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# Etiology, pathogenesis, and treatment of acute uremia : with special attention to the use of the peritoneum as a dialyzing membrane

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# THE ETIOLOGY, PATHOGENESIS, AND TREATMENT OF ACUTE UREMIA WITH SPECIAL ATTENTION TO THE USE OF THE PERITONEUM AS A DIALYZING MEMBRANE.

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## Introduction

The purpose of this paper is to present the known facts about the uremic syndrome, and the various means by which this complex physio-chemical condition may be treated. As this is a broad subject, major emphasis will be placed on recent information and practices. The importance of the "crush syndrome" or "lower nephron nephrosis" is examined in the light of new studies and concepts of renal physiology based on changes in renal circulation. Certain conclusions are drawn which represent to the writer the important features derived from this study.

Best and Taylor[1] recognize two types of uremia, true, and false, or eclamptic. They describe true uremia as the terminal manifestation of renal failure characterized by muscular weakness, dyspnea, mental disturbances, increased tendon jerks, nausea and vomiting, muscular twitching stupor and finally coma with periodic breathing.

False or eclamptic uremia is characterized by epileptiform convulsions which are due, apparently, to cerebral edema, and may occur in the absence of renal insufficiency or of renal disease.

The symptoms of true uremia are associated with a high degree of nitrogen retention, but none of the known nitrogenous wastes, urea, uric acid or creatinine, is responsible; for none of them are toxic in relatively large doses. The diverse nature of the symptoms would suggest that they are due to more than one retention product, and it is believed[2,3] that absorption of putrefaction products, especially phenols, from the intestinal tract play an important part in the uremic syndrome.

Phenol, paracresol, indol, and other related substances are formed in the body as a result of processes involving deamination, decarboxylation and oxidation of the aromatic amino acids, tyrosine, phenylalanine and tryptophane. These phenols

appear to be formed chiefly, if not entirely, as a result of bacterial action on protein derivatives in the intestines. Under normal conditions, these substances are absorbed from the gastro intestinal tract, and are detoxified by conjugation with sulfuric or glycuronic acids. The adequacy of this detoxification depends upon the functional integrity of the liver, intestines and other organs that may be involved in these processes. Best and Taylor[1] state that the hepatic functions are defective in the uremic state and failure of the detoxicating function of the liver combined with renal insufficiency will permit the accumulation in the circulation of free phenols, as well as the less toxic conjugated compounds. Moreover, the symptoms of chronic phenol intoxication closely resemble those of uremia, and the introduction of aromatic amino acids into the rectum of uremic patients increases the severity of the symptoms. The onset of uremic manifestations coincides with the appearance of phenols in the cerebrospinal fluid.

Cantarow and Trumper[2] offer the following as an explanation for the symptoms in the uremic state: " Although there is little evidence that urea retention plays a significant role in the development of toxic manifestations, it has been suggested that,

according to the law of mass action, the retention of excretory products in the blood and body fluids may diminish the rate of disappearance of intermediary products which may be toxic and may thereby result in the accumulation of these substances which normally occur only in traces. Mason[3] found that high blood urea concentrations appeared to diminish the rate of disappearance of injected guanidine from the blood. It appears possible, therefore, that urea retention, while of itself relatively innocuous, may be indirectly toxic by favoring the accumulation in the body of poisonous products of intermediary metabolism".

A discussion of all the various types of renal pathology leading to uremia is outside the scope of this paper and only passing mention will be made of the most common of these lesions.

Glomerulonephritis[4] is an inflammatory condition affecting the glomeruli primarily but with secondary damage to the other parts of the nephron as well as the interstitial tissue later and may lead to renal failure and death due to uremia.

Nephrosis is a condition characterized by edema, albuminuria, low plasma protein and high

cholesterol levels. The lesion involved is mainly tubular degeneration. Toxic and lipoid nephrosis are common examples.

Arteriolar nephrosclerosis is primarily arteriosclerosis of the renal vessels causing ischemic atrophy of the glomeruli and tubules resembling that seen in chronic glomerulonephritis.

Among other chronic conditions of the kidneys which may lead to uremia is the intercapillary glomerulosclerosis described by Kimmelstiel and Wilson in long standing cases of diabetes often associated with benign hypertension in persons over forty years of age. In multiple myeloma the patient may develope anuria and die of uremia from atrophied tubules or dense casts which may excite a foreign body giant-cell reaction. Renal tuberculosis, congenital cystic kidney, obstruction of ureters, Wilms' tumor, cloudy swelling, fatty degeneration and amyloid degeneration are other causes of renal insufficiency.

In the recent war another type of lesion was recognized as causing anuria and death by uremia. This condition was first described in victims of air raids and was given the name "crush syndrome". Bywaters[5], who did the original work on crush nephritis,

suggested that the renal failure was due to blockage of the tubules by myohemoglobin casts, this pigment being derived from the injured muscle.

Lucke,[6] in his article on the "Lower Nephron Nephrosis" described the renal lesion as not being specific for the crush syndrome, but is found in any trauma, ischemia, burns, transfusion reaction, heat stroke, malaria, toxemia of pregnancy, alkalosis, sulfonamide intoxication and poisons. All of these conditions may show rapid progressive renal insufficiency complicated by shock and/or vomiting. The urinary manifestations include a decreased output usually in the first twenty four hours, which may persist and lead to anuria. There is a low pH, the specific gravity is low and fixed. There is a positive benzidine test for heme pigments, and proteinemia, granular and pigmented casts are present. There is an elevation of N.P.N. and potassium, and decrease in level of alkali reserve. There is an early but moderate hypertension which follows a definite sequence: first day there is a lowered blood pressure to shock levels, second day there is a restoration to normal and on the third day the blood pressure is elevated and maintained there.

The gross renal pathology consisted of a usually

swollen flaccid kidney from which the capsule strips easily. The cut surface oozes and the cortex bulges. The microscopic picture shows degeneration or necrosis in focal parts of the lower nephron. There is edema and cellular reaction in damaged tubules associated with thrombosis of adjacent veins. In the lower segment of the nephron there are casts of heme compound. In the upper nephron there is slight if any structural change. The glomerulus shows a decreased blood content, the capsular space is normal in width and contains an eosin staining granular, foamy or globular protein precipitate. The normal flat lining epithelium shows cuboidal swelling. The juxta-glomerula apparatus shows marked hypertrophy and increased granularity. The proximal segments are usually normal, but may show cloudy swelling, and heme casts are rarely found in this segment.

It is in the lower segment of the nephron that most pathology is seen. There is a wide range of damage varying from degeneration to necrosis and disintegration. Definite necrosis is seen on the third or fourth day. The lesions are characteristically focal. At times the most pronounced lesions are in the boundary zone or where the tubule is near a vein. There may be actual herniation and rupture of tubules at necrotic foci. Diverticuli are common in the

lower segment. Regeneration is evident after three-to-four days in the lower segment. New cells proliferate from undamaged epithelium and resemble endothelium at first and later become cuboidal. Casts are prominent, expecially in tubules immediately adjacent to thin walled veins. Non pigmented casts were less c common. Veins were observed to be involved in the general pathological picture as the normally thin walled tubules may rupture into the nearby veins and produce thromboses which are rarely occlusive. The collecting tubules were rarely observed to be involved in conspicuous degeneration, but heme casts were prominent.

The pathogenesis and functional disturbances observed in the lower nephron nephrosis are explained on the basis of the role of heme compounds, myohemoglobin and hemoglobin, and renal anoxia resulting from prolonged renal ischemia. The heme compounds are excreted through the glomerulus either by hydrostatic pressure, pores or increased permeability. When the hemoglobin concentration exceeds certain levels, it is believed that it exerts a specific transient vasoconstrictor action on the renal arterioles leading to a transient albuminuria via increased permeability of the glomerula membrane. Heme remains

in solution until it reaches the lower tubule and here it may be precipitated by unknown factors, perhaps by a low pH or an increased concentration of NaCl. The hemoglobin compounds are not in themselves considered to be toxic to the nephron, but toxic derivatives are most apt to form when the reaction of the urine is acid. Other nephrotoxic substances from injured tissue possibly include adenosine triphosphate. As long as the toxic factor from ischemic muscles is liberated slowly the liver is able to detoxify it. Uric and phosphoric acids may play a part in this condition as well as proteolytic enzymes from damaged muscle. The mechanism of oliguria is believed due to decreased renal circulation, obstruction of tubules and an unselective reabsorption of glomerulor filtrate. Extra renal factors which must be considered are: vomiting, dehydration, burns, hemorrhage, trauma and shock.

In order to better understand the problems in treating uremia, it will be well worth while to consider some of the physiological aspects of the kidneys, particularly the renal circulation. Trueta,[7] in a preliminary paper reported some interesting findings in his study of renal circulation. He found that with appropriate nerve stimulation,

the renal blood flow could be diverted from its commonly accepted course, and that, as a result, the cortex may be partially or wholly deprived of its supply. To locate the by-passing channels histologically, particulate material was injected in place of dyes, and was found to fill the vasa recta and their loops as well as a sub cortical phexus of vessels of more than capillary caliber, suggesting that these two sets of vessels were the anatomical channels involved.

The result of this experimental work stresses the importance of a mechanism by which a temporary or permanent cortical ischemia may be produced without arrest of renal circulation. In many of the conditions in which anuria is found, lesions in the cortex interpreted as being due to ischemia are constantly present, and in addition the medulla is found to be congested. An explanation for these lesions may be found in the neurovascular mechanisms demonstrated on experimental animals. It seems that nerve stimulation could be produced centrally or peripherally by a veriety of noxious agents as in the lower nephron nephrosis, and that the picture is the result of a defense mechanism by which the cortex of the kidney is excluded from the circulating

toxin or other noxious agents.

The same protective mechanism may fulfill another role in hemorrhage and shock or conditions with decreased blood volume by preventing the blood from reaching the filter of the kidney (cortex) and thus conserving fluid.

The concept of a functional change over, under various conditions to medullary renal circulation has obvious physiological, pathological and clinical implications. For instance, the interpretation of renal function tests must be reconsidered. The pathology of hysterical uremia, emotional anuria and post abortum and post traumatic uremia, and the response of these last two to splanchic block are readily explained.

Trueta[7] does not believe that the vasa recta are concerned with the nutrient requirements of the tubules in the medulla, but that their most important function seems to lie in the provision of an alternative route for the blood flowing through the kidney, whereby the important cortical circulation may to a variable degree, be shut down. Thus it becomes understandable how physiological diminutions in urinary output may be adjusted, for example, when large amounts of fluid are being eliminated

from the body by other routes without greatly diminishing the blood flow through the kidney. It seems reasonable to suppose that during active diuresis, the cortical circulation is fully open, while in anuria the medullary circulation is in action and the cortical circulation is thus bypassed.

In a more recent work Trueta[8] and his team of investigators showed that procedures which resulted in the appearance of a cortical ischemia included application of a tourniquet to a hind limb, stimulation of various nerves including sciatic, splanchnic and nervous plexi surrounding the renal artery, rapid hemorrhage, adrenalin, pituitrin, pitressin and staphylo-coccic toxins. Results indicated that the arterial vessels which are situated in the peripheral 2/3rds. of the cortical zone are more sensitive to stimuli than are those parts of the arterial tree situated proximal to those in the deepest layer of the cortex. These investigators have seen peripheral segments of the interlobular arteries to be markedly constricted and sometimes even completely closed, while the proximal segments were relatively unaffected and so allowed blood which was barred from access to the

peripheral cortex to make an intrarenal circuit through the medullary pathway.

The vessels which form the channels of the medullary pathway are those associated with the juxtamedullary glomeruli , those which form the channels of the cortical pathway are the vessels associated with the cortical glomeruli. The difference in the morphological arrangement of the vessels which make up the two pathway comprise two striking features: 1. A marked disparin size between the efferent vessels of the juxtamedullary glomeruli. 2. An equally marked disparity, both in size and arrangement between the repective vascular beds into which the efferent vessels of the cortical and juxtamedullary glomeruli empty.

The loops of Henle of the tubules of cortical glomeruli pass only a relatively short distance into the medulla and the thin segment of these loops are very short. On the other hand, the loops of Henle of the tubles of the juxtamedullary glomeruli descend deeply into the medulla, often extending as far as the medullary papilla, and the greater part of one of these loops is made up by the thin segment. One feature in common of these tubules is that part of the loop lies in the medulla and it must be of no small

significance that considerable parts of all loops of Henle including in each case the thin segment of the loop, are supplied by blood circulating through the medullary pathway. The difference in morphological arrangement of both the vascular and tubular structures associated with the cortical and medullary circulation respectively suggest the possibility that there are equally profound differences in their function.

A possible function of the vasa recta may be that of water reabsorption, as many of the vasa recta are near loops of Henle where these lie in the medulla and their walls are morphologically well suited for transfer of fluid. These vessels are most profuse in the sub cortical zone of the medulla and here the venous elements are strikingly predominent. Interstitial fluid may play a part in effecting a transfer of fluid between the tubules and vasa recta.

The above discussion on renal circulation aids us in understanding the severe and profound physiological change which occur in uremia. Advanced renal failure results almost invariably in a state of acidosis, which is therefore an almost invariable manifestation of the uremic syndrome. There is an

actual sodium deficit and depletion of the alkali reserve which is contributed to by failure of the ammonia-forming and acidification mechanisms in the kidneys with the consequent loss of excessively large quantities of sodium in the urine; by polyuria, at times, especially in chronic glomerulo-nephritis, with consequent elimination of excessive quantities of sodium in the urine, by excessive vomiting which usually contains appreciable amounts of sodium chloride; by diarrhea, with the loss of large amounts of sodium, and by retention in the body of excessive quantities of anion, including phosphate, sulfate and undefined organic acids.

The problem of combating the condition of uremia has been one of the most perplexing and serious in medical history and as yet there is no completely satisfactory method, although many investigators have studied the problem, and have presented several ingenious approaches to the solution of this condition.

One of the attempts to alleviate anuria has consisted of gastric lavage. Oschner, Vermouten and Hare[9] used continuous gastric lavage and removed considerable quantities of urea with a consequent lowering of N.P.N blood level. Bliss Kastler and Adler[10] were able to demonstrate considerable amounts

of urea in vomitus of uremic animals, but expressed the opinion that the prospects of gastric lavage as a satisfactory means of extrarenal excretion is not encouraging since, in cases of uremia, nitrogen accumulation exceeds the maximal rate of removal. White and Harkin,[11] after continuous irrigation with hypertonic fluids of high intestinal loops of dogs made uremic by bilateral nephrectomy, found that such a procedure resulted in removal of fairly large amounts or urea, but did not appreciably prolong the life of the animals, although the average terminal blood urea nitrogen level was decreased by about twenty six percent. Fine, Frank and Seligman[12] tried continuous irrigation of a loop of ileum in one of their cases, but found so poor a clearance of blood urea by this means that they estimated that perfusion of a loop two hundred inches (five meters) long would be required to achieve a blood urea clearance of ten cubic centimeters per minute, the approximate clearance necessary to avoid development of uremia.

The wide variations in the results obtained by different investigators using different segments of gastro intestinal tract as a means of excreting waste products indicates an unsatisfactory method and points out the need for further study to explain the inter-

change of fluids, electrolytes and other crystalloids across the wall in different segments of the intestinal tract.

The principles involved in attempting to use a surface other than the glomerulus for a dialysis consist of the fact that crystalloids in solution diffuse across semi permeable membranes until equilibrium is reached, and that colloids such as protein do not diffuse across a membrane separating a non diffusable and a diffusable substance on the other, the concentration of diffusable non electrolytic substances per unit of water on each side of the membrane will eventually become equal but their concentration per unit volume will be less in the solution containing the non diffusable substance. In the kidney a glomerular filtrate is produced which is similar to blood plasma except for the absence of protein. Since the action of glomerular filtration is considered to be a purely physical one, it should be possible to substitute a semi permeable membrane for glomerular filtrating sufface.

Abel, Rountree and Turner[13] were the first to adopt the above principles and devise a means of external dialysis consisting of a closed container enclosing a branched system of celloidin tubes through

which blood flowed. They used sodium chloride in six tenth per cent solution as a dialyzing fluid. Other attempts at external dialysis, i.e., development of an artificial kidney, consisted, at first, of circulating of arterial blood with return through the venous side through several coils of cellulose acetate tubing ( sausage casing) bathed in warm tap water.[14] The tube was two and one half centimeter in diameter and presented the primary disadvantage of the ratio of volume to surface area. Later smaller tubing was used which gave better results. From these experiments it was shown that blood could be circulated outside the body and that with a reasonable length of dialyzing tubing, moderate amounts of non protein nitrogen can be removed in short periods.[33] When twelve and ninety seven hundredths grams of N.P.N. were removed from a patient[14] by this method and readings of the blood showed only a slight depression of the level of N.P.N., it was obvious that the removal was bringing down the level of these toxic substances in the vital fixed tissues of the patient.

The peritoneum has long been recognized as an excellent dialyzing membrane with a filtering surface of approximately twenty two thousand square centimeters in the average adult, compared with an approximate

glomerular filtering surface of fifteen thousand square centimeters.[15]

Cunningham[16] describes the structure of the peritoneum as consisting of a connective tissue layer made up of cells and fibers covered by a layer of flattened endothelial or mesothelial cells. He believes that the mesothelial cells are distinct cellular entities but may have some very close type of association. After irritation the mesothelial cells undergo change in size, shape and arrangement, tending to become more numerous and generally rounded up. Most, if not all, of the particulate matter that is absorbed from the peritoneal cavity passes directly through the living cytoplasm of the mesothelial cells.

Fleisher and Loeb[17] experimented on peritoneal absorption using uranium nitrate and sodium chloride. They found that the relative absorption of sodium chloride from the peritoneal cavity is decreased in experiments with animals one day after injection of uranium nitrate. The diminished relative absorption of sodium chloride stands in relation to the high sodium chloride percentage in blood serum. In this case the movement of sodium chloride appears to have been regulated in conformity with the laws of diffusion.

Putnam[18] studied the osmotic equilibrium between

blood plasma and fluids in the peritoneal cavity and found that certain dialyzing fluids showed a decrease in volume while others showed a temporary increase in volume, which he believed was due to an irritating action of the fluids. He found that salt concentration of less than one per cent are well tolerated in animals and showed a decrease in volume and at the same time there appeared urea, protein, and sugar in the fluid. He concluded that crystaline solutes and water tend to diffuse through the peritoneum and capillary endothelium both from and to the blood stream in such a way that solutions in the peritoneal cavity come into a more-or-less complete osmotic equilibrium with blood plasma. Colloids do not pass from plasma into peritoneal fluids although even particulate matter is absorbed from serous cavities. The mechanism of transmission either from or to the peritoneal cavity is based on the passage of small molecules through a permeable or semi-permeable membrane; passage of small and large molecules and perhaps particulate matter through microscopic or ultramicroscopic spaces, or some form of vital activity, phagocytosis by serosa cells. To explain passage of small molecules but not large ones in both directions through the peritoneum, Putnam states, "We are forced

to predict the existence of a membrane, not necessarily endowed with vital powers, microscopically continuous, but physically pervious to particles of size of molecules of phenosulphthalein or smaller. Such a membrane might be cellular or intercellular. In addition we must imagine some mechanism by which all fluids introduced into the peritoneum are progressively absorbed together with particles even of microscopic dimensions which they may contain."

Clark[19] demonstrated that the rate of absorption of a substance across the peritoneal membrane is proportional to the rate of diffusion of that substance. When a solution of sodium chloride was introduced, because the rate of diffusion of chloride is greater than the average rate of diffusion of the constituents of blood, a fairly rapid rate of absorption of fluid occured early, whereas, later, various slowly diffusible substances entered the peritoneal fluid from the blood stream and as the osmotic pressure of the peritoneal fluid increased, the absorption of water became slower.

Hahn and Miller,[20] using radioactive iron in dogs, found that the red blood cells containing the iron in hemoglobin could be given intraperitoneally. They found that the diaphragmatic portion of the peritoneum

is most active but other-areas participate in the red cell uptake. The peritoneal absorption varies widely in different dogs and in the same dog, at different times. The intact red cells pass readily from the peritoneal cavity into lymph spaces in the diaphragm and other areas of the peritoneum. These cells move along the lymphatics and through the lymph glands with little or no phagocytosis and eventually into the large veins through the thoracic duct.

On the basis of the above principles, peritoneal irrigation has been used in an attempt to treat uremia,[21] for it was known that crystalloids in circulating blood readily diffuse into fluid placed in the peritoneal cavity and considerable amounts of N.P.N. substances can be removed from the blood in uremic animals. In one of the earliest attempts to utilize peritoneal dialysis in the treatment of clinical and experimental uremia, saline was introduced into the peritoneal cavity and transient clinical improvement was noted. However, if a five per cent solution of glucose is used, there is a decrease in total electrolytic concentration in body fluids and water was transferred from the extracellular to the intracellular compartment with resulting production of symptoms of acute dehydration.[22] This situation emphasizes the fact that if the

normal electrolyte pattern of the extracellular fluid is to be re-established, the irrigating fluid must have a normal electrolyte pattern.

Different investigators have reported their experiences with the use of peritoneal dialysis in the treatment of uremia. Basset, Brown and Keitman[23] used peritoneal irrigation continuously for twenty-one days in a patient with subacute glomerulonephritis who became almost completely anuric two days before irrigation was started. The flow of urine was not re-established and the patient died. The total nitrogen removed by the way of the peritoneal cavity was two hundred and fifty seven and eight tenths grams. Substantial reductions in the concentration of blood N.P.N. and serum inorganic phosphorus were obtained at first, but as the patient lost edema fluid, these values rose above the pre-treatment levels. This was thought to have been due to a more rapid loss of water from the body than of N.P.N., rather to an increase in nitrogen catabolism.

Abbott and Shea[24] felt that intermittent washings of the peritoneal cavity would cause less difficulty and would be less apt to produce a state of overhydration. It was also felt advisable to use a sterile solution which chemically resembled an ultra-

filtrate of plasma. Peritoneal lavage of a five per cent solution of dextrose, Ringers and Hartman's solution was used to determine the time of maximum diffusion of nitrogenous products one hundred cubic centimeters per kilogram of lavage fluid was given intraperitoneally. The five per cent dextrose in distilled water caused a marked hemoconcentration and an increase in plasma protein concentration while the plasma chloride concentration fell to very low levels. These changes were due to a shift of electrolytes into the ascitic fluid and water into the intracellular compartment with a resulting dehydration of the extracellular fluid phase. Ringer's solution caused only sight increase in plasma and plasma protein concentration with a slight increase in plasma chloride levels. Considerable amounts of bicarbonate was lost from the extracellular fluid while chloride passed from the injected fluid into the extracellular compartment. It was concluded that the factors which lead to death when kidney failure occurs can apparently be corrected or prevented by employing peritoneal lavage for short periods and that the normal daily output of urea nitrogen can be approximated or exceeded by the use of peritoneal lavage. The maximum diffusion of urea nitrogen into the lavage fluid apparently occurs

in from two to four hours. It is believed that the best means of lavage consists of intermittent injections and withdrawals of a solution which has a chemical composition, similar to that of interstitial fluid and which is made slightly hypertonic by the addition of small amounts of dextrose or gelatin or pectin.[24]

British workers[25,26] report varying results on the use of renal decapsulation as a means of treating anuria. One group[25] reported a case of anuria following incompatible blood transfusion in which they tried to promote diuresis by the administration of fluids. They were unable to relieve the anuric condition and felt justified in doing a renal capsulectomy, and on operation they found the kidneys to be swollen. They noted a remarkable expansion of the kidneys following section of the capsule and on the basis of the subsequent diuresis they suggest that the relief of tension was an important factor in renal recovery. They also had used the peritoneum as a dialyzing membrand and believed it played a large part in the recovery of the patient as a large quantity (seven grams) of urea was recovered from the peritoneal washing. One of their most interesting points shown by the pathological findings was therise in blood urea level after the peritoneal irrigation

became inefficient owing to the blockage of the tube. Possibly the introduction of seven liters of twice normal saline into the peritoneal cavity reduced the volume of vascular fluid by osmotic pressure and that affected the kidney by relieving edema.

The other British workers,[26] describing their treatment of acute renal failure complicating abortion, found that decapsulation was not of benefit and seemed to tip the scales against the patient. They could not believe that mechanical pressure on the tubules by the acute swelling of the confined kidneys as a cause of anuria. Conservative measures, using fluids to overcome negative fluid balance, consisting of five per cent hypertonic dextrose in physiological saline in amounts of three to four pints daily by slow intravenous deip has been the most efficient means of increasing diuresis and replenishing the mineral content of the plasma. Two good results were obtained by splanchnic blocks which break up the reflex arc through which sympathetic reflexes pass. In any case of anuria, the British investigators warn against overhydrating the patient and further embarrassing the overloaded kidney.

Muirhead, Vanatta and Grollman,[27] using an artificial kidney, were able to prolong the life of

nephrectomized dogs up to nineteen and a half days. They point out the fallacy of trying to evaluate the efficiency of any artificial kidney in terms of removal of urea or N.P.N., for the animals from which most urea was removed had the shortest survival periods. Their experience with twenty seven cases of oliguria seems to contradict the general statement that the mortality of patients with acute renal insufficiency is eighty to ninety per cent. They found that the course of urinary output in their patients followed a characteristic curve with a period of anuria or ologuria followed by diuresis. The peak of diuresis may occur on the eighth to eighteenth day, depending on the severity of the case.

From the foregoing description and discussion of the treatment of anuria, it is obvious that at present there is no general agreement as to what measures are the most favorable and adequate for treatment. On the one hand, there is a school of thought[28,32] that believes conservative measures consisting of: (1) overcoming peripheral vascular shock when present by prompt administration of whole blood or plasma, (2) administering only such amounts of water and glucose solutions as are required to prevent dehydration; and (3) administering adequate amounts of salt and water when

diuresis sets in so as to maintain a normal water and electrolyte balance, are safer and more effective than procedures using artificial kidndys, peritoneal lavage or other measures for removal of waste products.

It has been pointed out[28] that acute renal failure is often a self-limited reversible disease, and that the reparative power of the kidney is great, and the clinical problems encountered are different in each case, and hence in the management of acute renal failure, strict individualization of treatment is essential.

In the conservative management of the anuric patient, careful clinical appraisal of the patient's condition during the period of acute renal failure is of paramount importance. Daily evaluation of the state of nutrition, of the circulation of the fluid requirements of the patient must be made. Early measures include replacement of blood and protein as needed to combat shock, the use of vasodilating agents such as heat and x-ray, applied over the kidneys and aminophylin, and histamine diphosphate. Sympathicolytic agents such as tetra ethyl ammonium chloride have been used for the porpose of blocking renal sympathetic stimulation and renal vasoconstriction. The use of diuretic agents in the early stages of acute

anuria is to be condemned as they may cause additional renal damage, especially the mercurial agents. Paravertebral block of the renal sympathetic ganglia with procaine hydrochloride should be helpful if renal supression is due to renal vaseconstriction.

In the period of oliguria or anuria, dietary measures must be taken to combat the anorexia, nausea and vomiting which are usually present in prolonged cases of anuria. Intake of protein should be reduced to a minimum in order to lessen the excretory load that protein metabolism imposes on the kidney, and also to prevent increasing azotemia and further renal damage. However, the diet must be sufficiently high in carbohydrate and fat so that the protein sparing properties of these foodstuffs will prevent the breakdown of endogenous stores of protein and the patient will be kept in positive nitrogen balance.

The rice fruit diet of Kempner[29] and the high carbohydrate, high fat, low protein diet of Borst[30] should be ideally suited for this porpose, because it is felt that if the patient could eat a low protein diet, sufficiently high in carbohydrate and fat to prevent breakdown of endogenous protein, the rate of accumulation of nitrogenous and other waste products in the blood would be materially retarded. Thorn[31]

has stated that during the early stage of anorexia and vomiting, fifteen per cent solution of glucose used as an intravenous infusion will reduce the breakdown of endogenous protein; yet a hypertonic solution must be used with great caution in order that the fluid may not be pulled from the extracellular spaces into the circulating blood, with consequent production of hydremia. When acidosis is present, five per cent sodium bicarbonate or sixth molar sodium lactate may be used.

In the postanuric stage with resumption of urine formation and onset of diuresis, the danger of dehydration must be realized and watched for by laboratory studies of chloride and other electrolyte levels and fliud balance.

On the other hand there is a group[15,21,24,25] that believes there is definite indication for the use of peritoneal lavage in those conditions associated with acute urinary suppression on the basis of temporary renal damage, or a reversible kidney lesion, as in the many conditions met with in the lower nephron nephrosis syndrome. They believe that the efficiency of peritoneal irrigation in terms of urea clearance suggest that this technique may be the basis for an adequate clinical substitute for renal function for

a period of time sufficient to allow the kidneys to regain their function. However, it is emphasized[15] that from the standpoint of therapeutic value, patients who have renal failure and uremia secondary to advanced organic renal parenchymal damage should be considered as unsatisfactory candidates for peritoneal lavage, because, although temporary alleviation of symptoms with regression of laboratory evidence of azotemia may occur during the lavage period, signs and symptoms of progressive renal failure and uremia again ensue as soon as the procedure is terminated.

The choice of a proper solution for use in peritoneal dialysis is very important in this procedure if the normal electrolytic balance is to be maintained. Various solutions have been used which were considered to be physiological but proved to be unsatisfactory because of alterations in plasma chloride and carbon dioxide combining power levels, or because they produced acidosis or edema.

A suitable perfusing fluid should be: 1. One that will not alter the normal electrolyte pattern of the plasma and extracellular fluid, 2. one that permits a maximal diffusion of nitrogenous and other waste products of a crystalloid nature into it, 3. One whose tonicity should be such as to insure against water

exchange, in so far as possible. The solution should be as non irritating to the peritoneum as possible in order to reduce hyperemia and exudation with decrease in the efficiency of the filtering membrane.

Hartman's, Kolff's and the "A" solution of Abbott and Shea[15,24] appear to fulfill the above criteria. To these sterile solutions, penicillin is added in an attempt to inhibit contamination of the fluid and bacterial growth in the peritoneal cavity. A sterile solution of heparin is added to inhibit the formation of fibrin on the peritoneal surface. As protein has been recovered from the perfusing fluid in sizable amounts and this fact in association with a decrease of the value of plasma protein levels suggests that there is a loss of protein across the peritoneum, and for this reason, gelatin pectin or acacia may be added to the fluid in an attempt to block loss of protein.

The apparatus consists of a flask, siphon tubes, a constant temperature water bath and a peritoneal inlet tube. The outflow tube is connected by a section of rubber tubing to a constant suction apparatus. A Berkefeld filter may be used in the system as further prophylaxis against peritoneal infection. Rubber or stainless steel tubes have been used as inlet tubes

with a large base mushroom tip catheter or a stainless steel sump drain has been used. Leakage of fluid around the peritoneal tubes, matting of the omentum and intestinal coils due to peritoneal irritation with resultant channeling and a loss of fluid, and peritoneal infection are three immediate complications of the procedure.[15,25]

The optimal time for starting peritoneal lavage in cases of renal insufficiency will depend on the appearance of clinical evidence of uremia or until it seems certain that spontaneous resumption of kidney function will not occur, and the failure of routine conservative measures to induce diuresis.

In order to make use of the greatest possible area of peritoneal surface, the inflow tube should be inserted in one of the upper quadrants of the abdomen and the outflow tube in the opposite lower quadrant. The rate of inflow is adjusted to allow as rapid a flow as possible without causing discomfort to the patient, or to allow a rate of flow of thirty to fifty cubic centimeters per minute, which was found by Seligman, Frank and Fine[21] to be the optimal rate.

During the lavage period it is very important to watch the electrolyte balance of the patient's blood carefully by doing a daily determination of the blood

urea, plasma chloride and carbon dioxide combining power. If the lavage fluid is electrolytically correct, the blood levels for these tests should maintain themselves at normal or near normal levels without the necessity of parenteral replacement. Parenteral therapy is used to supply needed vitamins, water balance, nutrition and to correct anemias and hypoproteinemia. Fifteen hundred to two thousand cubic centimeters of fluid daily should be adequate to maintain water balance and avoid the danger of overhydration. Five per cent dextrose in distilled water is the fluid of choice for nutrition and fluid level balance.[15]

It is believed that continuous lavage is more effective than intermittent, and that it should be maintained until the level of urea in the blood falls to less than one hundred miligrams per one hundred cubic centimeters and until the twenty four hour excretion of urine exceeds one thousand cubic centimeters in volume or until the amount of urea excreted in urine equals or exceeds the amount excreted in the dialysate in the corresponding twenty four hour period.

## Summary

An explaination for the symptoms of uremia is presented on the basis of altered physiology in the body of a uremic patient. Special attention is paid to the mechanism of production of the so called lower nephron hephrosis with a detailed description of both gross and microscopic pathology. The studies of Trueta on renal circulation and their implications is fully detailed. The various methods of utilizing an artificial kidney are presented and the results noted. The use of the peritoneum as a dialyzing membrane is discussed and the results of various investigators are compared. The indications for and against peritoneal dialysis are presented, the choice of an adequate solution, the precautions and obstacles to be considered and the method of perfusion are explained.

## Conclusions

The question of treatment in acute uremia resolves itself into two phases. The first consists of conservative measures in which shock, if present, is combated and fluid balance is maintained and overhydration avoided until spontaneous recovery of renal function takes place. The second phase consists of more active measures, including splanchnic block and peritoneal dialysis or use of an artificial kidney when clinical judgement decides conservative measures and spontaneous recovery will not suffice. Then the peritoneal lavage must be continuous for at least eighteen days, or until renal function has recovered. Renal capsulectomy is not entirely abandoned, but is considered as a possible procedure.

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