THE SYNDROME OF EXTRARENAL AZOTEMIA

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An elevation of the nonprotein nitrogen level in the blood in diffuse bilateral kidney diseases has been known to occur for some time; for instance, in glomerular nephritis, pyelonephritis, nephrosclerosis, heavy metal poisonings, renal tuberculosis, and congenital cystic disease. However, in 1914 Tileston and Comforte[1] in routine examinations of patients' blood for nonprotein nitrogen studies, using Folin's then new and accurate method of determination, noted a rise in the nonprotein nitrogen blood level in three cases of intestinal obstruction. They could demonstrate no kidney malfunction, and the nonprotein nitrogen returned to normal with cure of the patients.

The term "azotemia" refers to an increase in the level of the blood nonprotein nitrogen. In a normal person the level is usually given as 25 to 35 mg. per 100 c.c. of blood, and any value over 40 mg. per cent is considered abnormal. Urea, uric acid, creatinine, creatine, ammonia, amino acids, and some undetermined nitrogenous substances are the factors included in the nonprotein nitrogen. For practical purposes, an increase in the blood nonprotein nitrogen is usually due to an elevation of the urea or undetermined nitrogen, since the amounts of uric acid, ammonia, creatine, and creatinine are so small that huge increases would have little effect on the total nonprotein nitrogen.[2]

Many terms have been used to describe the azotemia which is not due primarily to renal disease. Among these are extrarenal, prerenal, hypochloremic azotemia or uremia. As stated above, these terms imply that there is no renal damage, but as will be shown later, there is an element of functional renal changes in most cases. It would seem then that the term extrarenal azotemia is somewhat of a misnomer but long usage gives the term proper connotation.

The phenomena of extrarenal azotemia has been noted in the following conditions: Intestinal and pyloric obstruction, gross intestinal hemorrhage, cholelithiasis, acute enterocolitis, cancer of the stomach, intestinal tumors, atrophic gastritis, hypertrophic gastritis, subacute pancreatitis, Addison's disease, excessive perspiration, rhinorrhea, polyuria, shock, starvation, congestive heart failure, Weil's disease, pneumonia, diabetes mellitus, burns, and drug intoxications.[3] The cause of azotemia in these dissimilar conditions may be explained by a few basic physiological mechanisms.

With normal conditions prevailing the level of nonprotein nitrogen of the blood is dependent on: (1) The adequacy of renal function in eliminating nitrogen in the urine, (2) in the amount of water available to perform this function, and (3) on the rate at which protein is broken down in the body.[4] The factors which influence the output of urine were summarized by Cubitt as follows: (1) The urine pressure, (2) changes in the secretion -- reabsorption activity of the tubule cells, (3) the blood pressure in the glomerular capillaries, (4) the area of the capillary bed from which filtration is taking place, (5) the osmotic pressure of the colloids in the plasma of the blood contained in the glomerular capillaries, (6) nervous control, and (7) hormonal control.[5]

Glomerular filtration pressure is a function of the difference between the hydrostatic pressure in the glomerular capillaries and the osmotic pressure of the colloids in the blood plasma (normally 30 mm. of Hg) plus the urine pressure in the intraglomerular space. The latter is normally negligible. The effective glomerular filtration pressure is thus produced by the balance in favor of the hydrostatic pressure.[6] If, therefore, the

blood pressure is reduced sufficiently, there should be a cessation of kidney filtration. This fact was proven by Lasser and Husfeldt[7] who produced a fall in blood pressure by using spinal anesthesia, and studied the effects of alteration of blood pressure on renal function. These investigators noted that urine output diminished directly with the fall in blood pressure until a systolic level of approximately 70 mm. of Hg was reached. The experiments were not carried beyond that point but the authors felt that a fall slightly below 70 mm. of Hg would cause complete cessation of urine output. With a diminution in urine production there would be a consequent retention of nonprotein nitrogen. The fall in blood pressure in Addison's disease and in shock-like conditions is apparently one of the causes of the azotemia.

As pointed out before, Tileston and Comforte noted a rise in the blood nonprotein nitrogen in three cases of intestinal obstruction. Speculatively, they attributed the phenomena to increase in production of nitrogen waste products and to dehydration due to vomiting. Subsequently an elevated nonprotein nitrogen has been noted in many unrelated diseases in which there is a loss of salt; for instance, in persistent vomiting, diarrhea, rhinorrhea, and excessive sweating. The loss of chlorides and rise in nonprotein nitrogen blood level in the above states caused much speculation as to the possible relationship between the two phenomena, hypochloremia and azotemia.

Blum[8] and his co-workers, arguing teleologically, thought the rise in nonprotein was a compensatory phenomena. With a loss of chlorides, the osmotic pressure of the blood would be decreased and the organism compensated for this decrease by nitrogenous retention. However, cell membranes

are permeable to nonprotein nitrogen and, therefore, it cannot raise the osmotic pressure.[9] They also believed there was an element of decreased kidney function due to chloride loss and this also caused nitrogenous retention.

Haden and Orr,[10] [11] in experiments in which animals were starved, their duodenum ligated, and adequate fluid intake maintained, attributed the rise in nonprotein nitrogen to a concentration of the blood plasma and to great increase in the tissue destruction taking place as shown by marked increase in nitrogen excretion.

Peters and others[12] thought the accumulation of nonprotein nitrogen in the blood was due to dehydration and consequent inability of the kidney to excrete sufficient amount of urine. Peters also believed that there was an increased catabolism of body protein.

Landis and his co-workers[13] have shown that when individuals were placed on a diet of constant protein content and adequate fluid intake, the average twenty-four hour urea clearance varied directly with sodium chloride restriction sufficient to produce hypochloremia. With restriction of salt intake the blood urea nitrogen rose and the urea clearance diminished. If sodium chloride was given, the twenty-four urea clearance increased and the blood urea nitrogen became normal. These investigators argued that since the fluid intake and urinary output were adequate, dehydration could not explain the changes in renal function. They think that the chloride ion must be a factor in renal function.

McCance[14] using four persons with normal kidneys who were given adequate fluid intake but salt-free diet and made to perspire profusely caused

azotemia to develop in each case. Renal function studies showed the urea clearance to be sixty per cent of normal. Clausen,[15] however, could not confirm the findings of Landis or McCance.

Kerpel-Fonrius[16] with some ingenious experiments on rabbits has shown that these previous investigators had been studying the wrong factor for the cause of azotemia in salt loss. In one set of rabbits he produced a loss of chloride without loss of sodium; in the other he produced a reduction of the blood sodium without diminishing the chlorides. All animals were given sufficient fluids. The animals with hypochloremia without hyponatremia showed no dehydration or azotemia. The animals with low hyponatremia showed dehydration and azotemia despite adequate fluid intake. Thus, it was shown that the important ion was sodium and not chloride in the production of azotemia due to salt loss.

Gomori and Podhradszky[9] pointed out the true significance of the above experiments as related to azotemia in humans. They believe that sodium loss leads to dehydration and thus causes azotemia, whereas loss of chloride is not itself a cause of azotemia. They argue that much needless speculation and experimentation could have been eliminated if the basic work of Gamble[17] had been heeded. Gamble and his co-workers, in 1925, postulated that a loss of sodium entailed a loss of water from the body fluids. He stated that "following obstruction of the pylorus there occurs in the vomited stomach secretions a loss of Na as well as Cl from the body. The sum of the concentration of the acid radicals in the body fluids being determined, owing to the adjustability of HCO_3, by the fixed base concentrations, a loss of chloride does not deplete the total ionic concentration whereas

loss of sodium does and also removes an equivalent of HCO_3." Reduction of the ionic content of the body fluids by withdrawal of Na is therefore the significant factor in the rapid dehydration following pyloric obstruction. The depletion of the total ionic content of the plasma and of the interstitial body fluids will be accompanied by an approximately parallel loss of water with the result that a normal total ionic concentration tends to be sustained at the expense of reduction of volume.[18] The dehydration involves blood plasma and intercellular fluids before it does intracellular fluids; the latter are preserved at the expense of intercellular and plasma fluids.[19]

Therefore, dehydration cannot be repaired by water alone but electrolytes must be given because if blood sodium is low, increased water will not remain in the plasma.

Consequently, Gomori and Podhradszky think that a hyponatremia will cause exsiccosis despite sufficient fluid intake and concomittently, azotemia. Dehydration would cause azotemia by the following mechanisms: By simple hemoconcentration and, therefore, relative increase in the non-protein nitrogen and by its effect upon the colloid osmotic pressure of the blood. As stated before the colloid osmotic pressure of the blood is normally 25 to 30 mm. of Hg. Gomori and Podhradszky in experiments on cats showed that with dehydration, the osmotic pressure of the blood proteins increased, in some cases to 60 mm. of Hg. The effective glomerular filtration pressure would consequently be greatly reduced and kidney function depressed. They, therefore, consider hyperproteinemia in dehydration an important factor in the causation of extrarenal azotemia. The fact that dehydration

also tends to lower blood pressure and to increase blood viscosity must also be considered. Diminished capillary pressure will decrease the effective glomerular filtration pressure and increased blood viscosity would impede the flow of blood through the kidney. These two factors would also tend to impair kidney function.

It is evident that hypochloremia and hyponatremia cause azotemia but by different mechanisms. In a patient who vomits only gastric secretions, a hypochloremia is produced and also an alkalosis for there is little sodium lost and, therefore, the blood sodium level remains stable. Chloride causes azotemia only in so far as the amount of fluid lost in the vomiting produces exsiccosis. When one considers that the secretions of digestive fluids amount to five to seven liters daily and this is two to three times the volume of the blood plasma (Rowntree)[20], it is seen that vomiting of gastro-intestinal fluids may amount to considerable fluid loss.

If, on the other hand, there is a loss of pancreatic secretion with its high sodium content there is produced a hyponatremia with a loss of fluids by the mechanism described, i.e. the blood plasma and extracellular fluids are diminished irrespective of fluid intake. Consequently there is dehydration with elevation of the blood nonprotein nitrogen by the mechanisms described. Incidentally, a loss of sodium would cause an acidosis.

That pure dehydration may cause a rise in the nonprotein nitrogen of the blood has been shown by Coller and Maddock[21] who performed experiments on normal adults. All the factors known to effect renal function were controlled and kept at an adequate level. The subjects were given

fluids only sufficient for caloric requirement and there was adequate salt intake. In each case the blood nonprotein nitrogen rose from a normal of 30 to 32 per cent to 40 to 45 per cent after two to four days of dehydration. The specific gravities rose to values of 1.031 to 1.041, while the daily urine excretion dropped to 440 to 480 c.c. Treatment with fluid alone caused reversion to normal of the blood and urine within one or two days.

Meyler[22] believes the rise in nonprotein nitrogen in dehydration is due to toxic protein destruction. The nitrogenous end products are not excreted sufficiently because there is a more or less marked oliguria. Renal function is also impaired under the influence of the lack of fluid and the hypotension.

Peters and Van Slyke[2] also emphasize the importance of protein catabolism in influencing the level of the blood nonprotein nitrogen. It seems possible that protein catabolism might occur at such a rate that the kidneys would be unable to excrete the nitrogenous waste products rapidly enough to prevent a rise in the blood level.

The role of the kidney in the production of extra renal azotemia is strongly supported by Fishberg.[23] He argues that the tests of kidney function afford direct evidence of the functional impairment of the kidneys in extrarenal azotemia. According to Fishberg a fundamental criterion of impairment of renal function is a concentration of the urine disproportionately low in comparison to the volume. A specific gravity of 1.020 is evidence of good kidney function when the urinary volume is very small, e.g. under 400 c.c. in twenty-four hours. Such a disproportionately low

concentration of the urine is demonstrable in at least the vast majority of instances of extrarenal azotemia. In most of the patients with extrarenal azotemia, comparison of the specific gravity with the urinary volume shows that the concentrating ability is definitely decreased, i.e. impairment of tubular reabsorption has been added to diminished glomerular filtration. Fishberg says that if one follows the course of a case, progressive impairment of the concentrating ability is evident. At the start there is oliguria accompanied by a fairly high specific gravity of the urine, which then progressively decreases despite the fact that the urinary volume does not rise and may also decrease. The interpretation that Fishberg gives these facts is that first, only glomerular filtration is retarded but that later impairment of tubular function occurs. The specific gravity of the urine may become fixed around 1.010 despite oliguria, just as occurs in primary renal diseases and it may be several days after the cause of the extrarenal azotemia is removed before the concentration power of the kidney is restored.

Necropsy reveals nothing wrong with the kidneys in many cases, but in most there are intact glomeruli but the tubules have degenerative changes such as cloudy swelling, hyaline droplet degeneration, fatty changes, or even necrosis of isolated cells. These changes are nonspecific and the primary pathogenic factor according to Fishberg in most, if not all, instances of extrarenal azotemia is decreased blood flow through the kidneys. In the common conditions leading to azotemia circulatory failure of a peripheral type is present. This results in a decreased venous return and, therefore, a diminished cardiac output. The symptoms are those of shock and some or all of these symptoms to a greater or lesser degree are

present in azotemia. The cause of peripheral circulatory failure is a decrease in circulating blood volume. The drop in cardiac output is manifested by decreased blood flow through the organs, the kidneys as well as others.[24] Since Van Slyke et al have shown that urea clearance is a direct function of the amount of blood flow through the kidney, it follows that urea retention will occur with decreased blood flow. Therefore, Fishberg says, a decrease in blood flow through the kidney diminishes simple filtration and also the decrease in blood results in a limited oxygen supply to the kidney, which ordinarily has a great oxygen consumption. The low oxygen tension effects kidney function and may also explain the degenerative changes seen in the kidney at necropsy.

This explanation by Fishberg of the mechanism of extrarenal azotemia seems entirely sound, but the emphasis is too much on the kidney itself and does not take into account the effect of dehydration on the hemodynamics and water balance of the organism.

Because of the many metabolic functions of the liver it is not surprising that a derangement of the liver may affect the blood level of nonprotein nitrogen. The deaminization of function of the liver was demonstrated by Bollman, Mann and Magath[25] on hepatectomized dogs. In these animals deaminization did not occur and there resulted a rise in amino acid nitrogen in the blood and a decrease in urea nitrogen. A rise in the blood nonprotein nitrogen due to amino acid nitrogen has been noted clinically.

These five mechanisms outlined, fall in blood pressure, dehydration, increased protein catabolism, local kidney disturbance, and liver

damage, can be employed to explain the elevation of the blood nonprotein nitrogen in various clinical entities. In a given case several of the mechanisms may enter into the picture for they are interrelated and these combined actions culminate in the elevation of the nonprotein nitrogen blood level.

Azotemia occurs, as has been pointed out, in many varied and unrelated clinical conditions. An analysis of the causation in a few instances will be attempted according to the mechanisms outlined.

Since Tileston and Comforte first reported their cases, innumerable investigators have noted the rise in nonprotein nitrogen in cases of protracted vomiting caused by such conditions as pyloric and intestinal obstruction, hyperemesis gravidarum, and severe gastritis. The conditions have been studied both clinically and experimentally. The cause of the azotemia as has been shown is direct loss of fluid by vomiting, and if intestinal in origin there is loss of water. The fluid loss with consequent dehydration leads to hemoconcentration and a relative rise in nonprotein nitrogen content of the blood.

Severe gastro-intestinal hemorrhage as a cause of azotemia has been shown repeatedly. It has been closely studied, particularly in the Scandinavian countries. Here several mechanisms interact as a cause of the axotemia. Primarily there is shock with a fall in blood pressure and a redistribution of the blood. The hemorrhage also results in fluid and salt loss with resultant dehydration and disturbance of the hemodynamics. Also, much of the blood lost is digested and reabsorbed, and being mostly protein, it also will influence protein metabolism. [26,27,28,29]

Diseases of the liver may cause an extrarenal azotemia. Stadie[30] and Van Slyke noted this in a case of acute yellow atrophy, Stander in[31] chloroform poisoning, and Wakeman and Morell[32] in careful studies on chemistry and metabolism in experimental yellow fever. Not very rarely when convalescence seems smoothly initiated after operation on the gall bladder or common duct, after an interval of one to six or even more days, malaise develops, the temperature rises, oliguria sets in, the nonprotein nitrogen rises, the patient becomes restless, and then perhaps delirious or comatose, and may succumb with the clinical picture of uremia. A similar picture has been observed following traumatic pulpification of the liver and may occur during acute liver degeneration or in acute exacerbation of chronic liver disease. While marked degeneration of the renal tubules may be found at necropsy, in other cases despite azotemia and the clinical picture of uremia, little morphological change in the kidneys is demonstrable. The syndrome just described has been spoken of as the hepatorenal syndrome or "liver death".[33,34,35]

Unfortunately, discriminating chemical studies are not available in most cases. It would seem logical, however, that with marked liver damage with rise in nonprotein nitrogen, it could be attributed to disturbance in deaminization function of the liver and consequent rise in amino acids in the blood.

In diabetes with acidosis, either in coma or precoma or in complete absence of cerebral symptoms, marked retention of nitrogen may be found as is well known. Significant azotemia is present in about one-half of comatose diabetics. The azotemia may continue to mount after the patient

has been brought out of coma by insulin. The azotemia usually occurs only after a protracted period of acidosis with polyuria.[36]

Peters et al[37] attribute the azotemia to dehydration and salt depletion as well as acidosis. This is due to loss of fluid from polyuria and loss of base for ketone neutralization. There is, therefore, a decrease in blood volume, with consequent decrease in blood pressure and increase in the percentage of blood protein. This decreases filtration pressure and raises the osmotic tension.

In the crisis of Addison's disease, there is a rise in the nonprotein nitrogen of the blood. The same occurs in a much more pronounced degree in experimental removal of the suprarenal glands as pointed out by Marshal and Davis[38] and confirmed by Rowntree.[39] Later the role of the adrenal glands in sodium metabolism was demonstrated by Loeb.[40] It was shown that in adrenal insufficiency there was a loss of sodium from the blood via the urinary route.

The work of Gamble[17,18,19] adequately shows that loss of sodium entails water loss. Dehydration and the low blood pressure of Addison's disease would seem to explain the rise in nonprotein nitrogen of the blood. However, some investigators do feel that the adrenal gland does control the kidney excretion of urea directly.[41] Loeb et al were unable to explain the azotemia of Addison's disease by purely extrarenal factors. From the evidence of their experiments they postulated "that the adrenal cortical substance acts on the kidney to control the excretion not only of the sodium but also of urea. In adrenal insufficiency, the rate of salt excretion

is increased while urea elimination is retarded.

The adrenal gland has been indicted as the cause of extrarenal azotemia in other conditions other than pure adrenal insufficiency. Wohl and Brust[42] in experimental intestinal obstruction of dogs noted definite histologic alterations in the adrenal gland. The zona glomerulosa had a "moth eaten" appearance with loss of cell contour, and shrunken nuclei, while the zona fasiculata had a granular cytoplasm apparently devoid of lipoid material. Similar changes have been noted in severe burns in which there is marked azotemia (Simpson[43]). He also noted hemorrhagic changes in the adrenals in conditions such as pneumonia and other infectious diseases in which there may also be a rise in the nonprotein nitrogen. It would seem that the adrenals may play a larger part in the production of extrarenal azotemia than it is generally considered.

In coronary thrombosis with shock, the nonprotein nitrogen occasionally rises notably and may exceed 100 milligrams per cent, as reported by Steinberg.[44] Nitrogen retention was present in five of six fatal instances of myocardial infarction studied by Steinberg. He noted very high specific gravities of the urine and usually albumin and casts were present. Urinary suppression was common. He emphasized that continued elevation of nonprotein nitrogen indicated a poor prognosis.

Widespread burns are a frequent cause of azotemia. Underhill et al[45] first showed the marked concentration of the blood in severe burns. The loss of fluids from the denuded areas, the tremendous shock present with extensive burns, and absorption of devitalized tissue explain the rise in non-

protein nitrogen. The sodium chloride metabolism in burns has been studied by Davidson[46] and diminished blood sodium is another factor. The role of the adrenals has already been pointed out.

The occurrence of increased blood nonprotein nitrogen in traumatic shock and shock-like states has been studied by Moon.[47] He discusses the causes as being mainly drop in blood pressure and loss of effective blood volume due to shunting into stagnant depots. The appearance of azotemia postoperatively is common, according to Derow.[48] He emphasized lowered blood pressure, insufficient fluid intake, vomiting and increased protein catabolism as causal factors.

The clinical manifestations of extrarenal azotemia are, of necessity, modified and usually overshadowed by the basic causal diseases. The main features are weakness, dizziness, mental confusion progressing to stupor or coma. There may be vomiting and diarrhea. The skin and mucous membranes are dry and inelastic and there may be deposition of uremic crystals on the skin. The eyeball is inelastic and there may even be a urinous breath. Muscular twitchings may be present. The blood pressure is low. Indeed, Fishberg states that extrarenal azotemia may resemble classical uremia due to renal insufficiency in all its manifestations. Harrison and Morton[49] are of the same opinion.

The laboratory findings are of great value in determining the presence of extrarenal azotemia. The urine will show a diminished volume output and an elevated specific gravity. The reaction is usually alkaline except in a few cases such as diabetic acidosis. Renal function tests are

within normal limits. In the blood one will find an elevated nonprotein nitrogen. Possibly the dehydration is extensive enough to show an increase in the cellular elements and hemoglobin. The hematocrit value may be elevated. The blood chloride level should be low and the blood sodium level may be lowered though not necessarily so. The carbon dioxide combining power is either increased or decreased depending on the underlying factors. Usually it is increased indicating an alkalosis.[23]

To differentiate extrarenal azotemia from uremia due to renal insufficiency one must consider the entire clinical picture.[42] The onset is sudden whereas in true uremia it is insidious. There is no history of preceding nephritis, no rise in blood pressure, and no abnormal changes in the retina.[42] Wohl and Brust have summarized this matter in the following chart.

	Chronic Glomerular Nephritis	Extrarenal Azotemia
History of preceding nephritis	May be present	Absent
Blood pressure	Increased	Usually normal or low.
Eye Grounds	Usually show exudate, hemorrhage or vascular change.	Negative
Respiration	May be Cheyne-Stokes	Usually shallow and rapid, but regular.
Urine	Acid, low fixed specific gravity, albumin & casts, red blood cells usually present. Chlorides not significantly altered.	Alkaline in hypochloremic type. Specific gravity variable, usually high. Albumin and casts may be present but disappear with improvement in clinical condition. Red blood cells not abnormal.
Kidney function tests	Always show marked impairment of renal function.	May show impairment at height of disorder. Improvement occurs with clinical improvement.

Blood chlorides	Not altered significantly (normal or slightly reduced).	Diminished in hypochloremic coma. Variable in other cases.
CO_2 combining power of blood plasma.	May be markedly diminished.	Increased in hypochloremic cases. Normal or decreased in other types.
Blood count and hemoglobin	Reduced	Normal or elevated.
pH	Usually low	Usually high.
Therapy	Course of diseases not influenced by admintration of salt.	Salt and fluid administration curative in early cases.

A common misconception is that the level of the blood nonprotein nitrogen in extrarenal azotemia rarely increases to the level seen in organic renal disease. Actually values of 100 to 200 milligrams per cent are common and Fishberg mentions a patient in whom the blood nonprotein nitrogen increased to 400 milligrams per cent in three days.

TREATMENT

The rational treatment of this syndrome should be based on the diagnosis of the underlying pathologic process and the rectification of it. Thus, if a patient has intestinal or pyloric obstruction, or fistulae, operative procedures are indicated; where there is diabetes mellitus it should be properly regulated with insulin and diet; when due to adrenal insufficiency the condition is corrected by substitution and salt therapy; if due to extensive burns coagulants should be used. Such treatment will prevent the continuance of the factors causing the azotemia.

If the causative disease can be corrected, the next step in treatment of

extrarenal azotemia is based on the determination of the mechanisms responsible for the production of the azotemia. This consists primarily of supportive and replacement therapy and the prevention of undue loss of fluid and electrolytes.

Thus if the azotemia is due to shock, the systolic blood pressure should be maintained above 70 mm. of Hg. The patient's bed should be placed on shock blocks and external heat applied. The circulating blood volume should be restored by the administration of fluids - glucose, saline or blood intravenously. Various stimulating drugs may be indicated as well as oxygen.

The value of fluids in preventing the toxic process of intestinal obstruction was noted first by Hartwell and Houget.[50] This has been substantiated by many investigators subsequently, and intravenous saline is now employed widely.[51] Since dehydration and salt deficiency usually act concomitantly to cause azotemia, they can be rectified by the same procedure. Fluids should be administered orally, hypodermically or intravenously. The use of intravenous physiological saline is perhaps the best, although if there is pure dehydration with no salt loss, five per cent glucose could be used. Coller and Maddock used the following scheme for administration of fluids: Sufficient fluid to (1) furnish 1500 c.c. for urine excretion, (2) to replace abnormal losses such as vomitus, diarrhea, or drainage from intestinal or biliary fistulae, (3) to replace water used for vaporization from the skin and lungs which will amount to 1000 to 1500 c.c. per day in the uncomplicated case, but may rise to 3000 c.c. per day if there is the increased heat production of fever or hyperthyroidism, or the sweating of hot, humid climates, (4) water for the restoration of

depleted body fluids of the dehydrated patient. They recommend that the initial infusion be estimated on the basis of six per cent of the total body weight in serious dehydration.

The syndrome of extrarenal azotemia is an important concept when its value in differential diagnosis is considered. Heretofore, the diagnosis of renal disease has been made when routine blood chemical studies revealed an elevated nonprotein nitrogen. Whereas, in reality, the increase in nonprotein nitrogen may actually be due to factors extrinsic to the kidney. Such an occurrence might actually be disastrous if a patient with acute intestinal obstruction were refused surgery because he had "nephritis" on the basis of an elevated blood nonprotein nitrogen with no other demonstrable evidence of renal disease. The multiplicity of diseases in which extrarenal azotemia occurs is impressive and the determination of the blood nonprotein nitrogen ought to be a routine procedure in clinical practice.

BIBLIOGRAPHY

1. Tileston, W. and Comforte, C.W.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease. Arch. Int. Med. XIV:620,649, 1914.

2. Peters, J.P. and Van Slyke, D.D.: Quantitative Clinical Chemistry, Williams and Wilkins, Baltimore, 1931, 266,304.

3. Rafsky, H.A., Weingarten, M.: The Clinical Significance of Prerenal Azotemia in Digestive Tract Disease, New York State Jour. Med. 1086, 1092, June 1, 1939.

4. Peters, J.P.: Critical Estimate of Laboratory Procedures in Disorders of Metabolism, Bull. N.Y. Academy of Med., X:415-444, 1934.

5. Cubitt, Alan W.: The Problem of Anuria: A Review of Recent Work on Renal Physiology, with Report of Two Cases, Brit. Jour. Surg., XXIV:215-226, 1936.

6. Best, C.H. and Taylor, V.B.: Physiological Basis of Medical Practice, William Wood and Co., Baltimore, 1937, 599.

7. Lasser, H.C. and Husfeldt, Crik: Kidney Function and Blood pressure, Jour. Clin. Invest., XIII, 263-278, 1934.

8. Blum, L., Srabar, P. and Van Coulaert, C.: L'Azotemia par manque de sel, son mecanisme, Ann. de Med., XXV, 34-39, 1929.

9. Gomori, P. and Podhradszke, L.: The Mechanism of Extrarenal Hypochloremic Azotemia, Acta Med. Scandinav., XCII, 347-355, 1937.

10. Haden, R.L. and Orr, T.G.: Chemical Changes in Blood after Pyloric Obstruction, Jour. Exper. Med., XXXVII, 377,381, 1923.

11. Orr, T.G. and Haden, R.L.: Chemical Factors in the Toxemia of Intestinal Obstruction, Jour. Amer. Med. Assn., XCI, 1529, 1928.

12. Peters, J.P.: Salt and Water Metabolism in Nephritis, Medicine XI, 435-535, 1932.

13. Landis, E.M., Elson, K.A., Bott, P.A. and Shiels, E.: Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, Jour. Clin. Invest. XIV, 525, 541, 1935.

14. McCance, R.A.: Medical Problems in Mineral Metabolism, Lancet, 1, 643, 704, 1936.

15. Clauser, Johs: Studies on the Relation Between Hyperazotemia and Sodium Chloride Deficiency, Acta Med. Scandinav, XCI, 523, 540, 1937.

16. Kerpel-Fronius, E.: Zur Pathogenese der Hypochloramischer Azotemia, Ztschr. f. d. Ges., Exper. Med., XCVII, 733, 748, 1936.

17. Gamble, J.L. and Ross, S.G.: Dehydration Following Pyloric Obstruction, Jour. Clin. Invest., 1, 403, 1925.

18. Gamble, J.L. and McIver, R.A.: Body Fluid Changes Due to Upper Intestinal Obstruction, Jour. Amer. Med. Assn., XCI, 1549, 1556, 1928.

19. Gamble, J.L.: Dehydration, New England Journal of Medicine, CCI, 909-917, 1929.

20. Rowntree, L.G.: The Volume of Intestinal Secretions, Physiol. Rev., II, 116, 124, 1922.

21. Coller, F. and Maddock, W.G.: A Study of Dehydration in Humans, Ann. Surg., CII, 947, 960, 1935.

22. Meyler, C.: Uremia due to Dehydration, Acta Med. Scandinav., XC, 475, 488, 1936.

23. Fishberg, A.M.: Hypertension and Nephritis, Lea and Febiger, Philadelphia, 1939, 55, 66.

24. Van Slyke, D.D., Rhoad, R.L., Heller, J. and Alving, R.R.: Determination of Kidney Blood Volume by Urea Clearance, Am. Jour. Phys., CIX, 336, 387, 1934.

25. Bollman, J.L., Mann, F.C. and Magath, T.B.: Studies on the Physiology of the Liver, XV; The Effect of Total Removal of the Liver on Deaminization, Am. Jour. Physiol. LXXVIII, 258-269, 1936.

26. Ingegno, S.E.: Elevated Blood Urea of Acute Gastro-intestinal Hemorrhage and its Significance, Amer. Jour. Sc., CXC, 770,774, 1935.

27. Borst, J.G.G.: Cause of Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage from Peptic Ulcer, Acta Med. Scandinav., XCVII, 68, 88, 1938.

28. Christiansen, T.: Biochemical Changes in the Organism Produced by Massive Intra-Intestinal Hemorrhage, Rev. Gastroenterol, IV, 166, 180, 1937.

29. Alstead, G.: Azotemia following Hemorrhage in Gastro-intestinal Tract, Amer. Jour. Med. Sc.,CXCII, 199, 208, 1936.

30. Stadie, W.C. and Van Slyke, D.D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver. Arch. Int. Med., XXV, 693, 804, 1920.

31. Stander, H.J.: A Chemical Study of a Case of Chloroform Poisoning, Bull Johns Hopkins Hospital, XXV, 46-49, 1924.

32. Wakeman, A.M. and Morrell, C.A.: Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys, I. Concentration of Nonprotein Nitrogen Nitrogenous Constituents in the Blood, Arch. Int. Med., XLIX, 290, 305, 1930.

33. Schutz, C.B., Helwig, F.C. and Kuhn, H.P.: A Contribution to the Study of So-called Liver Death, Jour. Amer. Med. Assn., XCIX, 633-636, 1932.

34. Editorial, Liver Death, a Hepatorenal Syndrome. Jour. Amer. Med. Asnn., XVIII, 301, 302, 1937.

35. Cybronberg, S.: Vicarious Function of Liver in Clinical and Experimental Azotemia, St. Jr. Med., XXXIX, 1316, 1321, 1939.

36. McCance, R.A. and Lawrence, R.P.: The Secretion of Urine in Diabetic Coma, Quart. Jour. Med., IV, 53,59, 1935.

37. Peters, J.P., Buger, H.A., Eisenman, A.J. and Lee, C.J.: Total Acid-Base Equilibrium of Plasma in Health and Disease, VI. Studies in Diabetes, Jour. Clin. Invest., II, 167, 211, 1925.

38. Marshal, E.K. and Davis, D.M.: The Influence of the Adrenals on the Kidneys, Jour. Pharm. and Exper. Therap., VIII, 525, 550, 1916.

39. Rowntree, L.G.: Studies in Addison's Disease, Jour. Amer. Med. Assn., LXXXIV, 327, 335, 1925.

40. Loeb, R.F.: Chemical Changes in the Blood in Addison's Disease, Science, LXXVI, 420, 421, 1932.

41. Loeb, R.F., Atchley, D.W. and Stohl, J.: The Role of Sodium in Adrenal Insufficiency, Jour. Amer. Med. Assn., XIV, 2149, 2154, 1935.

42. Wohl, L.A. and Brust, J.R.: Extrarenal Azotemia Differentiated from Renal Azotemia, Trans. Amer. Therap. Soc., 31, 39, 1935.

43. Simpson, C. K.: Pathology of the Adrenal Gland in Relation to Sudden Death, Lancet, I, 851, 856, 1937.

44. Steinberg, C.L.: The Prognosis of Coronary Thrombosis Based on the Nonprotein Nitrogen in the Blood, Jour. Lab. and Clin. Med. XX, 279-287, 1934.

45. Underhill, F.P., Carrington, G.L., Kapsinow, R., and Rack, G.T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significance of Systemic Treatment, Arch. Int. Med., XXXII, 31, 49, 1923.

46. Davidson, E.C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, Arch. Surg, XIII, 262, 277, 1936.

47. Moon, V.H.: The Occurrence and Clinical Significance of Hemoconcentration, Ann. Int. Med., VIII, 1633, 1648, 1939.

48. Derow, H.A.: Significance of Postoperative Rises of Blood Nonprotein Nitrogen, New Eng. Jour. Med., CCXII, 509-511,1935.

49. Harrison, T.R. and Morton, F.M.: The Pathogenesis of the Uremic Syndrome, Medicine, XVI, 1-44, 1937.

50. Hartwell, T.G., and Houget, S.B.: Experimental Intestinal Obstruction in Dogs, Jour. Amer. Med. Assn., LIX, 82, 86,1912.

51. Gomori, P. and Frenreisz, C.: Influencing Hypochloremic Azotemia with Hypertonic and Physiological Saline Solution, Acta Med. Scandinav., XCII, 503, 514, 1937.

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