Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Extrarenal Uremia

Volume XI Friday, April 19, 1940 Number 25

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INDEX

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William A. O'Brien, M.D.

I. LAST WEEK

Date: April 5, 1940

Place: Recreation Room, Powell Hall

Time: 12:15 to 1:20 p.m.

Program: Movie: "Opening Day"
Gastroscopy
James B. Carey
Discussion
Macnider Wetherby
N. L. Leven
Owen H. Wangensteen
Gerald T. Evans

Present: 158

- - -

Date: April 12, 1940

Place: Recreation Room, Powell Hall

Time: 12:15 to 1:20 P.M.

Program: Movie: "Goofey and Wilbur"
Medical Photography
A. TerLouw

Present: 180

Gertrude Gunn,
Record Librarian.

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II. MOVIE

Title: "How to Raise a Baby"
A Robert Benchley Short
Released by: M-G-M.

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III. ANNOUNCEMENTS

1. THE ANNUAL ADDRESS of the C. M. Jackson Lectureship sponsored by the Phi Beta Pi Fraternity will be given by Dr. Walter C. Alvarez of the Mayo Foundation. Subject: Functional Gastrointestinal Disturbances, - Friday, April 26, 1940 at 8:15 p.m. in Medical Sciences Amphitheatre. Public Cordially Invited.

2. The CITIZENS AID SOCIETY LECTURESHIP sponsored by the Cancer Institute will be given by Dr. John J. Bittner, National Cancer Institute fellow, Roscoe B. Jackson Memorial Laboratories, Bar Harbor, Maine. Subject: Breast Cancer as Influenced by Nursing. Tuesday, April 30, at 8:15 p.m. in the Medical Sciences Amphitheatre.

3. The annual MEDICAL TECHNOLOGY BANQUET sponsored by Orbs, honorary medical technology society, will be held Thursday evening, May 9, at 6:30 p.m. in the Minnesota Union. Tickets 75¢.

4. VISITORS - EXECUTIVES' COUNCIL, University Hospitals, April 12:

A. B. Cook, University of Michigan, Ann Arbor.
Arthur J. Sullivan, University of Michigan, Ann Arbor.
Al Scheidt, Michael Reese Hospital, Chicago.
Stanley Ferguson, Chicago Lying-In Hospital.
G. O. Whitecotton, University of Chicago Clinics.
Albert W. Snoke, Strong Memorial Hospital, Rochester, N. Y.
Gordon Meade, Strong Memorial Hospital, Rochester, N. Y.
Lawrence Bradley, Strong Memorial Hospital, Rochester, N. Y.
Glen Clasen, University Hospitals of Cleveland.
G. W. Brugler, University Hospitals of Cleveland.
J. B. H. Martin, University of Indiana, Indianapolis.
E. J. Schea, University of Indiana, Indianapolis.
Robert Neff, University of Iowa, Ia. City.
Verne Pangborn, University of Iowa, " "
R. J. Conner, University of Iowa, " "
Sanford Johnson, University of Iowa," "
L. G. Schmelzer, University of Wisconsin, Madison.
A. B. Solon, University of Wisconsin, Madison.
C. C. Clay, St. Barnabas Hospital, Mpls.
Paul H. Fesler, Nopeming Sanatorium, Nopeming.
R. C. Buerki, Comm. on Graduate Medical Education, Chicago.
Peter D. Ward, Charles T. Miller Hospital, St. Paul.
R. M. Amberg, University of Minnesota
Charles Hayden, University of Minnesota Hospitals.
Robert Schenck, University of Minnesota Hospitals.

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IV. EXTRARENAL UREMIA

William W. Moir
John A. Layne

Definition

Extrarenal uremia is a clinical state characterized by elevation of the blood nonprotein nitrogen, loss of extracellular fluid and electrolyte (dehydration), blood pressure which is either normal or decreased, and oliguria which may progress to anuria. The primary factors responsible for the development of the uremia are extrarenal in origin. Should these factors persist even for relatively short periods of time, or be sufficiently marked in degree, unalterable changes occur in the kidney, and result in definite impairment of renal function. In the cases in which death occurs, however, structural changes in the kidney are either entirely absent or are of insufficient degree to account for the failure of renal function.

Extrarenal uremia may be differentiated from renal uremia by the normal appearance of the eyegrounds, blood pressure which is normal or low, the pattern of the previous illness, the high specific gravity of the urine (unless complicated by irreparable kidney damage), and usually a prompt response to adequate therapeutic measures. By definition are excluded from classification as extrarenal uremia all infectious or inflammatory renal disease, as well as tumors, strictures, anatomical variations or other causes of obstruction at any place in the urinary tract, nervous imbalances or paralyses which prevent the normal excretion of urine, as well as any damage to the parenchyma of the kidney from any cause.

Conditions in which extrarenal uremia may occur

It is important to recognize that extrarenal azotemia may occur as a complication or sequel to a number of disease conditions in which the patient may present no complaints referable to the uremia and in whom the elevation of the blood urea may be entirely overlooked unless sought for. The recognition and the degree of the uremia is important, moreover, in influencing the prognosis and treatment of the underlying disease. A complete list of these diseases is impracticable, but the diseases in which a significant degree of retention of nonprotein nitrogen in the blood has been found to occur most frequently are those in which dehydration was a prominent feature, whether it be from excessive diarrhea, vomiting, oligodipsia, or other causes. Similar factors are probably responsible for the retention of nonprotein nitrogen which occurs following severe burns, intracranial hemorrhage, and other similar conditions, but the discussion of these is not within the scope of this paper. In diabetic coma, a rise in the blood nonprotein nitrogen occurs in from thirty to fifty per cent of the cases. Extrarenal factors are frequently responsible for this increase; however, in many of the cases in which the uremia does not respond to treatment and death occurs, structural changes may be demonstrated in the kidneys at necropsy. Because of the role which extrarenal factors play in this condition, it will also be considered in the following.

The rise in nonprotein nitrogen following massive bleeding into the gastrointestinal tract is due in part, at least, to digestion and absorption of blood protein. Since elevated values of blood nonprotein nitrogen obtained after a gastrointestinal hemorrhage may be said not to represent a "fasting" level, many of these cases cannot properly be called extrarenal uremia. Because the blood nonprotein nitrogen may be elevated in this condition in the absence of structural changes in the kidney, a discussion of this subject is also included.

Dehydration

This state is brought about by an inadequate intake of water, and as a rule, in addition, an abnormal loss of extracellular electrolyte and water as a result of vomiting, diarrhea, diuresis, sweating, or through a fistulous tract. Clinically, this syndrome is character-

ized by oliguria or anuria, hemoconcentration, poor circulation, and diminished turgor of the skin. Other terms such as exsiccosis, anhydremia, and hypohydration have been proposed for this condition, but none of these are, as yet, in general use.

In dehydration the evidences of loss of fluid volume are confined chiefly to extracellular fluid. Extracellular fluid is characterized by its content of large amounts of sodium, chloride, and bicarbonate, and small amounts of potassium, phosphate, and magnesium. Blood plasma, lymph, interstitial fluid and cerebrospinal fluid represent its chief sources in the body. Gastric juice, bile, and the intestinal secretions are modified forms of extracellular fluid. Sweat and urine are also modified types of extracellular fluid which are lost to the body normally (within certain limits).

The intracellular fluid contains almost exclusively potassium and magnesium (basic ions) and organic phosphate and proteins (acid ions). Although the amount and concentration of these ions within the cell may vary, the relation of the amounts of these substances to another remains surprisingly constant[28], even in starvation, fever, and dehydrated states. Cellular membranes separate the two compartments containing the extracellular and intracellular fluid. Water is free to move between the two in response to osmotic forces. The effective osmotic pressure of these two compartments is due largely to concentrations of sodium and potassium, respectively. Therefore, the distribution of these two univalent bases is a very important, if not the chief factor, in controlling the distribution of body water.

Special manifestations of the loss of extracellular electrolyte and the resultant change in electrolyte pattern of the serum are also important. If the loss of sodium from the body is greater than the loss of chloride, acidosis results, since less than the normal amount of sodium is available to form bicarbonate. More than the normal concentration of bicarbonate is found in the serum if the loss of chloride exceeds that of sodium and alkalosis results.

All types of severe dehydration are accompanied by the essential features of shock. We refer here particularly to the inability of the body to maintain the blood circulation and blood pressure primarily because of decreases in the volume of the circulating fluid and not because of cardiac failure. Part of the picture of vascular collapse is believed to be dependent on arteriolar constriction, which, by preserving circulation to the brain, aggravates the deficiency in circulation elsewhere. As is well known, if severe shock is allowed to persist several hours, no therapy is effective.

Patients suffering from severe dehydration may be brought to the hospital in such a severe state of shock that the blood pressure cannot be obtained in the extremities by the usual methods. Although no direct measurements of the pressure in the renal artery in man have been made under these conditions, it does not appear unlikely that there is a corresponding decrease in arterial pressure here, also. The effect of a decreased pressure in the renal artery upon urine secretion has been repeatedly demonstrated under experimental conditions. Hermann[46] applied an adjustable clamp to the renal artery and showed that urine elimination increased or decreased when the renal artery was narrowed or reopened. Richards and Plant[74], using heart-lung-kidney preparations in rabbits, showed that changes in the perfusion pressure were accompanied by parallel changes in the rate of urine secretion. Of singular importance, moreover, are the observations of Visscher[92] in working with heart-lung-kidney preparations in dogs. He found that, when the blood supply to the kidney is completely interrupted for three or four minutes, reestablishment of blood flow through that organ is very slow and requires many hours, and that normal urinary function does not return in acute experiments if the complete interruption of blood flow exceeds 3 to 4 minutes.

That dehydration may lead to uremia is well known, and its seriousness has long been recognized, especially by pediatricians and physicians in tropical countries. Both starvation and thirst lead to excessive protein distribution. Despite severe dehydration, the kidneys may

continue to produce urine, although the quantity is generally less than normal. The urea apparently stimulates the excretory functions of the kidney and further aggravates the dehydration. A similar condition may occur as a result of polyuria preceding and eventually contributing to coma in diabetes mellitus. The dehydration, therefore, may be fairly severe in cases in which the volume of urine is near normal. In severe dehydration, however, marked oliguria or complete anuria develop.

It has been shown from the foregoing, therefore, that dehydration may lead to uremia in two ways; namely, through the inability of the body to maintain the normal circulation of blood and blood pressure because of a decrease in the volume of the circulating fluid, and because of the excessive catabolism of protein (endogenous). A third way in which dehydration leads to retention of nonprotein nitrogen is as follows.

The colloids of normal blood exert an osmotic pressure of 25 to 30 millimeters of mercury[66]. The arterial pressure in the glomeruli of the kidney, therefore, must be greater than 30 millimeters of mercury to insure formation of urine. It would appear, therefore, that the increased concentration of colloids in the blood in dehydrated states would require a greater arterial pressure in the kidney for glomerular filtration to occur.

It has been noted by Peters and Van Slyke[72] that most of the extrarenal factors that affect nonprotein nitrogen, urea, and uric acid do not influence creatinine to the same extent. Meyers and Laugh[68] stated that blood creatinine levels above 2.5 milligrams per cent occur almost without exception only in conditions with renal involvement. Increases in the level of blood creatinine have been found to run parallel to increases in nonprotein and urea nitrogen in the dehydrated states which follow high intestinal obstruction in man and animal by many investigators[60]. On the other hand, there have been an almost equal number of reports of experiments performed under similar conditions in which the rise of nonprotein and urea nitrogen were not followed by a rise in the creatinine level in the blood[39,40]. From the data at hand it is not clear just what "toxic" factors operate to cause a rise in blood creatinine levels in certain cases. A normal level of the blood creatinine in these conditions strongly suggests that increased catabolism of protein is a major factor in raising the level of the other constituents of the nonprotein nitrogen. From our own, as well as the observations of others, it is clear that hypercreatininemia is not a pathognomonic sign of nephritis or of irreparable kidney damage, nor that any considerable elevation of blood creatinine occurs only when loss of renal function approaches a fatal termination.

The specific gravity of the urine is an extremely useful finding, not only in differentiating extrarenal from renal uremia, but also is of aid in the prognosis in any given case where the factors responsible for the retention of nitrogen are believed to be chiefly extrarenal in origin. A small amount of urine of high specific gravity is characteristic of dehydrated states. When the dehydration is relieved by adequate amounts of extracellular electrolyte and water, the volume of urine increases, its specific gravity falls, and the level of nonprotein nitrogen in the blood returns to normal. On the other hand, if the dehydration has been sufficiently severe or prolonged before the start of active therapy, irreparable renal damage may have occurred. These cases are characterized by a relatively "fixed" specific gravity of the urine which is present at the time the patient enters the hospital or develops soon after this. It is these cases which are often found to be refractory to all therapeutic measures and which usually terminate fatally.

Obstruction of the Gastrointestinal Tract

Obstruction at the outlet of the stomach or in the upper jejunum regularly cause an elevation of the nonprotein nitrogen, increase in the carbon dioxide combining power of the plasma, and a de-

crease in the level of the plasma chlorides[22,36,39,44,60]. These changes appear, however, only when considerable fluid has been lost to the body, and usually require a minimum of forty-eight hours for their development[93]. The rise in nonprotein nitrogen under these circumstances is not due to the absorption of toxic products of protein digestion from the obstructed intestinal loops. The administration of saline in adequate amounts in these conditions is followed by a prompt return of these levels to normal. Moreover, uremia develops when the site of the obstruction is at the pylorus and exogenous protein is prevented from reaching the intestine.

The factors responsible for the elevation of the blood nonprotein nitrogen in these conditions appears to be chiefly extrarenal in origin. It has been shown by Whipple and his associates[22,60], Haden and Orr[39,40,41], and others, that the destruction of endogenous protein is increased in obstruction of the gastrointestinal tract. This destruction may be due to the combination of starvation and dehydration. The paraoral administration of physiological saline greatly lessens or prevents this increased catabolism of protein.

Walters, Kilgore, and Bollman[93] found that dogs with duodenal fistulae develop chemical changes in the blood similar to those occurring after intestinal obstruction. These changes, in the main, could be prevented by the administration of physiological salt solution.

Persistent vomiting, in the absence of organic obstruction in the gastrointestinal tract, if sufficiently prolonged and severe to produce dehydration and starvation, will cause an increase in the level of blood nonprotein nitrogen[72]. (See Case No. 3.) It is of interest, moreover, that the production of nausea and vomiting, independent of demonstrable changes in blood pressure or in hemoconcentration, result in a considerable fall in both urea and creatinine clearance, besides a decrease in rate of urine flow[19]. It has been found, moreover, that the clearance of urea falls more rapidly than does the clearance of creatinine.

It has been suggested that the uremia which develops in high intestinal obstruction is a physiologic retention of urea to compensate for changes in the osmotic pressure of the plasma due to hypochloremia, and this condition has been called "hypochloremic uremia." That this conception is in error now appears to be clearly established. In extrarenal uremia, the chloride level of the blood is usually normal or slightly elevated, and low values occur only when there is loss of chloride from the body (prolonged vomiting of gastric secretion), or when chloride is retained in the tissues (burns, pneumonia). That dehydration is the chief cause of uremia in these cases has been clearly shown from the experiments of Glass[38]. Hypochloremia was produced in dogs by gastric lavage or vomiting induced by apomorphine, half an hour after the injection of histamine. Sufficient food and water were allowed the animals, and neither dehydration or starvation occurred. Moreover, they lost little weight during the experiment and at postmortem the organs had a normal content of water. In the terminal stage of his experiments, the chloride content of the blood (and the body) had fallen to half its normal level. No increase of nonprotein nitrogen occurred in the blood except immediately before death.

There can be little doubt that prolonged dehydration resulting from upper intestinal obstruction may not only impair the efficiency of the kidney but produce irreparable renal injury. The rates of excretion of both urea and phenolsulfonephthalein were found to be diminished in dogs in which acute upper intestinal obstruction had been produced experimentally[60]. The marked rise in the carbon dioxide combining power of the blood which occurs in patients suffering from a high (but not complete) obstruction of the gastrointestinal tract, who have been given additional alkaline powders containing sodium bicarbonate has also been suggested as additional evidence in favor of an impairment of renal function[20]. The normal individual can excrete seven grams of sodium bicarbonate per hour, according to Cooke[20], and amounts greater than this are seldom, if

ever, given clinically.

The presence of albumin and casts in the urine does not necessarily indicate a kidney lesion which is demonstrable by our present histologic methods. The presence of these structures is frequently found in the urine of patients with extrarenal uremia, and their disappearance usually coincides with the return of normal urinary flow and the fall in the level of blood nonprotein nitrogen to normal.

Nevertheless, even though the power of the kidney to excrete nitrogen is impaired, the chief causes of accumulation of nonprotein nitrogen in the blood of patients or animals with high intestinal obstruction are dehydration and the increased destruction of protein. Moreover, such data as are available indicate that the kidney can concentrate urine to a high degree in these conditions, that even in spite of oliguria it can excrete in concentrated solution far more than the normal amount of nitrogen, and that nitrogen accumulation can be mitigated by the subcutaneous or intravenous administration of physiological salt solution.

Diarrhea

Dehydration may develop as a result of the water loss in severe diarrhea. If this becomes sufficiently grave, or if the fluid intake is inadequate, the level of the blood nonprotein nitrogen rises because the volume of urine is so greatly reduced. The loss of electrolyte in diarrheal stools is characterized by the fact that more sodium than chloride is excreted, and acidosis is the rule. Toxic destruction of protein exaggerates the effects of the dehydration. The diarrhea in Asiatic cholera may become so extreme and the blood volume so reduced that urine excretion is abolished. In the severer cases of cholera, the blood may be so thick that it will not run into the capillary tube of an hematocrit without the aid of suction[75]. Moreover, a blood pressure of 50 millimeters or less systolic is not uncommon in severe cases of this disease. The role which these factors (severe dehydration and hypotension) play in producing or contributing to the retention of nonprotein nitrogen has already been presented.

A definite relationship has been shown to exist between continued low blood pressure in the acute stages of the disease and post-choleraic uremia. Uremia has been found to develop most frequently in two classes of cholera patients - (1) very acute cases early in the disease; the majority of these recover if adequate therapeutic measures are instituted promptly; (2) mild cases in whom treatment is not started until 48 hours or longer after the onset of the disease, and a low blood pressure has persisted for a relatively long period of time. A high percentage of these patients die in uremia, urinary function having never returned to normal.

The marked effect of diarrhea in producing dehydration is illustrated by the study of Underhill and Errico[91] in dogs. These investigators found that the single administration of a saline purgative produced a distinct concentration of the blood (as measured by the hemoglobin percentage), up to 120 per cent of normal, reaching the maximum change during the second hour, with return to normal in six to eight hours. It has been recognized for some time that when sudden loss of water occurs from the body, the composition of the blood is much more affected than when the same loss is brought about more gradually. Vegetable purgatives, on the other hand, which do not depend upon the withdrawal of large amounts of fluid into the wall of the gut for their action, do not produce any change in the concentration of the blood.

Severe diarrhea interferes with the absorption of protein from the intestine and the fecal nitrogen loss may be considerable. In diarrhea brought about by exclusion from the intestine or insufficient production of pancreatic ferments there may also occur a considerable amount of undigested protein material in the stool.

The Treatment of Dehydration

This involves principally the replacement of extracellular electrolyte and

water, and the maintenance of the normal circulation and volume of the blood. Shock, if present, must be combatted first, and a blood transfusion of from 10 to 20 cc. per kilogram of body weight is given as soon as possible. One cannot predict which patients with dehydration severe enough to produce hypotension will recover from circulatory collapse when extracellular electrolyte and fluid have been restored, and it is safer to transfuse these patients should any doubt exist. Hemoconcentration may be brought about by shock alone; an increase in the erythrocyte count is not, therefore, a contra-indication to transfusion. Anemia may be an additional reason for giving a dehydrated patient a transfusion.

The restoration of extracellular electrolyte and water is accomplished by subcutaneous or intravenous infusions of physiologic solutions of sodium chloride or its modifications. In certain cases of acidosis, adjustment of acid base equilibrium may be accomplished by intravenous infusions of sodium bicarbonate or sodium lactate when saline solutions are found to be inadequate. In alkalosis, physiological saline is the appropriate treatment. The reduction of bicarbonate by the intravenous administration of dilute hydrochloric acid has been used in pediatrics[4,12]. The oral as well as intravenous administration of ammonium chloride has also been employed[28a,33a]. Only when salt is not necessary should dextrose solutions alone be used.

If nausea and vomiting are present, nothing should be given by mouth. Water and food which is regurgitated not only does no good, but actually does harm by increasing the loss of electrolyte in the gastric secretions. The same unfavorable result may be brought about by food (less often by water) when these aggravate a severe diarrhea.

No rule can be given as to how much sodium chloride and water must be given to a dehydrated person. Recovery from clinical evidences of dehydration, an increase in the daily output of the urine to more than 800 cc., a fall in the specific gravity of the urine to below 1.022, and an increase in the chloride concentration of the blood and urine may be used as a guide.

On the other hand, should the dehydration have been sufficiently severe or prolonged prior to the onset of therapy, irreparable changes may have occurred in the kidneys. These cases are characterized by continued oliguria or even anuria, specific gravity of the urine may show fixation at about 1.010 to 1.012 (see Case No. 4) and progressive elevation of the nonprotein nitrogen may occur, with fatal termination. It is in these cases that the continued administration of fluid, leading to venous congestion, cardiac embarrassment, the collection of fluid in the serous cavities, and pulmonary and peripheral edema, is contraindicated. If the oliguria persists in these instances, the continued administration of fluid is not only of no avail, but may actually shorten the life of the patient. In such instances the use of hypertonic saline[76] (10 per cent) or glucose (50 per cent) solutions have been reported to be of value by some authors. Neither these, nor the various other diuretic agents which have been suggested in these conditions are specific for the relief of the anuria, although their trial probably is advisable when this condition is met.

REPORT OF CASES

Case No. 1.

A 53-year old night watchman, was admitted to the medical service of the University of Minnesota Hospitals on February 19, 1937. During the evening of February 17 he developed chilly sensations, and at about 10:00 p.m. began to have frequent, loose, watery stools. This diarrhea persisted throughout that night and for the next two days, during which time he remained at home. In addition, he was unable to retain food or fluid by mouth, and vomited frequently. Blood was not observed in the stools. He experienced no additional chilly sensations or chills and his temperature did not exceed one degree of elevation.

He was admitted to the University Hospitals on the third day of his illness

in an extremely dehydrated state. Temperature was 97.2°F. The patient was conscious and oriented, and there were no convulsive movements. The skin was cold and had lost its normal turgor. The blood pressure could not be obtained in either arm nor could a pulse be palpated in either radial artery. The cardiac rate at the apex was 88 per minute. The surface of the tongue was coated and dry. The mucosa of the pharynx was a dull, dark red, and the patient spoke in a low, hoarse voice. On indirect laryngoscopic examination, there could be demonstrated a marked hyperemia of the mucosa of the larynx and the arytenoids. The vocal cords were normal in appearance and motion, and the hoarseness was attributed to the marked dehydration. Ophthalmoscopic examination revealed no abnormal changes in the fundi. The lungs were resonant throughout, and the breath sounds were normal. The heart was normal in size, shape, and position. The heart tones, however, were very faint; no murmurs were audible. The abdomen was somewhat tense; there were no areas of tenderness, however, and no masses were palpable. Rose spots were not present. The spleen was not palpable. Rectal examination was negative. There were no significant findings on neurologic examination.

Laboratory Examinations: The urine contained a trace of albumin and a few granular casts and white blood cells in the centrifuged sediment. The specific gravity of the urine at the time of admission, unfortunately, was not determined. Hemoglobin was 115 per cent; the erythrocyte count was 6,500,000. The leukocyte count was 8,600 of which 85 per cent were polymorphonuclear and 15 per cent were lymphocytes. The Wassermann and Kahn tests of the blood were negative. The level of the blood metabolites is shown in Table I. There was neither gross nor occult blood present in the stool. Bacillus paratyphosus B. was isolated from both feces and urine, and agglutinins against this organism were present in the patient's blood in a titer of 1 to 400.

The diagnoses were: paratyphoid B. fever, dehydration, and uremia of extrarenal origin.

Treatment and subsequent course. External heat was applied and the patient was given a transfusion of 400 cc. of citrated blood. Following this, the blood pressure readings of 120 systolic and 78 diastolic could be obtained. The blood pressure subsequently remained at about this same level. Small amounts of strong tea and boiled milk were given orally. Intravenous fluids (5 per cent glucose in physiological saline) were given in the amounts indicated in Table I. Indications of the patient's severe state of dehydration was the fall of 30 per cent in the initial hemoglobin percentage and erythrocyte count when fluid equilibrium had been restored and the fact that, in spite of an average daily fluid intake of 4400 cc., the patient's daily urinary output did not exceed 600 cc. until his fifth day of treatment. As soon as an adequate urinary output had been established, the nonprotein nitrogen content of the blood, which had reached a high level of 202 milligram per 100 cc. of blood on the fourth day in the hospital, gradually returned to normal levels during the following week. Of interest is the fact that the creatinine content of the blood, although not determined at as frequent intervals as the nonprotein nitrogen, decreased steadily from the time of admission and did not exhibit a similar rise. The phenolsulphonephthalein test in this case was further evidence of the presence of renal damage. On the patient's fifth day in the hospital the excretion of the dye was only 17 per cent in two hours; the urinary output on this same day was 1400 cc. Thirteen days later, at which time the level of the nonprotein nitrogen and creatinine were normal, there was 65 per cent excretion of the dye in two hours.

The patient's diarrhea was readily brought under control with the use of bismuth subcarbonate and calcium carbonate in doses of ten and five grains respectively administered four times daily. At the end of his ninth day in the hospital, the stools were normal in consistency and number, and his diet was gradually increased. The patient's temperature did not exceed 99°F, and his pulse varied between 80 to 90 per minute. He steadily improved, and was able to be

Table I

Case No. 1

Date	Days of Illness	Days in Hospital	N.P.N. mgm. %	Creatinine mgm. %	Uric Acid mgm. %	Chlorides mgm. %	P.S.P. Excretion in 2 hours %	Hgb. %	Erythrocytes in millions	Intake c.c. Oral	Intake c.c. I.V.*	Output c.c.
2-17	1											
2-18	2											
2-19	3	1	151	17.5	7.5			115	6.5	200	4300	100
2-20	4	2	85.5							450	3000	300
2-21	5	3	160	4.7	6.9					2000	3000	550
2-22	6	4	202							1700	3000	600
2-23	7	5	122	2.5			17	112	5.2	2400	3000	1400
2-24	8	6	104							2300	3000	550
2-25	9	7								2000	1500	1000
2-26	10	8	65.2			680				2100	2000	1130
2-27	11	9	32.3	1.06						3650	1500	2450
2-28	12	10								1800	1500	2400
3-1	13	11	35.4	0.86	2.2					1900	1500	1200
3-2	14	12						78	4.1	4000	1500	1700
3-3	15	13								550	1500	700
3-4	16	14								4950		1200
3-5	17	15								4300		1600
3-6	18	16								4000		1150
3-7	19	17								3650		750
3-8	20	18					65			3725		800

*5% glucose in physiological saline.

up by the end of his third week in the hospital. His hoarseness disappeared as soon as his hydration returned to normal. At the time of his discharge on the 27th day all tests of renal function were normal and paratyphoid B. organisms could no longer be obtained on culture of either the urine or feces.

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Case Number 2.

A 27-year old white male was admitted to the University of Minnesota Hospitals in a confused and disoriented state on August 29, 1939. The history was obtained from his father who accompanied him. A diagnosis of peptic ulcer had been made four years previously. The patient had never taken adequate care of this condition, however, and during the previous month he had experienced almost constant epigastric distress and had vomited frequently,--as often as several times daily. In addition, the patient had taken a considerable amount of sodium bicarbonate during this period, but the exact amount could not be determined. One week before his admission, he became confused, apathetic, uncooperative, and was taken to his local hospital. He failed to improve there, and was transferred to this hospital on August 29.

Examination. The patient was confused, disoriented, and uncooperative. He was quite dehydrated, and the skin had lost its normal turgor. Temperature was 99.6°F (rectal); pulse rate was 98 per minute. Blood pressure was 112 systolic and 68 diastolic. The fundi appeared normal. The pharyngeal mucosa was diffusely injected. The lungs and heart were normal. The abdomen was scaphoid; there were no areas of tenderness, and no masses were palpable. Both the Chvostek's and Trousseau's signs were positive.

Laboratory examinations. The highest recorded specific gravity of the urine was 1.016. It contained from a trace to 2+ albumin and a few hyaline casts. Hemoglobin was 99 per cent. The leukocyte count was 27,400 of which 86 per cent were polymorphonuclear, 10 per cent were lymphocytes, and 4 per cent were eosinophiles. The Wassermann and Kahn tests of the blood were negative. The benzidine and guaiac tests were positive for the presence of occult blood in the stool. The levels of the blood urea nitrogen, chlorides, calcium, and carbon dioxide combining power, and the plasma proteins are shown in Table II.

The diagnoses were: peptic ulcer; dehydration, alkalosis, and extrarenal uremia from prolonged vomiting.

Course. Physiological saline, or 5 per cent glucose in saline was given intravenously (Table I). The oral intake was augmented by gavage feedings. In addition, the patient received 10 milligrams of thiamin chloride, 50 milligrams of nicotinic acid, and 100 milligrams of ascorbic acid paraorally each day, as well as calcium gluconate intravenously and dihydrotachysterol after the low level of blood calcium had been noted.

The patient's condition remained poor in spite of all therapy and his confusional and disoriented state persisted with little change. As shown in the table, his urinary output during the last six days of life did not exceed 300 cc. daily in spite of an average daily total fluid intake of 3900 cc. There was no evidence of pyloric obstruction after the patient was admitted to the hospital, and he retained his gavage feedings without vomiting. The patient's general condition did not warrant roentgenologic examination. On September 2, his temperature rose suddenly to 102°F (rectal) and remained at approximately this level until his death three days later. On September 3 a discrete maculopapular rash developed on the face, trunk, and legs (the cause of this was undetermined), and a bilateral sustained ankle clonus appeared. There were no other changes in the neurological examination, although the patient's mental condition became somewhat worse. On the following day, the patient became dyspneic, and coarse bubbling râles appeared at both lung bases. Roentgen examination of the chest

revealed a marked hazy density, radiating out from both hilar regions, the appearance of which was interpreted as being consistent with an extensive pulmonary edema. The blood pressure varied between 120 to 144 millimeters of mercury systolic and between 60 to 90 millimeters diastolic up to the time of exitus on September 4. Unfortunately, no determinations of the blood chlorides were made during the last two days of life. It does not appear (see Table II) that sufficient salt was given to raise this level to normal. The possibility exists, therefore, that the hypochloremia may have contributed to this patient's death.

Necropsy Findings*. Only the positive findings are recorded. There was a generalized maculopapular eruption over the trunk, shoulders, and thighs. The peritoneal cavity contained 500 cc. of a clear, yellowish fluid. The liver extended 5 centimeters below the right costal margin in the anterior clavicular line, 10 centimeters below the xiphoid process, and weighed 1900 grams. There was 1000 cc. of amber, serous fluid in the left pleural cavity, 800 cc. of a similar fluid in the right, and about 20 cc. in the pericardial cavity. The surfaces of all the serous cavities were smooth, shiny, and glistening. The left lung weighed 1220 grams, the right 1050 grams. The bronchi were filled with frothy fluid. Marked edema was present in both lower and in the right middle lobes and to a lesser extent in the upper lobes. No pus was seen anywhere in the lungs. On the left anterior wall of the duodenum just distal to the pylorus there was a chronic ulcer measuring 2 by 1 centimeters. There was no evidence of perforation or hemorrhage. The right and left kidneys weighed 150 and 175 grams respectively and appeared normal on section. Except for a mild edema of the foreskin, there were no other significant changes in the urinary tract. The spleen weighed 220 grams and was normal on section; permission for examination of the head was not granted.

Microscopic examination. Liver: This organ showed an atrophy of the liver cells around the central veins. The sinuses were only mildly congested with blood.

Lungs. The appearance varied in different parts of the lungs. In general, the alveoli are filled with fluid, without evidence of inflammation. In a few areas, however, the alveoli are filled with polymorphonuclear leukocytes, erythrocytes, and fibrin, and a few large macrophages.

Kidneys. There were no significant changes present in the glomeruli, arterioles, or tubules. A moderate amount of protein and a few desquamated cells were present in the lumen of the tubules.

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Case Number 3.

A 54 year old male was admitted to the medical service of the University of Minnesota Hospitals on May 2, 1937. On April 29, three days prior to admission to this hospital, the patient developed intermittent sharp, crampy, abdominal pains, radiating from posterior to anterior, in the distribution of the sixth to tenth thoracic nerves. This pain was not relieved or aggravated by food. He vomited frequently during this period, and was unable to retain either food or fluid.

Examination. Patient was a white male, 54 years of age, in a moderately dehydrated state, somewhat undernourished, but in no acute distress. Pupils were irregular, and reacted sluggishly to light. Fundi were normal except for an early optic atrophy on the right. Blood pressure was 110 millimeters of mercury systolic and 56 diastolic. The configuration of the heart was of the left ventricular type. A protodiastolic murmur was present over the aortic area, and was transmitted downward along the left border of the sternum. The second tone over the aortic area was tambour in quality. There were no abdominal masses or tenderness. The deep reflexes were markedly hypoactive or absent, position and deep muscle sense were impaired in the lower extremities, and the Romberg test was positive.

*Necropsy performed by Dr. C. J. Lind.

Case No. 2.

Table II

Date	Fluid Intake- cc. Oral	(1) I.V.(2)	Urine Output c.c.	B.U.N. mgm. %	Blood Chlorides mgm. %	CO_2 Combining Power Vol.%	Blood Calcium mgm.%	Plasma Proteins-Gm.% Total	Albumin	Globulin	Blood Pressure
8-29			200								112-68
8-30	1700		300								
8-31	1000	3000	120								120/64
9-1	2300	5000	250	236	345	87					140/82
9-2	450	3000	200	243	452	67	5.5	6.6	4.0	2.6	144/92
9-3	1000	4500	150	238			6.2				148/88
9-4		1500		196			4.5	5.7	3.2	2.2	112/86

(1) Includes fluids administered by gavage.
(2) Intravenous fluids, for the most part, consisted of 5% glucose in saline. 3500 cc. of the total was physiological saline alone. Glucose in distilled water was not used at any time.

Laboratory Examination. The specific gravity of the urine was 1.032; neither albumin nor casts were present. Hemoglobin was 83 per cent; leukocytes were normal. The Wassermann and Kahn tests of the blood were positive. The level of the blood metabolites is shown in Table I.

The diagnoses were: Syphilitic heart disease, with aortitis and aortic insufficiency; gastric crises of tabes dorsalis; uremia of extrarenal origin.

Course and Treatment. Five per cent glucose in physiological saline was administered intravenously in the amounts shown in the table. Large amounts of fluid were not given intravenously because of the presence of the cardiac lesion. Not until the patient's sixth day in the hospital, however, did the urinary output exceed 800 cc. Following the administration of fluids, the level of the blood nonprotein nitrogen fell rapidly to normal limits. The level of the blood creatinine, taken at the time the nonprotein nitrogen was 65 milligrams per cent, was 0.99 milligrams per cent. The patient had no further complaints while in the hospital, and was discharged from the hospital on May 13, 1937, to the Out-Patient Department for antisyphilitic therapy. Roentgen examination of the gastrointestinal tract was negative.

Table III

Date	Days of Vomiting	Days in Hospital	N.P.N. mgm. %	Creatinine mgm. %	P.S.P. Excretion in 2 hours %	Intake - cc. Oral	Intake - cc. I.V.*	Output cc.	Blood Pressure
5-2-37	3	1					1500	200	110/56
5-3-37	4	2	143				3000	350	142/65
5-4-37	5	3	65	0.99		600	1500	550	132/52
5-5-37	6	4	35.8		75	600	1500	750	
5-6-37	7	5				1300	1350	450	
5-7-37	8	6				2200		1800	
5-8-37	9	7				2100		800	

*5 per cent glucose in physiological saline.

The Occurrence of Uremia in Diabetic Coma

The cause of nitrogen retention in diabetic coma has not yet been adequately explained. Hyperglycemia itself has no influence on this condition, since cases of coma occur without nitrogen retention. Furthermore, as Brunton[14] demonstrated, in the cases where retention of nitrogen does occur, no constant relation exists between the levels of sugar and nonprotein or urea nitrogen in the blood.

Insulin has no specific effect on either the level of nonprotein nitrogen or the urinary nitrogen excretion, although Joslin[49] has considered it possible that large doses of insulin in diabetic coma may be a factor in causing nitrogen retention. Insulin may occasionally cause hematuria[31,54], but the vast majority of well-treated diabetics, who have taken insulin for many years and who have not developed any evidences of renal damage, is strong evidence that this substance does not injure the kidney. Moreover, retention of nonprotein nitrogen occurred in diabetic acidosis before the advent of insulin, and mild cases of renal insufficiency occurring in diabetic coma are quickly relieved by its use. The cases which require the most insulin are those in which the diabetic coma is the most severe and in which, therefore, nitrogen retention would most probably occur.

The increase in nonprotein nitrogen appears to be a manifestation of the coma itself. Dehydration with a consequent relative increase in concentration of the chemical constituents of the blood may contribute toward elevating the level of these metabolites. Polyuria previous to the onset of coma, loss of fluid by vomiting, the excessive excretion of water vapor by hyperpnoea, and lack of an adequate fluid intake are the important factors concerned in the production of this state. The studies of Rowntree, Brown, and Roth[78] have demonstrated a reduction in plasma volume in diabetic acidosis. Bulger and Peters[16] interpreted the increase in hemoglobin erythrocyte count and plasma proteins in diabetic acidosis as evidence of dehydration. On the other hand, nitrogen retention may first occur only after the patient has been brought out of coma and dehydration is no longer present[64], and in such instances, may even progress to a fatal outcome. It would appear, therefore, that while dehydration is often a definite factor in causing nitrogen retention in diabetic coma, it is not the whole explanation.

Blum, Grabar, and Van Caulaert[9] have suggested that the increase in blood urea in diabetic coma was due to the depletion of chlorides in the plasma and tissues following a prolonged period of acidosis, and reported two cases of coma with marked nitrogen retention which

improved upon increasing the chloride intake in the diet. In this country, Root[77] reported three cases of diabetic coma with oliguria and nitrogen retention in which 60 cc. to 130 cc. of 10 per cent salt solution injected intravenously was followed by prompt improvement, resumption of the urinary flow, and relief of the nitrogen retention. In the majority of cases of diabetic coma with nitrogen retention which have been reported in the literature in which the chloride metabolism was investigated, the plasma chlorides were found to be either increased or normal. The evidence at hand, therefore, suggests that in diabetic coma it is not possible to regard increase in the blood urea as secondary to reduction in plasma chloride, nor, as has been suggested, that retention of urea occurs to compensate loss of chloride and maintain the osmotic pressure of the blood plasma where hypochloremia is present.

Diabetic patients, apart from complications, may suffer from their disease for long periods without the occurrence of nitrogen retention in the blood. Some degree of disturbance of nitrogen metabolism is present in diabetes. The difficulty in maintaining a satisfactory nitrogen balance in diabetes is evidence of this disturbance. In the pre-coma stage and in coma itself, this excessive catabolism of protein, largely of endogenous origin, is even more marked, and the loss of nitrogen in the urine may become enormous. However, a normally functioning kidney is capable of excreting these nitrogenous waste products. Should there develop a disturbance in tubular reabsorption, such as is believed to occur in diabetic coma, this increased catabolism of protein would produce a more rapid rise in blood urea nitrogen than would otherwise occur.

A failing circulation and low blood pressure, which have been shown to cause nitrogen retention, are often prominent signs in diabetic acidosis, and these factors may play a considerable part in the production of the uremia.

Direct injury to the kidneys through excretion of the ketone bodies or the acidity produced by them has been suggested by some authors[85] as the cause of the uremia. The objections to this hypothesis are:

1. There is no experimental proof that these substances are toxic to the kidney. Furthermore, if they were toxic, one would expect to find definite and uniform pathological changes in the kidney, comparable to the effects of mercuric chloride and other recognized toxins.

2. Severe ketosis may be unaccompanied by any signs of renal insufficiency.

Further experimental proof, therefore, is necessary before we can ascribe to these substances the cause of the uremia in diabetic coma.

Casts and albuminuria do not occur more commonly in healthy diabetics than in other persons. On the other hand, albuminuria is the rule in diabetic coma and is regularly accompanied by showers of short granular casts (the so-called "coma casts"). These casts, first described by Ebstein[30], tend to disappear as soon as the coma has begun to yield to treatment. Furthermore, they have been observed in severe ketosis apart from fatal coma and are not necessarily associated with functional renal failure.

It would be worthwhile to know what percentage of patients in diabetic coma have retention of nitrogen in any stage of the condition. Our series is too small to determine this point. Of the twenty-five cases reported by Lyall and Anderson[57], elevation of blood urea occurred in nineteen. Joslin[50] reports that twenty per cent of fifty-five patients with coma observed in a two-year period had on admission a nonprotein nitrogen value of 45 milligrams per cent or over.

Pathology. The reports of pathological studies of the kidneys from patients succumbing to diabetic acidosis accompanied by uremia are somewhat conflicting. The majority of writers, including Argy[6], Metzger[65], Warburg[94],

Snapper[85], Kraus and Scylo[52], describe the kidneys as being large, yellow, or fatty. No such agreement, however, is present in the histological descriptions of the kidney. Changes in the glomeruli suggesting early acute or mild subacute nephritis have been reported by Paddock[71], and Lowenberg and Joel[55]. More frequent are the reports of tubular disease. Argy[6] reported a necrosis of the tubules; Elmer and Schoos[32] noted vacuolation, granulation, and swelling of the tubules, and changes resembling those of nephrosis were reported by Metzger[65], and Bayer[7]. Labbe' and Boulin[53] compared the changes in the kidney to those resulting from mercuric chloride poisoning. On the other hand, many authors, such as Appel and Cooper[5], Weiss[96], and Coburn[20] were unable to find any renal damage at necropsy. While it appears from the conflicting nature of the above reports that there are no changes which are characteristic of the kidney in diabetic coma accompanied by nitrogen retention, changes have been demonstrated in the tubules by a majority of observers. This suggests that the uremia and oliguria which develops in some of the patients with this condition is due, in part at least, to a disturbance in tubular reabsorption. It can be stated, moreover, that the kidneys are not of the secondarily contracted type usually associated with nitrogen retention.

Prognosis. Although a moderate degree of nitrogen retention in the blood in the early stages of coma is not necessarily of grave significance, prolonged retention of any considerable degree is a serious prognostic sign. In the group of 51 cases of uncomplicated diabetic coma with elevation of blood urea collected by Labbe' and Boulin[53], and Lyall and Anderson[57], there were twenty-nine cases in which the blood urea was under 100 milligrams per cent; six deaths occurred in this group. In the twenty-two patients in whom the blood urea level was above 100 milligrams per cent, fourteen of the patients died. When oliguria persists in diabetic coma after adequate therapeutic measures have been instituted, the prognosis is very grave.

When recovery from coma occurs, the renal changes apparently are transitory. This would argue against any very permanent degree of renal damage in these cases. Whether repeated attacks of coma predispose the kidney to such changes is not clear from the data at hand or from reports of cases in the literature.

Treatment. The treatment of the uremia occurring in diabetic acidosis is essentially that of the underlying condition. Insulin is given to reduce the hyperglycemia and glycosuria, and physiological saline intravenously or subcutaneously is used to overcome the dehydration. Hypertonic saline solutions have been used by several authors (John[48], Root[77]) in successfully combating suppression of urine following coma. Blood transfusions have been suggested by Coburn[20], and many writers have advocated the use of isotonic solutions of sodium bicarbonate. The use of hypertonic glucose solution has been credited by some authors with the re-establishment of urinary flow[37]. Decapsulation of the kidney[52] has even been tried, although unsuccessfully. It appears, therefore, from this lack of a uniform treatment, that there is as yet no specific measure for combating the uremia which occurs in diabetic acidosis.

Uremia Occurring in Diabetic Acidosis; Study of Cases at University of Minnesota Hospitals

This study is concerned with the incidence of retention of nonprotein or urea nitrogen in diabetic patients above 16 years of age admitted to the University of Minnesota Hospitals in definite acidosis or in coma during a three year period from July 1, 1936 to July 1, 1939. During this period there were a total of 434 admissions for 316 diabetic patients. Of this number, 128 patients were males and 188 females. Their ages varied according to decades as follows:

Years	Patients
0 - 10	35
11 - 20	68
21 - 30	26
31 - 40	44
41 - 50	68
51 - 60	77
61 - 70	84
71 - 80	30
81 - 90	2

The major reason for admission of these patients to the hospital, and the number of admissions are as follows:

Control of diabetes	78 admissions
Diabetic acidosis or coma	56 admissions
Skin infections (Boils, carbuncles, and cellulitis)	25
Arteriosclerotic gangrene	25
Hypoglycemia	10

Admissions for nondiabetic or miscellaneous causes comprised the remainder.

A level of 40 milligrams per cent was selected as the upper limit of normal for the blood nonprotein nitrogen, and 20 milligrams per cent for the urea nitrogen. The criteria for the diagnosis of acidosis were: a level of 45 volumes per cent or lower of the carbon dioxide combining power, the presence of acetone or diocetic acid or both in the urine in appreciable amounts, and the clinical picture of acidosis or of coma.

In the group of diabetic patients above the age of 16, there were 31 (30 patients) who were admitted in severe acidosis. Eleven of these were males, nineteen females. In this group of 31 admissions, in 19 either the nonprotein nitrogen or urea nitrogen of the blood had been determined.

In ten of the nineteen patients there was elevation of nonprotein or urea nitrogen. (See Table I). There were five males and five females in this group, and the average age was 51 years. The blood sugar on admission varied between 495 and 723 milligrams per cent, the carbon dioxide combining power between 13 and 40 volumes per cent. In the table are shown the levels of nonprotein or urea nitrogen present at the time of admission to the hospital. In the five patients who died, death occurred within 48 hours in every case, and subsequent determination were usually not performed. In the five who lived, these levels had usually returned to normal limits within 96 hours after starting active therapy. The amounts of insulin given to all of these 10 patients attests to the severity of their diabetes.

In the 19 admissions for diabetic acidosis in which the level of nonprotein or urea nitrogen in the blood had been determined during this same period, there were nine admissions (8 patients) in whom there was no nitrogen retention. The average age for this group was 37.1 years. The blood sugar on admission varied between 105 and 400 milligrams per cent. The relatively low level of the blood sugar in some of these patients at the time of their admission to the hospital was due to the fact that they had received rather large amounts of insulin by their local physicians before starting to this hospital. The carbon dioxide combining power of the blood varied between 14 and 43 volumes per cent. The amounts of insulin administered to these patients during the first 48 hours of active therapy were not as large as in the group in which there was nitrogen retention. An average of 216 units per patient were given during this time period to the latter group, whereas in the group without nitrogen retention, only an average of 130 units per patient were required. This indicates chiefly that the degree of acidosis was more severe in the former than in the latter group of patients. All of the patients in whom there was no retention of nonprotein or urea nitrogen in the blood recovered.

This series is too small a one on which to base conclusions concerning prognosis in these cases. In our experience, however, diabetic coma occurring in the older age groups is more likely to be accompanied by nitrogen retention and oliguria; a fatal outcome may occur in these patients in spite of adequate therapy for the diabetes.

Table IV

Cases of Diabetic Coma or Severe Acidosis over 16 years of age, admitted to University Hospital in three year period (July 1, 1936 to July 1, 1939) in which a determination of the nonprotein or urea nitrogen had been done.

No.	Age	Sex	On Admission to Hospital				Total insulin given in first 48 hours Units	Outcome
			Blood sugar mgm. %	B.U.N. mgm. %	Blood N.P.N. mgm. %	CO_2 Combining Power Vol. %		
A. Cases with Elevation of Nonprotein or Urea Nitrogen								
1	40	F	543	27		15	185	R
2	77	M	632		105	21	285	D
3	47	M	633		72	14	255	D
4	63	F	565	57		21	200	R
5	39	M	495	40		18	125	R
6	22	M	723	21		17	365	R
7	44	F	703	58		14	180	D
8	56	F	553	38		34	260	D
9	75	M	632	72		40	95	R
10	48	F	590	50		13	230	D
B. Cases with Normal Nonprotein or Urea Nitrogen								
1	34	F	400		38	14	195	R
2	30	F	150		26	45	110	R
3	16	M	131	15		36	50	R
4	22	F	238		24	24	170	R
5	52	F	105	18		36	75	R
6	67	F	412		30	43	65	R
7a	17	F	253		31	31	155	R
7b	18	F	204	16		23	265	R
8	78	F	392	11.5		35	85	R

Case No. 4

A 44 year old housewife was admitted to the Medical Service of the University Hospitals on December 1, 1938 in a comatose condition. The history, as obtained from relatives, revealed that the patient was not known to have had diabetes but had suffered from polydipsia and polyuria for the past year. On November 27, 1938, these symptoms became more marked, and on the following day she complained of headache, anorexia, fatigue, and abdominal cramps. During the following two days the patient's condition remained about the same, and she was confined to her bed most of the time. On the morning of December 1, she became very drowsy and gradually lapsed into a comatose state later in the day. Her physician was then called, and she was referred to this hospital with a diagnosis of diabetic coma.

Examination. At the time of admission to the University Hospitals on the evening of December 1, the patient was in a dehydrated and comatose state. Respirations were Kussmaul in type, and an acetone odor was present on the breath. The patient was pulseless and the blood pressure could not be obtained. The apical rate was regular and 100 per minute. Temperature was 98 degrees F. (rectal). The face was flushed. The eyeballs were soft. There were no significant changes in the fundi. The remainder of the general physical examination was essentially negative except for diffuse abdominal tenderness; no masses were palpable, however. The extremities were cold, but otherwise normal.

Laboratory examinations. The urinalysis revealed a 4 plus glycosuria and was positive for acetone. Albumin varied from a trace to 2 plus, and numerous coarse granular casts were present. The specific gravity of the urine remained fixed between 1010 and 1012. The Wasserman and Kahn tests of the blood were negative. The level of blood metabolites is shown in Table V.

Treatment and subsequent course. Measures to combat shock were instituted immediately. External heat was applied, physiological saline and blood were given in the amounts listed in the table, and the patient received 160 units of regular insulin within the first five hours. Within four hours after starting active therapy, the patient was considerably improved and able to respond to questioning. At this time her blood pressure was 112 millimeters of mercury systolic and 65 diastolic. In spite of receiving 5000 cc. of fluid intravenously during her first five hours in the hospital, only 300 cc. of urine were excreted (through a catheter) during this same period.

On the morning of her second day in the hospital (14 hours after admission) the blood sugar was 170 milligrams per cent and the urine showed a one plus glycosuria. The patient had received 160 cc. of molar sodium r-lactate with 800 c.c. of distilled water during the night, and her carbon dioxide combining power at this time was 35 volumes per cent. The urine still contained one plus acetone, however, and an acetone odor was present on the breath. For the most part her condition remained fairly good that day, and her blood pressure remained at about 140 systolic and between 60 to 70 diastolic. The blood urea nitrogen was 58.1 milligrams per cent, but her urinary output did not exceed 30 cc. that day. Various measures, including the intravenous injection of 50 per cent glucose solution and 20 per cent sodium chloride solution were employed in an effort to promote a diuresis, but without avail.

Her condition gradually became poorer on the following day, accompanied by a progressive fall in blood pressure, decrease in urinary output and rise in the level of blood urea nitrogen to 83 milligrams per cent. Her diabetic state remained readily controlled during this period, and relatively small amounts of insulin were required. The glycosuria did not exceed one plus, but the carbon dioxide combining power failed to rise above 35 volumes per cent. The intravenous administration of additional fluids was contraindicated, since the patient developed ascites, edema of the face, eyelids, and lower extremities,

and rales at the bases of the lungs. The blood volume was measured at this time (five hours before the patient's death), and found to be 6.9 liters, of which 4.1 liters were plasma. The venous pressure was 12.5 centimeters of saline. The temperature rose terminally to 104 degrees F. (rectal), and the patient expired within 48 hours of the time of admission to the hospital.

Gross Postmortem Examination.* Severe posterior hypostasis was present. The cervical veins were markedly distended. The peritoneal cavity contained about 1000 cc. of clear amber fluid. The right and left lungs weighed 290 and 250 grams respectively. There was no edema of the lungs. The right and left kidneys weighed 130 and 150 grams respectively. Their surfaces were slightly and finely granular, and their markings slightly indistinct. There were no lesions elsewhere in the urinary tract.

Microscopic Postmortem Examination. The arterioles and glomeruli of the kidneys appeared unchanged. A moderate fatty degeneration of the tubular epithelium was present, and there was a mild amount of precipitated protein within the lumen of the tubules.

Table V

Days of Illness	Days in Hospital	Blood Sugar mgm. %	CO_2 Combining Power Vol. %	B.U.N. mgm. %	Creatinine mgm. %	Uric Acid mgm. %	Intake - cc. Saline I.V. or Subcut.	Intake - cc. Sodium Lactate	Intake - cc. Blood	Output cc.	Sp.Gr. of Urine	Blood Pressure	Insulin Units	Urine Sugar
5	1	703 578	14 14				4500		500	300	1.012	112/65	160	4 plus
6	2	170	23 35	58			3000	1000		150	1.010	144/72	20	Trace
7	3		19 32	77 83	5.3	5.3				30	1.010	118/52	20	Neg.

*Performed by Dr. Lawrence Berman

Elevation of the Blood Nonprotein Nitrogen Following Hemorrhage into the Upper Gastrointestinal Tract

In the past few years there have been numerous reports (2,10,11,18,24,25,26,29,47,66,79,81,88) of elevation of the blood nonprotein or urea nitrogen following hemorrhage into the upper gastrointestinal tract. Sanguinetti[79], who was among the first to note this condition, suggested that the retention of nonprotein nitrogen was due chiefly to absorption of products of decomposition of the blood. Since he thought that this resulted in a state of intoxication which might prove fatal, he recommended cecostomy in order to remove the blood. The recent experiments of Schiff and his associates[80] have shown, however, that the ingestion of amounts as great as 2000 cc. of citrated human blood by healthy individuals is not toxic.

Other factors have been advanced to explain the elevated level of nonprotein nitrogen. These comprise dehydration, starvation, shock, and impairment of renal function. The role played by dehydration in causing extrarenal uremia has already been presented and, in certain instances, decreased blood volume acts as a contributing factor in producing uremia. Furthermore, if the hemorrhage is of sufficient degree to cause shock, further retention of nonprotein nitrogen may occur. These factors are not negligible in cases severe enough to require hospitalization of the patient.

After severe hemorrhage, nitrogen catabolism has been shown to be accelerated[15,33]. This acceleration, however, may be an expression of the reduction of blood volume similar to changes that occur in shock and dehydration. Except in cases in which previous renal damage exists or follows upon severe dehydration or shock, impairment of kidney function is probably not a contributing factor in the development of the uremia following gastrointestinal hemorrhage. This is attested to by the absence of hypertension, the secretion of urine of high specific gravity, and normal tests of kidney function during this period[87]. Anemia appears to have no characteristic effect on nitrogen metabolism[72]. Although high values for blood and urine nonprotein nitrogen have been reported in patients with anemia, these abnormalities can probably be ascribed to associated renal disease or extrarenal factors such as already discussed.

Renal function, as measured by the rate of clearance of urea, inulin, and phenol red, is not altered following the intragastric administration of 2000 c.c. of citrated blood in normal subjects[80]. These determinations were performed at the time the urea nitrogen content of the blood was increased. These observations add further support to the contention that upper gastrointestinal hemorrhage, when uncomplicated by other factors, does not produce renal damage. No determinations have been made of the level of creatinine in the blood or urine under similar experimental conditions.

Sanguinetti[79], Ingegno[47], and others have suggested that the most significant factor in elevation of the nonprotein nitrogen of the blood in this condition was the digestion of the protein of the blood in the gastrointestinal tract, as no rise occurred when the blood was lost entirely through vomiting[29]. To test this hypothesis under controlled conditions, Schiff and his associates[80] give citrated human blood to a group of 15 individuals free of obvious renal disease. The blood was brought to room temperature and allowed to flow by gravity into the fasting stomach through a Reyfuss tube. In other experiments it was also introduced into the jejunum, upper ileum, and colon by means of a Miller-Abbott tube. About thirty minutes was required for the introduction. One thousand cubic centimeters were administered as a single dose to seven individuals, and a total dosage of 2000 c.c. were given to eight patients during a period of twelve hours. No nausea, vomiting or other ill effects followed the administration of the blood.

When the blood was given into the stomach, the urea nitrogen began to rise within two to four hours and reached a maximum of 30 to 46 milligrams per cent within twelve hours. Return of the urea nitrogen to normal levels occurred within eighteen to thirty-eight hours. When the

blood was given into the jejunum or upper ileum, the maximum rise in the blood urea nitrogen was somewhat less and occurred later (twelve to twenty-eight hours) This is apparently due to the fact that greater opportunity for digestion and subsequent absorption was present when the blood was introduced initially into the stomach.

It was also noted by these same workers (Schiff, et al) that following introduction of blood into the colon no significant change in the blood urea nitrogen was observed. This may be explained by the virtual absence of digestion and absorption in this region and coincides with clinical experience in cases of hemorrhage from the colon. This fact may be of value in differentiating colonic from gastric or duodenal hemorrhage.

Under experimental conditions as the above, the increase in the level of the blood urea nitrogen depends upon the amount of blood administered at a given time. This rise is apparently due to the protein content of the blood, as comparable rises occur following the ingestion of equivalent amounts of protein in the form of meat[80]. It appears, therefore, that the rise in the level of nonprotein or urea nitrogen of the blood which follows hemorrhage into the upper gastrointestinal tract uncomplicated by dehydration or shock, should not be spoken of as a type of extrarenal uremia, since it represents, rather, a non-fasting level of these metabolites.

Following hemorrhage into the upper gastrointestinal tract, neither sex nor age appears to be of significance in causation of the increased level of the nonprotein or urea nitrogen, although Ingegno[47] found the group of patients having an elevated urea to average ten years older than the group having normal values.

No significant correlation appears to exist between the degree of anemia in patients suffering from acute gastrointestinal hemorrhage, and the level of nitrogen retention in the blood[81]. It should not be inferred from this that the amount of blood loss bears no relationship to the degree of nitrogen retention. It is to be expected that the initial level of hemoglobin before the hemorrhage would vary widely in any group of such patients, and that a similar degree of variation would exist in their state of hydration and the degree of hemoconcentration at the time the blood levels were determined. Moreover, the rate of passage of the blood through the bowel determines the amoung of digestion and absorption of its protein content. Schiff and his coworkers[80] found that one individual had five loose bowel movements containing bright red blood twelve hours after receiving blood into the jejunum.

The passage of a tarry stool by a patient does not necessarily presage an increase in the nonprotein nitrogen level of the blood, even though the blood loss occurs from the upper intestinal tract. Daniel and Egon[27] found that a tarry stool could be produced in healthy subjects by the oral ingestion of 50 to 80 c.c. of venous blood. From the experiments of Schiff, it would appear that this amount is not sufficient to cause a significant rise in the level of nonprotein nitrogen.

The level of the blood nonprotein nitrogen following gastrointestinal hemorrhage is of some prognostic value, however. Its significance when dehydration or shock are present in severe degree have been discussed in a preceding section. When normal evacuation of the blood occurs from gastrointestinal tract, the level of blood urea nitrogen was found to have usually returned to normal limits within 72 hours after the intragastric administration of the blood, even with amounts as great as 2000 c.c. A persistently high level of the nonprotein nitrogen following upper gastrointestinal hemorrhage suggests that one or more of the following factors are present:

1. Previous kidney disease. The history of the patient, the ophthalmoscopic appearance of the fundi, blood pressure, specific gravity of the urine, and other tests of renal function may indicate the presence of previous renal damage.

2. The production of marked renal damage

through dehydration or shock, occurring concomitant with the gastrointestinal hemorrhage. This complication has been discussed in a preceding section.

3. Delayed passage of the blood through the jejunum and ileum may cause the level of nonprotein nitrogen to return to normal more slowly than would otherwise occur. The presence of blood in the colon, however, does not cause an increase in the level of the blood nonprotein nitrogen.

4. Continued bleeding. This not only increases the amount of blood (and protein) in the intestine, but tends to decrease the volume of the circulating blood volume, and so decreases glomerular filtrate. In the absence of demonstrable renal disease, therefore, a persistently high level of the blood nonprotein nitrogen is a serious prognostic sign, and one which demands prompt and vigorous treatment. The treatment of gastrointestinal hemorrhage, which is directed toward the prevention of further loss of blood, as well as the restoration of the normal blood volume, is, however, outside the scope of this report.

Summary

The factors leading to the development of uremia of extrarenal origin and the extent to which they may produce actual renal damage have been presented. Foremost among these is the loss of extracellular electrolyte and fluid, irrespective of cause. The factors which are responsible primarily for the development of extrarenal uremia may lead to the development of irreparable renal damage if they are of sufficient severity or duration. The specific gravity of the urine has been found to be of aid not only in the prognosis of such cases, but in differentiating uremia of renal origin from that of purely extrarenal causes. The treatment of this condition is discussed and four case reports are presented.

Inasmuch as retention of nonprotein nitrogen occurs in somewhat less than half of the cases of diabetic coma, a consideration of the extrarenal factors which lead to the development of uremia in this condition is also presented. In the majority of the cases of diabetic coma who develop uremia and fail to respond to adequate therapeutic measures, some degree of damage of the tubular epithelium can be demonstrated at necropsy. Although the extent of the histologic change in such instances is usually insufficient to account for the degree of uremia, it is not improbable that the excretion of ketone bodies by the kidney results in some degree of renal damage. Such cases, therefore, do not represent unqualified types of extrarenal uremia.

Also included in this presentation is a discussion of the use of nonprotein nitrogen which follows hemorrhage into the gastrointestinal tract. This increase in the level of the blood nonprotein nitrogen is apparently due to the protein content of the blood. This condition, therefore, when uncomplicated by dehydration or shock, should not be referred to as a type of extrarenal uremia, since it represents a non-fasting level of these metabolites.

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V. GOSSIP

"Let's Talk About Your Baby" by H. Kent Tenney, Jr., Associate Professor of Pediatrics, University of Wisconsin Medical School is just off the press. It originally appeared in 1934 as a little book published privately by Dr. Tenney for his patients. The University of Minnesota Press is responsible for the second and revised edition, and it sells for $1.00. The reviews by Edward Shaw, San Francisco; Albert D. Kaiser, Rochester; William A. Mulherin, Augusta, Ga.; Philip Van Ingen, New York City; Morris Fishbein; Henry L. K. Shaw, Albany; Borden S. Veeder, St. Louis; Leo Kanner, Baltimore; and our own Irvine McQuarrie; are so out of the ordinary in their frank praise that this in itself arouses one's curiosity. Most outspoken is Dr. Veeder who says, "I have a particular prejudice against books on the care of the baby. However, I enjoyed your book immensely and think you have done a very good job. It is most unusual in its attitude." The foreword is by Dr. Brennemann. There are seven chapters, a small record form, and an illustrated cartoon depicting normal development. The baby speaks for himself throughout much of the book. A smart child is he in his approval of sound pediatric practice. Physicians could well afford to give this book to their patients as part of their newborn advisory service. The book also could be recommended for medical students as well as interns and fellows....The Executives Council of the University Hospitals in this area made a favorable impression on everyone during their visit here last week. Both physicians and lay executives made up the group. Most of them looked young, and all of them appeared to have a good grasp of the special problems of university hospital administration. Staff problems in these institutions differ from those of the voluntary group. Most amazing is the ratio between resident staff (interns, fellows, and residents) and patients which averages one such person for every six to eight patients. One institution actually reported a ratio of 1:4. Some of our visitors were confused about our staff meeting, so we are sending them this bulletin to show them what we usually do....The Annual Meeting of the Medical Six-O'Clock Club was held this week. The new deal involved change of toastmaster and sabbatical leave for many of the old jokes. An old favorite was recalled in the person of Gordie Kamman, and new stars blazed across the firmament as the house came down with the sallies of Leo Radiologist Rigler and Buck Rogers Larson. The Medical Six O'Clock Club is an old institution which has been under the wing of Incas, honorary medical society, these many years. I knew it back in the days of its great revival under Obstetrician and Gynecologist Donald G. Tollefson, Los Angeles, who brought it back after it had temporarily died a political death. In former days, it lampooned the faculty with great vigor and effectiveness. Now it allows the faculty to lampoon itself. It meets once a year in the spring where formerly it met each quarter. In the transition days, one of these meetings was an all-medic dance....Staff members who do not belong to the Minnesota State Medical Association are welcome to attend any of the sessions of the Convention after the usual formula of registration (no fee). The dates are April 22, 23, and 24. Because of the unusual excellence of the program of round table luncheons the list is included in this issue of the Bulletin. If you are in Rochester on any of these dates, be sure to go to one of these luncheons.....The Department of Obstetrics and Gynecology has a new map showing the residence of patients in Minnesota with carcinoma of the cervix.....One of the large picture magazines spent most of last week preparing a story of the University of Minnesota Students' Health Service. The uncertainty of the appearance of such stories which share the fate of all other news items when news breaks is commonplace in modern journalism. The Health Service was originally studied by one of the subcommittees on the cost of medical care. It is generally acknowledged that with its new unit at the Agricultural Campus, its well-informed staff, and its comprehensive program there are no other better services in the country. Its present director, Dr. Ruth E. Boynton, is also enjoying national distinction through her office as president of the Student Health Service Association. There will be a special course in this field at the Center May 2 - 4, 1940.

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VI. MINNESOTA STATE MEDICAL ASSOCIATION

ROUND TABLE LUNCHEONS - Price, 75¢

Monday, April 22, 12:15 p.m.

Roentgen Therapy for Inflammatory Conditions: A. U. Desjardins, Rochester.
Management of Nephritis: N. M. Keith; M. W. Binger, Rochester.
Treatment of Peritonitis: J. M. Waugh, Rochester.
Oxygen Therapy: W. M. Boothby; W. R. Lovelace, Rochester.
Arthritis: Russell L. Cecil, New York City; P. S. Hench, C. H. Slocumb, Rochester.
Anesthesia: J. S. Lundy; E. B. Tuohy, Rochester.
Peripheral Vascular Disease: E. V. Allen; N. W. Barker, Rochester.
Diseases of the Blood and Their Treatment: C. H. Watkins; B. E. Hall; M. M. Hargraves, Rochester.
Diagnosis and Management of Common Skin Lesions: P. A. O'Leary, Rochester.
Management of Urinary Tract Infections: J. L. Emmett; E. N. Cook; T. L. Pool, Rochester.
Refraction: A. D. Prangen, Rochester.

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Tuesday, April 23, 12:15 p.m.

Chemotherapy (Sulfanilamide, etc.): W. W. Spink, University of Minnesota.
Office Gynecology: J. J. Swendson, St. Paul.
Management of Associated Injuries with Craniocerebral Injuries: Harry E. Mock, Chicago.
Medical Management of Gall Bladder Disease: E. T. Herrmann, St. Paul.
Diseases of the Kidney from a Diagnostic Standpoint: Bernard H. Nichols, Cleveland.
Allergy: A. A. White, Minneapolis.
Management of Peptic Ulcer: O. H. Wangensteen, University of Minnesota.
Common Diseases of the Rectum: W. A. Hansler, Minneapolis.
Contributing Causes of Arthritis: Paul B. Magnuson, Chicago.
Care of the Premature: A. V. Stoesser, University of Minnesota.

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Wednesday, April 24, 12:15 p.m.

Acute Abdominal Emergencies: John O. Bower, Philadelphia.
Causes and Prevention of Fetal and Neonatal Deaths: Fred L. Adair, Chicago.
Prevention of Vitamin Deficiencies in Patients Having Acute Medical and Surgical Diseases: Norman Jolliffe, New York City.
Otolaryngology in General Practice: L. R. Boies, Minneapolis.
Health and Delinquency: E. K. Clarke, University of Minnesota; Paul L. Schroeder, Chicago.
Refraction and Its Limitations for the General Practitioner: M. C. Pfunder, Minneapolis.
Treatment of Heart Failure: J. F. Borg, St. Paul.
Sex Hormones: C. D. Creevy, University of Minnesota; R. J. Moe, Duluth.
Management of Diseases of the Prostate: W. E. Hatch, Duluth.
Industrial Health: J. L. McLeod, Grand Rapids.

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