ACUTE RENAL FAILURE

Lower Nephron Nephrosis*

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The term lower nephron nephrosis[20] is a recent embellishment in terminology for a pathological process that has a venerable and distinguished history. This syndrome may result from a variety of circumstances. It can arise from the use of sulfonamides, carbon tetrachloride, mercury, or numerous other drugs or poisons; from injuries which cause massive destruction of tissue, such as crushing injuries and burns; and from the destruction of blood cells within the circulation as the result of drugs, disease (e.g. blackwater fever), or transfusion with incompatible blood. Prolonged peripheral circulatory collapse may have a similar effect.[15, 24, 37, 43, 44]

Gross examination of the kidneys may reveal nothing more than slight enlargement and a pale swollen cortex. Histological examination usually reveals the presence of pigment and hyaline casts in the lower parts of the nephrons. There may be necrosis of the epithelium of any part of the tubule. Although in some instances the necrosis is most severe in the proximal tubular cells, the injury is most constant and usually most severe in the lower segments of the nephrons. Aside from mild swelling of the cells of Bowman's capsule early in the process, there are no discernible lesions in the glomeruli.[20, 21] Since the necrosis is almost entirely confined to the epithelial tissue, the process is reparable. Evidence of regeneration of the tubular epithelium may be seen as early as the fourth or fifth day of the disease. In two weeks the epithelium is largely restored and functioning, and in several months it may be impossible to detect any signs of the injury.[4] The most important inference to be drawn from the nature of the pathological process is that should the patient survive his other injuries, the renal lesions will be repaired.

The clinical expression of this pathological process is severe renal insufficiency with oliguria or anuria. The mechanism responsible for this has been disputed.[1] Some have claimed that the tubules are mechanically blocked by pigment casts and crystalline precipitates, solid or viscous liquid in character.[18] This seems unlikely as a major factor, since it is rare to find casts in more than twenty per cent of the tubules.[24] Moreover, dilatation of the tubules proximal to the casts is not a consistent phenomenon and seems dependent upon the manner in which the tissue is fixed prior to preparation of histologic sections; the dilatation of tubules may be largely an artefact.[21] Richards,[35] by direct microscopic observation of the kidneys of frogs

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poisoned with bichloride of mercury, noted that the power of active reabsorption and selective retention of diffusible substances by the renal tubules was abolished. Moreover, despite anuria, there was at least a normal rate of formation of glomerular filtrate. The implication of these observations is that the necrotic tubular epithelium was no longer a discriminating membrane, and that the bulk of the glomerular filtrate passed back into the body fluids through the diseased renal tubular epithelium. Less direct evidence of "back diffusion" is available. The U/P ratios of two substances that are excreted by the process of filtration only, without secretion or reabsorption by the tubules, should be identical. Simultaneous examination of the U/P ratios of creatinine and inulin in the dog has shown that these two ratios are not identical in lower nephron nephrosis.[37] Negative values for Tm_{PAH} which imply reabsorption (back-diffusion) of PAH at some point in the renal tubule have also been described in this disorder.[32] Since the tubular cells do not constitute a discriminating membrane in lower nephron nephrosis, the current techniques used to measure the rate of glomerular filtration and renal plasma flow may be invalid and cannot be interpreted with confidence in this disorder.

The pathogenesis of lower nephron nephrosis appears to be largely dependent on two factors: (i) some substance that has the ability to destroy renal tubular epithelium, abetted by (ii) anoxia of the renal tissue. These factors and the site of the most marked lesions of lower nephron nephrosis have physiological implications that are relevant to its prevention and treatment.

The modern concept of the formation of bladder urine is that a large volume of glomerular filtrate is converted to a much smaller volume of fluid which may vary considerably in composition and tonicity. The urine that reaches the distal tubule is reduced to about a fifth of its original volume, the composition has been altered, but it is still isotonic with the glomerular filtrate. It is in the distal tubule (the lower nephron) that water and solutes may be differentially reabsorbed, producing a hypotonic, isotonic, or hypertonic bladder urine.[38, 39, 47]

The extent to which the water is reabsorbed in the distal tubule is largely dependent upon the action of the antidiuretic hormone of the posterior pituitary gland. Verney's experiments[45] indicate that the secretion of antidiuretic hormone by the posterior pituitary gland is automatically regulated in accordance with the tonicity of the extracellular fluid. He postulates the existence of osmoreceptors somewhere in the region of distribution of the internal carotid artery which respond to variations in the effective osmotic pressure of the fluid about them. An increase in the tonicity of the fluid stimulates this receptor which, in turn, transmits the stimulus through the supra-optico-hypophysial pathway ultimately to promote the secretion of posterior pituitary hormone. Similarly, a decrease in the tonicity of the fluid bathing this receptor leads to a reduced stimulus to the posterior

pituitary gland and a graded suppression of secretion of antidiuretic hormone.

Certain lines of investigation strongly suggest that the neurohypophysis (directly or indirectly), or some other antidiuretic mechanism, may respond to stimuli other than those related to tonicity. Brun, Knudson, and Raaschou[2] demonstrated that the decrease in urine flow produced by the stationary standing position, while sustained in normal persons, was quite transient in patients with diabetes insipidus. Judson, Epstein, *et al.*,[17] observed the same difference in response between normal human subjects and patients with diabetes insipidus who were subjected to experimental venous congestion of the limbs. An antidiuretic response is often associated with a contracting plasma volume following a large paracentesis in cirrhotics with ascites.[26, 36] Holmes and Cizek[15] observed an increase in thirst with some retention of water in excess of salt in dogs whose extracellular fluid and plasma volumes had been diminished by experimentally induced salt depletion. According to Leaf and Mamby[19] the serum of dogs with contracted extracellular volume and hyponatremia has more than the usual antidiuretic activity.

These data support the hypotheses that an increase in tonicity of the body fluids and a contraction of the extracellular volume may both be stimuli for release of antidiuretic hormone, which increases reabsorption of water in the distal tubule and concentrates the solutes present in the distal tubular urine.

It is logical to assume that if there is a noxious agent among the solutes of the distal tubular urine, an increase in its concentration will promote a greater degree of damage to the tubular cells. There is direct experimental and clinical evidence to support this. Haskell, *et al.*,[14] found that eighty per cent of dogs survived a usually lethal dose of bichloride of mercury if a diuresis was promoted by an injection of normal saline soon after the administration of this poison by stomach tube. Corcoran and Page,[5] Harrison, *et al.*,[13] and Maluf[22] report that it is more difficult to produce renal insufficiency with intravenously administered hemoglobin in well-hydrated animals. Peters, *et al.*,[29] proposed a radical but successful departure from the conventional mode of early therapy in patients suffering with intoxication from bichloride of mercury that emphasized the promotion of an adequate urine flow by the prompt administration of fluids. Further insight may be gathered with respect to this problem from a consideration of the fact that a hemolytic transfusion reaction rarely leads to lower nephron nephrosis in patients with renal insufficiency characterized by an inability to concentrate urine.

The modifying influences of the state of hydration, circulatory dynamics, and the concentration of the urine on the development of lower nephron nephrosis are strikingly illustrated in the responses of a patient (C23592) to three separate hemolytic reactions. The first of these occurred during

convalescence from a right thoracolumbar sympathectomy. The patient was not dehydrated and was given an infusion of a liter of normal saline following the reaction. It is reasonable to assume that this was a hemolytic reaction, since the urine became dark in color and gave a positive reaction to guaiac, and there was an elevated concentration of total bilirubin in the serum. Despite this, there was no suppression of urine flow. A second hemolytic transfusion reaction occurred on the day of the second operation. This reaction was superimposed on a background of dehydration and peripheral vascular collapse and was followed by a lower nephron nephrosis. She sustained a third hemolytic reaction to an infusion of washed red cells on the fifteenth day following the onset of the lower nephron nephrosis. This reaction occurred at the time when the patient was in the diuretic phase of recovery from the prior renal tubular damage. The diuresis of dilute urine continued without interruption. The absence of a highly concentrated urine associated with the normal state of hydration and the infusion of saline at the time of the first reaction, and the inability to concentrate the urine at the time of the last hemolytic reaction are probably the factors responsible for the lack of injury to the renal tubules. In contrast, the development of lower nephron nephrosis following the second reaction was probably conditioned by the state of dehydration and peripheral vascular collapse.

It has been claimed that an acid reaction in the urine enhances the deleterious effect of a noxious agent on the tubular epithelium. However, several groups of investigators[5, 9, 13, 22] have established that the increased damage is associated with the dehydration that may accompany the acidosis and not with the acidosis *per se*. When the urine of experimental animals was made acid, but care was taken to assure proper hydration, there was no increase in the incidence of renal insufficiency following the administration of solutions of hemoglobin, methemoglobin, or hemolyzed erythrocytes. The beneficial effects of infusions of alkaline solutions in hemorrhagic shock are not striking[16] and may be related to the effects on volume and tonicity of body fluids rather than to acid-base balance.

A contracted extracellular fluid volume may influence the development of lower nephron nephrosis by a mechanism unrelated to its influence on the concentration of urine in the distal tubule. A decrease in the volume of the extracellular compartment resulting from dehydration is usually apportioned between the two major components of this compartment, the interstitial fluid and the plasma. The degree to which blood volume loss may be compensated by a movement of fluid from the interstitial space into the blood stream is conditioned, in part, by the volume of the interstitial fluid. Warren, Merrill, and Stead[46] found that in dogs subjected to tourniquet shock the quantity and pressure of the extracellular fluid was as important in determining the size of the plasma volume as was the quantity of circulating plasma protein. Weston, *et al.*,[48] investigated the response to hemor-

rhage in dogs whose intake of water had been restricted for eighteen to thirty hours prior to the bleeding, as compared with a group which had been allowed free access to water. It required a smaller bleeding to produce shock in the dehydrated than in the control animals. Others[16] have reported that the administration of normal saline prior to experimental hemorrhage protects animals against an otherwise lethal bleeding. Moreover, a contracted plasma volume associated with dehydration, even in the absence of hemorrhage, may be sufficient in itself to lead to a compensatory selective vasoconstriction in certain organs in the interest of maintaining an adequate flow of blood to more sensitive areas. The renal vascular tree participates in this vasoconstriction[18, 43, 49] and the renal blood flow is often reduced. Since this vasoconstriction aids in the maintenance of a normal blood pressure despite a decrease in the blood volume, renal ischemia and consequent anoxia may precede gross evidence of peripheral vascular collapse. This anoxia may in itself produce severe acute renal insufficiency,[12, 81] and it potentiates the effect of other nephrotoxic agents. Lastly, the prolonged vasoconstriction may eventuate in irreversible peripheral vascular collapse.[10, 11, 33, 34, 50]

The preparation of patients for scheduled surgical procedures frequently provides for the omission of all food and fluids for twelve or more hours prior to operation. Losses of fluid are incurred during this period by way of the urine, insensible perspiration, and sweat. The latter will vary in amount depending on fever and the weather. The patient at the time of operation is in the so-called hydropenic state, in which it is postulated that there is near-maximal antidiuretic activity with a urine flow of about a half cubic centimeter a minute. In the operating room the patient, covered with several layers of cloth, sustains additional losses of fluid as insensible perspiration, sweat, and frequently vomitus and blood. It has been estimated that in the course of a major operation under general anesthesia in average climatic conditions, a patient may lose at operation two to four liters of fluid through the skin and respiratory passages. Losses may be even greater during prolonged operations in extremely hot weather. General anesthesia in itself has an antidiuretic effect. Thus, the two stimuli calling forth antidiuretic activity, increase in tonicity, and contraction of the body fluids, co-exist. The fluid losses, in themselves, may be sufficient to promote a state of peripheral vascular collapse, for which the most common therapy is transfusion of whole blood. If the operation is a long and difficult procedure, the losses of fluid will increase and many transfusions may be administered. Each transfusion carries with it the hazard of a reaction which may be hemolytic in character. Should such an unfortunate accident occur, it has been allowed to develop at a time when the products of hemolysis will be maximally concentrated in the distal tubules, and when these tubules may have endured anoxia secondary to renal vasoconstriction. The stage is admirably prepared for the development of a lower nephron nephrosis.

Insofar as proper hydration can modify this unfavorable setting, it should likewise prevent or at least minimize this type of lower nephron nephrosis. Proper hydration does not imply that the patient need be given inordinate volumes of fluids, but enough saline and glucose solution should be administered at the start of an operation to compensate for antecedent losses and to provide for the losses of salt and water that may be anticipated during the operative procedure. Continuous intravenous infusion of five per cent glucose in water and some saline, regulated to promote the excretion of a reasonably dilute urine and to compensate for losses of sweat and blood, will provide protection against the concentration in the distal tubule of a substance toxic to the renal tubular epithelium. Since dehydration itself contributes to the production of shock, it is quite possible that the provision of these fluids in advance may reduce the necessity for transfusions.

This discussion should in no way be interpreted as a condemnation of the use of transfusions. The availability of whole blood and the ease with which it may be administered represent a major advance in the therapy of shock. Certain considerations, however, are implicit in this argument: (i) peripheral vascular collapse may be primarily caused by, or certainly contributed to, by losses of fluids other than blood; (ii) to the extent that dehydration can cause or contribute to peripheral vascular collapse, this latter can be prevented or modified; therefore, proper hydration will reduce the necessity for transfusions; and (iii) since the use of multiple transfusions increases the risk of a hemolytic reaction, there is a specific responsibility to prepare the patient in such a manner that this type of accident will lead to as little damage as possible.

The management of a patient before and during a surgical procedure has been selected simply for the purpose of illustrating the nature of the problem with respect to the prevention of lower nephron nephrosis. Proper hydration characterized by a normal volume and tonicity of the body fluids is just as important in the protection of the renal tubular epithelium during the administration of sulfonamides, other chemo-therapeutic agents, or transfusions of blood in medical diseases.

One is frequently presented with the clinical problem of a patient who has been oliguric for a matter of hours, arising out of a situation that *may* have produced a lower nephron nephrosis. Overemphasis and overstatement of the dangers of expansion of the volume of the body fluids have engendered a fear of salt and water. In such a situation the assumption is too frequently made that there is, in fact, a state of lower nephron nephrosis. Fluid and electrolyte therapy are now directed toward the prevention of edema; little thought may be given to the problem of the precise pathogenesis of the oliguria. This reduced flow of urine could result merely from an inadequate replacement of fluid losses. The successful repair of such a situation must achieve a restoration of the volume, tonicity, and disposition of the body

fluids. A contracted plasma volume, hyponatremia, or both, may, in themselves, be responsible for a small flow of urine. Acute hyponatremia even in association with an expanded volume of body water can have dire consequences, and if this state is not corrected, a true lower nephron nephrosis may develop. The prompt and adequate correction of these abnormalities encourages a return of renal function to normal dimensions or, at least, may minimize the severity and duration of the disorder. If the correction of these abnormalities fails to induce a proper flow of urine, little would appear to have been lost. This correction need not proceed to the point of inducing edema, although the harmful effects of minimal overexpansion of the extracellular compartment seem negligible. There is ample evidence that a reasonable excess of fluid is to be preferred to dehydration.

There is less controversy[3, 25, 29, 41, 42] concerning the management of the patient with an established lower nephron nephrosis. This is a self-terminative illness, and the aims of therapy are to restore and to maintain the internal environment in a state as near normal as possible, to retard the rate of protein catabolism, and to make it possible for the patient to exploit the earliest return of renal function. Fluids are initially administered in such volume and composition as to compensate for antecedent losses. The tonicity of the body fluids should be brought to and maintained at a normal level. Hyponatremia should be corrected with hypertonic saline. The amount of sodium necessary to raise the concentration of this ion to a normal value must be calculated on the basis of the fact that its osmotic effect is distributed throughout the entire volume of body water, although sodium itself is largely confined to the extracellular compartment.[27, 28] A reduction in the concentration of bicarbonate in the serum in this disorder most commonly results from its displacement by stronger acids. If the concentration of sodium in the serum is normal, this acidosis cannot be modified unless the concentration of sodium is raised above normal. This would substitute the discomfort of thirst for what is usually a symptomless acidosis. However, if hyponatremia and a depressed concentration of bicarbonate in the serum co-exist, some of the sodium may be administered as sodium bicarbonate which will modify the acidosis. Needless to say, peripheral vascular collapse should be treated with whole blood, washed red cells, or a colloidal solution such as albumin, depending on the particular circumstances in a given patient.

Having thus restored circulatory efficiency, and the volume and sodium concentration of the body fluids, only current losses should be replaced. The patient should receive enough water and salt to replace obvious extrarenal losses and enough water, in addition, to provide for losses through the skin and respiratory passages. The latter seldom exceed 1000 cc. a day unless the body temperature is elevated or sweating is profuse. One hundred grams of carbohydrate in doses spread throughout the twenty-four hours

will provide a maximum protein-sparing effect and will retard the rate of accumulation of nitrogenous end-products and potassium. Cardiac decompensation should be promptly treated with a digitalis preparation.

One feature of the treatment during this expectant stage has been much neglected. Absolutely nothing should be given by mouth until the patient has been free from vomiting and nausea for at least twenty-four hours. If this injunction is meticulously observed, the use of tubes and suction is unnecessary. Attention to this detail will minimize extrarenal losses of fluid and electrolytes. No food other than carbohydrate should be given until urination is resumed.

Under such a regimen very few patients will succumb to the effects of the renal insufficiency per se. Most patients can be maintained in a reasonable state of comfort and safety during the time that it may take for the lesion to heal. Stock[40] and others report the survival of patients in a comfortable state under such a regimen for as long as forty-nine days with complete renal insufficiency from neoplastic obstruction of the ureters. A patient (B76973) suffering with both lower nephron nephrosis and carcinomatous obstruction of both ureters, treated by this Service, survived thirty-five days with virtually complete anuria. During the first six days a total of 325 cc. of urine was obtained from the bladder; there was complete anuria during the last twenty-nine days. She was, however, in a state of reasonable comfort until the last days of her illness. There were periods of mental confusion during the last week, and she was almost comatose the last three days. Six days prior to death, chemical studies revealed an NPN of 220 mgm. per cent, serum bicarbonate and chloride of 17.8 and 78.2 mEq./L. respectively, sodium of 131.2 mEq./L., and a concentration of potassium in the serum of only 3.6 mEq./L.

An occasional patient may develop a high concentration of potassium in the serum, which may reach cardio-toxic levels. Elkinton and his coworkers[9] have demonstrated that this ion can be successfully removed with the use of a carboxylic ammonia exchange resin. This may be administered orally or instilled per rectum. This latter route is especially desirable in those instances where nausea or vomiting complicate the clinical picture. They advocate its use twice a day as a ten per cent suspension in a volume of 250 cc. of water. With this technique they were able to remove from twenty-one to seventy-three mEq. of potassium in a day. The concentration of potassium in the serum fell from as high as 7.7 to 5.4 mEq./L. This should be practised, however, only if the concentration of potassium in the serum is known to be high. Moreover, a high concentration of potassium in the serum should raise the question as to whether the administration of fluids and carbohydrate has been well regulated.

The value and proper rôle of the variety of artificial dialyzing procedures remain subjects for investigation.[7, 8, 23] Peritoneal lavage carries a serious

hazard of infection, and intestinal dialysis has been inefficient. It has been convincingly demonstrated by Merrill and his associates[28] and others that an artificial kidney of the Kolff design in competent hands is an efficient and reasonably safe dialyser. It is not certain, however, that the use of this instrument has materially altered the ultimate fate of a patient ill with lower nephron nephrosis. Our service has had no experience with the artificial kidney, and the fatalities with lower nephron nephrosis that have been encountered seem adequately explained on the basis of other aspects of the total disease picture than the renal insufficiency per se. It appears unlikely that the artificial kidney would have prevented these deaths. Further experience with this technique, nevertheless, may establish its utility and limitations in the management of this condition. The use of dialyzing procedures must be accompanied by expert knowledge and accurate chemical control. If these are not available, the use of an artificial kidney may well increase the mortality rate in lower nephron nephrosis.

The patient who is treated along the generally accepted principles of fluid therapy outlined above is in a situation to exploit the earliest phase of recovery. It is most important not to lag behind the diuresis in the prescription of fluids and electrolytes. Every advantage should be taken of the returning renal function to perpetuate and augment the increasing flow of urine. In the early stages of recovery the urine is dilute and its composition reflects a disability on the part of the tubules to differentiate in the reabsorption of water and solutes. This deficiency in tubular function is expressed in a concentration of NPN in the urine which is not much higher than that in the blood, while, since tubular reabsorption of electrolytes is impaired, sodium chloride may appear in relatively high concentration. Therefore, although the urine may contain very little non-protein nitrogen, losses of water and electrolytes may be quite large. If these losses are not replaced, the volume of the urine may be reduced, recovery delayed, and the concentration of NPN in the blood will continue to rise. Within a few days all aspects of renal function begin to improve, and in a few months even the most subtle analyses of renal function will fail to reveal any evidences of this severe disorder.

An attempt has been made in this discussion to focus attention on the *preventive* aspects of treating this disorder. The appropriate administration of fluids under circumstances where lower nephron nephrosis is a threat may prevent the disorder or, at least, reduce it to less disastrous proportions. A careful analysis, with the aid of appropriate laboratory examinations, of the sequence of events leading to a state of oliguria, and correction of the abnormalities of volume and tonicity of the body fluids, may be followed by a gratifying diuresis. A process that might have become lower nephron nephrosis may be forestalled. The maintenance of an internal environment as nearly normal as possible, by the intelligent administration

of water salts, and carbohydrate, will sustain a patient during the period of complete renal insufficiency and place that patient in an optimal state to respond appropriately when the lesion is repaired.

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