admitted June 28, 1915. Chronic tonsillitis and chronic nephritis. Phthalein output 34 per cent. Patient comes back in the fall in uremic convulsions, phthalein output of 12 per cent, alveolar CO_2 23.4 mgm.Hg., pH 7.3. Patient bled 350 cc., given bromide and chloral for control of convulsions, sweated by hot packs and given a large quantity of alkali. In forty-eight hours the phthalein returned to 24 per cent., urea nitrogen to 16 mgm. and patient showed Ambard's constant of .33, the condition of renal function being much as

that seen on previous admission. All manifestations of uremia and acidosis disappeared under treatment. The acute exacerbation of the nephritis subsided but the chronic nephritis persisted.

C. Uremia with progressive renal insufficiency, as exemplified by—

Collins, a young negro, twenty years of age, admitted to the hospital for chronic nephritis. On admission the renal function was fair. Functional studies were made at weekly intervals. Each examination revealed a slightly greater reduction of renal insufficiency. The patient showed a step ladder descent into absolute renal function and died a typical death in uremia. The proximity of uremia was known to us long before any clinical manifestations appeared.

D. Chronic stationary uremia.

A man was re-admitted about one year after his discharge from the hospital with a zero phthalein output. Nausea and vomiting were present from time to time throughout this entire year. The patient died on second admission with an exacerbation of his chronic uremia.

5. According to the predominance of functional or organic changes, it is extremely important to recognize whether the case is one in which the uremia is due to organic or functional changes. The development of uremia in a case of marked chronic interstitial nephritis offers little in a permanent way as a result of treatment, whereas in an identical clinical picture encountered in back-pressure kidney such as seen in cases of enlarged prostate the prognosis may be good. This is familiar to the surgeon but not as a rule to the internist. I have known of several instances where the internist and surgeon have differed as to prognosis. Following the use of

the constant catheter, forcing of fluids, and limitation of nitrogen intake, uremia has disappeared and in some instances, following a subsequent prostatectomy, renal function has returned practically to normal.

These factors bear directly on the treatment of uremia since it is evident that the treatment is dependent upon our acceptance of one or the other of these underlying causes. In the vast majority of cases the treatment adopted is based on the theory of retention of products of metabolism. Indeed, I feel that it is wise to pursue this line of treatment in every case of uremia. When edema of the brain is present the question of mechanical relief of cerebral pressure may need to be considered. Lumbar puncture may be of the greatest value in cases with marked headache dependent upon cerebro-vascular changes. If acidosis co-exists alkali should be administered but only to the point of correcting the acidosis, not indiscriminately in all cases of uremia nor in the large amounts recently advocated. In every case of uremia it is our duty to determine if possible the underlying cause and to treat the case accordingly.