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Diagnosis and Treatment of Certain Reversible Diseases of the Kidney

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Among the diseases of the kidney, acute glomerulonephritis, albuminuric nephrosis, and so-called lower nephron nephrosis might be considered as conditions in which the renal decompensation is reversible.

Acute glomerulonephritis is truly an acute disease. It is one in which there appears to be a systemic reaction to a toxin produced by a current or a preceding hemolytic streptococcus infection with the kidney as the focus of such reaction. The symptoms and findings in a patient with a relatively severe acute glomerulonephritis are fairly clear and even distinctive. The first sign which a patient may notice is the sudden appearance of dark, cloudy urine. If one analyzes such a specimen, he finds the reasons for its peculiar quality. There are suspended within it large numbers of red cells and casts. If the urine is acid, the acid hematin from degenerated erythrocytes produces a dark, coffee color. Albuminuria is present, but the quantity of albumin may be relatively small as compared with the large number of cells. One might assume that the relative relationship between cells and albumin in the urine approximates the relationship of cells to albumin in the blood.

Usually there is a moderate increase in blood pressure, and probably due to an increase in systemic capillary permeability a mild to moderate generalized edema occurs, even though hypoproteinemia of sufficient severity to produce edema is not present.

Addis emphasizes the point that an attack of acute glomerulonephritis has a sudden onset. He compares it to an explosive incident, the most acute phase of which lasts for from four days to a week. A gradual recession occurs during the succeeding four to eight weeks. The peculiar color of the urine changes toward normal as do the number of cells and casts. The amount of albumin is gradually reduced, the blood pressure rather quickly drops to within normal limits, and the edema disappears. At the end of four to eight weeks normal urine is the rule among those patients who recover from the disease. At the same time no further symptoms or abnormal findings are present.

At this juncture mention should be made of the fact that the mortality from acute glomerulonephritis during the acute stage is relatively small. Probably it does not exceed 5 per cent. Nevertheless, one must consider the possibility that only about 50 per cent of patients who have had acute glomerulonephritis have a complete disappearance of the
disease with no future latent trouble. Therefore, even though the phase of acute glomerulonephritis disappears, approximately one half of the patients are not completely cured, and a chronic form of glomerulonephritis follows.

Concerning the acute phase, unfortunately neither children nor adults particularly concern themselves with the color of their urine; and due to the fact that the foregoing findings may be quite mild, many have had acute glomerulonephritis without its having been diagnosed or without its presence having been known.

The treatment of a patient who has acute glomerulonephritis is a subject on which there are varied opinions. When one recognizes that there are many people who apparently successfully emerge from an attack without having known that they had it, and therefore without having given any consideration to its treatment, one can legitimately question whether there is such a thing as a sound therapeutic program. Given a case of acute glomerulonephritis, however, the physician has two objectives in mind to which a system of therapy is directed. These are (1) to try to save the lives of those who might otherwise die of the acute disease, and (2) to try to prevent the development of chronic glomerulonephritis in a higher percentage than might otherwise occur.

Addis suggests the following:

1. For the first few days a diet low in sodium chloride and high in carbohydrates, with a maximum of from six to ten grams of protein per day.
2. Water as the patient wants it. Do not push it or restrict it.
3. After the first few days the patient may be placed on a well-balanced diet.
4. Bed rest is probably one of the most important therapeutic procedures; but because of the fact that so many of these people do not feel too bad, it is sometimes difficult, especially among children, to keep them there.

When the urine shows signs of clearing, and the edema disappears, the patient may be given some ambulatory privileges. Depending upon the progress of a given patient, he may gradually work into normal activity from four to eight weeks after the onset.

There seems to be no relation between the intensity of acute glomerulonephritis and the severity of a preceding streptococcus infection. Also, it appears as though bacteriostatic agents, such as the sulfa drugs, neither prevent nor cure the disease.

Concerning nephrosis, which is a term first suggested by Friedrich Müller in 1904 in an effort to differentiate degenerative lesions in the kidney from those of a truly inflammatory nature, the modern physician recognizes a complicated and inadequately understood situation. Since Müller excluded degenerative vascular lesions such as nephrosclerosis from the classification of nephrosis, the term has been erroneously used in such a way as to imply primary disease of the renal tubules. Based upon ample evidence, this viewpoint of nephrosis must be discarded. As a matter of fact, one can no longer assume that the term nephrosis includes a single specific kidney lesion. The time has already come when one must refrain from describing histopathological lesions under the blanket term of nephrosis. In the interests of scientific accuracy the time may eventually come when, in accord with suggestions already made by many, the term may be discarded.

In clinical circles a purely morphologic approach to the subject of nephrosis has been replaced by a more physiologic concept. The so-called nephrotic syndrome is now the common denominator in classifying the nephroses. Although an exact classification is presently not generally agreed to, the current belief and
teachings of most investigators are that four types of nephrosis are recognizable. These are 
(1) true or lipoid nephrosis; (2) the nephrotic syndrome of chronic glomerulonephritis; (3) 
amyloidosis; and (4) syphilitic nephrosis. Syphilitic nephrosis is so rare at the present time as to warrant its exclusion from the viewpoint of differential diagnosis.

There are differences of opinion as to whether a separate disease entity of true or lipoid nephrosis actually exists, and also as to just what stage in the process of glomerulonephritis the nephrotic syndrome obtains. For purposes of clarification Bell's viewpoint of this situation is arbitrarily accepted. With the exception of tubular damage caused by toxic drugs or heavy metals, or by some metabolic disturbance such as is found in amyloidosis, or by the invasion of the tubules by an ascending infection such as in chronic pyelonephritis, tubular damage is secondary to glomerular disease. Assuming that in the human kidney the blood supply to the tubules is by way of corresponding glomeruli, one may easily understand how the blood supply to associated tubules can be diminished to the extent of causing tubular degeneration if the primary glomerular pathology is of a nature to diminish or stop blood flow. If the blood flow through a given glomerulus is completely occluded, a certain tubule in whole or in part might become functionless, depending upon whether the efferent vessel from a given glomerulus supplies a whole tubule or only part of one. In nephrosis, however, glomerular circulation, and therefore glomerular function, is usually quite good. As a rule, there is no gross evidence of impaired kidney function. The glomerular filter, however, shows an abnormal morphology and leaks serum protein, particularly serum albumin, which in the normal glomerulus does not pass through the filter.

From the viewpoint of the clinician, nephrosis, or the nephrotic syndrome, may be defined as a condition in which there are severe albuminuria, edema, decrease in plasma protein (albumin), increase in blood cholesterol, increase in susceptibility to infection, often a decreased metabolic rate, and an associated anemia. Bell differentiates between what is commonly called the pure form, or lipoid nephrosis, in which there is little or no hypertension or renal insufficiency, and which is most common among young children who apparently have not had acute glomerulonephritis, and a mixed form in which there may be a moderate degree of hypertension and renal insufficiency, and which follows acute glomerulonephritis.

When present, hypertension and renal insufficiency frequently go together and may be interpreted as representing kidneys in which glomerular circulation is impaired. Therefore, where there is no hypertension and no renal insufficiency, one assumes that the blood flow through the glomeruli is reasonably good, and that the amount of tubular damage would be neither severe nor extensive. The histological findings of this condition are in accord with such an opinion. If, however, the general picture or the nephrotic syndrome maintains, but in addition there coexists some hypertension and impaired function, one would assume that the blood flow through a considerable number of glomeruli is diminished. The histological findings in this situation also support such an assumption. This picture may be recognized as the mixed type of nephrosis.

According to Bell's description, the morphology of nephrosis, whether it be with or without hypertension, shows the basilar membrane to be thickened; and it is assumed that this abnormal situation permits serum albumin to leak through with the filtrate. Thickening of the membrane eventually may produce capillary occlusions, the results of which are similar to the well-recognized chronic glo-
merulonephritis, in which there are hypertension and possible azotemia, and which is differentiated from the more common form of chronic glomerulonephritis principally in that the albuminuria is more severe and more persistent and the number of red cells in the urine is less.

The opinion that the nephrotic syndrome represents what might be called subacute glomerulonephritis does not have much backing, but eventually it may assume the more common form of hypertensive, azotemic, chronic glomerulonephritis. Except in those cases where glomerular occlusion occurs, tubular function remains good, and the fact that considerable amounts of lipoid may be found in the tubular cells cannot be interpreted as a reason for any interference with tubular function. According to the more rigid definition of lipoid nephrosis, there should exist no elevation of blood pressure, no impairment of kidney function, and no hematuria. However, upon careful examination it is not unusual to find some red cells in the urine.

Even though one might wish to follow along with those who believe nephrosis to be only a manifestation of glomerulonephritis, the general clinical picture remains the same. One could reasonably reconstruct the situation in a logical fashion as follows: After the acute attack of glomerulonephritis in which the urinary findings are particularly those of hematuria and casts with moderate albuminuria, one could assume that if there were not complete healing of the acute glomerulonephritis, one of two things might happen. First, the endothelium of the glomerulus might proliferate, thereby gradually causing capillary occlusion with the production of hypertension and azotemia. The other possibility would be the assumption that instead of having endothelial proliferation, a swelling of the basilar membrane occurs. This would give rise to proteinuria, hypoproteinemia, and eventually edema. In such a situation kidney function would remain relatively good. If the basilar membrane swells sufficiently, partial or complete occlusion of varying numbers of glomerular capillaries might occur, in which situation there would exist a diminution of kidney function and hypertension along with the albuminuria. This would qualify as the mixed form of nephrosis.

Briefly, in the general treatment of nephrosis feeding large quantities of protein does not readily change the serum protein level. Nevertheless, the fact that the patient needs protein to maintain normal metabolism, and the fact that he is losing relatively large amounts in his urine, are sufficient reasons to give him a reasonably high protein diet. It is the opinion of the author that the diet should be well balanced, and on that basis it is rather difficult to get a patient to eat more than 100 to 150 grams of protein per day. The protein should be adequate not only in quantity but also in quality. As long as edema exists there should be restriction of sodium. When edema is sufficiently severe, diuretics may be used. One of the mercurial diuretics, for example mercuhydrin at weekly or semiweekly intervals, is usually quite beneficial. Some consider urea as the diuretic drug of choice. It may be given without danger to the patient whose serum N.P.N. is within normal limits. Even though the serum cholesterol is high, it is questionable whether any definite benefit results from the use of thyroid. The intravenous use of whole blood is of value in restoring serum protein and in replacing red cells when anemia is present. When edema is severe and sodium restriction is indicated, albumin solution may be used with benefit. When the serum proteins reach a concentration of approximately 5.0 grams per 100 cc., edema usually disappears as long as other therapeutic measures are maintained. Unless there are
contraindications, it is desirable for the patient to remain ambulatory.

On such a regimen improvement is the rule, and eventually the patient may resume the activities of a reasonably normal life. When the patient has been under adequate control for an extended period of time, a remission may be sufficient to show evidence of quite normal physiology with a marked reduction in the quantity of albumin in the urine. One must always keep in mind the susceptibility of the nephrotic patient to infections. Early and adequate doses of antibiotics usually will control such situations.

Lower nephron nephrosis, or acute toxic nephrosis, represents a reasonably well-identified clinical picture, the most noteworthy features of which are oliguria or anuria. Associated chemical and physiological changes result from such a renal shutdown. This condition follows one or more of a variety of precipitating causes, such as transfusion reaction, toxic drug reaction, such as with the sulfonamide drugs, and severe tissue trauma with or without vascular shock.

Strauss describes the initial onset with symptoms of "nausea, vomiting, weakness, malaise, sometimes pain in the abdomen or back, and abruptly or insidiously, oliguria or anuria."

With the appearance of anuria or severe oliguria usually there is a rise in arterial blood pressure, a steady increase in the concentration of serum nonprotein nitrogen, possible edema, and a possible increase in the serum potassium concentration.

It is generally believed that in this condition morphological damage in the glomeruli is not significant. Nevertheless, according to the evidence presented by Trueta, the initial disturbance seems to be a physiological one consisting chiefly of a severe vascular constriction which involves the interlobular and afferent vessels to the glomeruli in both kidneys, and thereby temporarily stops the flow of blood through glomeruli and the associated tubules. This could readily account for the sudden appearance of anuria or oliguria.

This phenomenon may last for a variable period of time; but frequently, by the time glomerular and tubular circulation are restored, significant tubular damage has already occurred. Morphological observations demonstrate degeneration of tubular cells which apparently fall into the lumina and mechanically occlude the tubules. If the hemoglobin or sulfonamide drugs are sufficiently concentrated in the filtrate, they may be precipitated in the tubules and further have a tendency to interfere temporarily with the flow of filtrate through them.

Many are of the opinion that the mechanical obstruction in tubules is of secondary importance in the production of oliguria or anuria and that the factor of primary importance is the extremely rapid reabsorption of all filtrate due to the absence of tubular cells. Regeneration of these cells begins in from 36 to 72 hours, and ordinarily develops to a point of being able to prevent such rapid reabsorption in from four days to approximately two weeks. At that time urine begins to appear. Thorn, Kugel, and others, report that after the onset of anuria, the average time for reappearance of urine is between the ninth and eleventh days. Some reports indicate that regeneration of tubules may occur as long as three weeks after the onset of anuria.

In this regard one becomes interested in how long a patient may live without the production of urine. There is evidence in support of the assumption that under what might be considered adequate and proper care a subject may live for as long as four weeks. If a patient with renal insufficiency such as is present with lower nephron nephrosis dies in less than three weeks, one becomes interested in the possible causes of death. Indications are
that relatively early deaths are due to (1) generalized edema, as well as pulmonary edema; (2) acidosis; (3) potassium intoxication because of hyperpotassemia. For those patients in whom tubular regeneration might occur, the immediate treatment should be directed toward keeping them alive as long as possible, or until diuresis begins. This means that edema should be prevented. Acidosis of sufficient severity to endanger life must be neutralized and toxic hyperpotassemia must be reduced. Even though there are some who support a hydration regimen as of therapeutic value, the present consensus is against it. In a state of anuria, and in the absence of significant sweating, an intake of from 750 cc. to 1,000 cc. of water will be required daily. Nothing should be given by mouth during the period of anuria, and sodium chloride intake should be prevented. The patient needs some calories, and therefore if the water and calories are given as a 15 per cent solution of glucose in distilled water, the problem of water and sodium chloride balance can be reasonably well handled.

If vomiting becomes a problem, the total quantity of vomitus should be measured, and an equivalent amount of isotonic saline can be added to the daily intravenous injection of the dextrose solution. If small amounts of urine are produced, this may be similarly measured, and the total quantity of water and sodium chloride can be added to the intravenous solution. Because of the fact that the foregoing treatment will contribute to cellular breakdown during the anuric phase, the potassium level in the blood may have a tendency to rise. Blood potassium levels should be checked daily, and electrocardiograms should be run at least every other day in order to observe possible toxic effects of potassium. If its concentration reaches a toxic level, or if acidosis occurs, these temporarily may be cared for by giving a liter of one sixth molar sodium lactate intravenously. Thereby the volume of extracellular fluid will be expanded, and this will help to dilute the toxic substances, and the sodium will help to replenish the alkali reserve. The author has observed symptoms of neuromuscular irritability in a patient with oliguria who was getting no sodium, and whose serum sodium level dropped during treatment, but whose symptoms cleared up promptly after the intravenous instillation of sodium chloride solution.

When the phase of diuresis occurs, quite large quantities of water and of the various salts are eliminated. Then it is particularly necessary to prevent dehydration and the excessive loss of sodium chloride. Water and salt in sufficient amounts to prevent dehydration will be required. After adequate regeneration of tubular cells has been accomplished, kidney function again becomes quite normal, and no further treatment is necessary.

Even though Hoffman, Marshall, and others advocate excessive hydration as a means of diluting the accumulating toxic products of metabolism during the anuric or oliguric phase, the probabilities are that it is much easier to "drown" such patients during the anuric stage than to dehydrate them. As a matter of fact, the relative dehydration may be the essential lifesaver. During the phase of regeneration the urinary output may reach two or three liters daily, at which time the dangers of "drowning" a patient are quite remote or even impossible.

There will be those patients with lower nephron nephrosis who are anemic. As a matter of fact, many of them will be those who developed their kidney trouble because of a transfusion reaction from blood which was being given them to treat their anemias. Strauss states that, after kidney function has been restored, transfusions of properly matched whole blood may be as safely given as to any other patient.
REFERENCES