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Acute renal failure: a review of the literature

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TABLE OF CONTENTS

INTRODUCTION AND PURPOSE

The problem of acute renal failure has long been known as a member of that family of disorders, "Bright's Disease", more specifically as acute Bright's disease. (1,2,3,4,5,6,7,8,9) Jeghers and Bakst (10) in 1938 devised the term "pre-renal azotemia" to describe the syndrome, underlining the fact that the primary difficulty was not in the kidney itself. Bywaters and his associates first delineated the syndrome in the years from 1941 to 1948. (11, 12, 13, 14, 15, 16) It was the second World War which precipitated the work of Bywaters. This emphasizes the close association between catastrophic illness and renal failure. Bywaters and his group were struck by the high incidence of anuria in patients who had undergone crushing injuries, hence the term "crush syndrome". (10) Lucke in 1946, writing in "Military Surgeon", emphasized what he thought to be the essential pathology of the disease and the term "lower nephron nephrosis" came into being. (17) His work was not substantiated by other investigators. (18, 19, 20) However, this term has become popularly accepted for the condition. After the second World War the study of acute renal failure slowed, but with the coming of the Korean conflict interest in the problem was renewed. By that time medicine had more tools to combat the usual causes of death in wounded soldiers. Antibiotics reduced the danger of infections, immunizations protected against endemic diseases, blood and blood substitutes aided the early treatment and/or

prevention of shock, and the rapid evacuation of severely wounded made possible operative treatment within hours of the time that a man was wounded. Renal failure remained a major hurdle for medicine to surmount. From the studies by the men and women associated with the Renal Insufficiency Center in Korea came many of the present concepts of pathogenesis and treatment of acute renal failure. (22, 23, 24, 25) The work of this group when with the concurrent work of Swan (26), Merrill (27), Van Slyke (28), Grollman (29), Kolff (30, 31, 32, 33, 34, 35) and Oliver (36, 37, 38), to name a few, has resulted in a fairly unified concept of the syndrome, from pathogenesis to treatment. This unified concept emphasizes the importance of acute renal failure in all aspects of medicine as discussed in the section of this paper entitled "Pathogenesis." Acute renal failure is not a problem confined to military or civilian disasters.

I have attempted to outline the present concepts of the syndrome of acute renal failure, including some of the history of the condition. This presentation will be neither exhaustive nor definitive since the mass of papers which have been written on the subject is too great to cover adequately and since the present concepts in themselves are not definitive in nature. Instead an attempt will be made to present a practical working approach to the problem of acute renal failure.

DEFINITIONS

Although all of the terms to be used in this paper are in common use in medicine, a few of them should be sharply defined so they will be clearly understood.

Acute renal failure: Acute renal failure occurs when the kidney fails to clear the plasma of normal metabolites in the absence of hypotension, dehydration or obstruction of the urinary tract. This definition will be discussed in greater length in the section on treatment.

Oliguria: Urinary output insufficient to clear the plasma of normal metabolites adequately is a broad definition of oliguria, but for the purposes of this paper a more precise definition is necessary. Stock (39) stated that oliguria exists whenever a 70 kilogram man excretes less than 250 cc. plus any water consumed in excess of 750 cc. per day, when that man is receiving 100 grams or more of carbohydrate per day. Stock reasoned that about 500 cc. of urine output per day is required by a normal 70 Kg. man, who is fasting and thirsting, in order to prevent retention of solutes. He referred to Gamble (40, 41) on this and most of the following. The minimal urine output may be reduced to about 250 cc. by the daily administration of 100 grams of carbohydrate relying on the protein sparing action of the carbohydrate preventing ketosis, as pointed out by Gamble. (41) Under these conditions of thirsting and with an intake of 100 grams of glucose, fluid in the form of urine and insensible water is lost at the expense of preformed

body water. Gamble demonstrated that a water intake up to 750 cc. will spare an equivalent amount of preformed body water without increasing fluid loss. (41) However, any water intake in excess of 750 cc. is excreted in the urine.

Teschan and his coworkers (24) set the minimum daily urine output simply at 500 cc. under thirsting conditions and used this figure as a criterion for eliguria. This amount seems to be the generally accepted minimum and any further diminution in the obligatory daily urine output shall be discussed as treatment of eliguria. I will refer to eliguria as a daily urine volume less than 500 cc.

Diuresis: According to Teschan (24) diuresis occurs when the daily urine volume equals or exceeds 1000 cc. after a period of eliguria.

PATHOGENESIS

Acute renal failure is not a disease of the kidney primarily, with the exception of failure caused by heavy metals, carbon tetrachloride, diethylene glycol and other specific nephrotoxins. The syndrome, therefore, is split immediately into two distinct entities. The first is an acute failure of the kidney which occurs as a complication of some grave insult to the organism and the second is a failure of the kidney due to the specific action of a material on that organ. A clear distinction between the two conditions will be shown later both from the standpoint of pathology and pathogenesis. It will be shown also that while the two conditions differ basically in their pathogenesis and pathology, toxic renal failure can be thought of as a relatively mild form of the renal failure which occurs as a complication of other injury. It is for this reason that the remainder of the discussion shall dwell for the most part on the latter syndrome.

According to Moon (42) there are some fifty diverse conditions which may lead to acute renal failure and he contracts these into ten general groups.

1. Extensive trauma and/or surgery.
2. Thermal injuries, including heat stroke.
3. Effects of atomic and roentgen radiation.
4. Severe infections.
5. Abdominal catastrophes.

6. Allergic reactions, including transfusion reactions.

7. Sundry metabolic disorders.

8. Poisoning with various drugs and chemicals.

9. Anesthetic agents, barbiturates and others.

10. Lack of oxygen, from whatever cause.

Recognition of these etiologic factors is not new, but grouping them all together and recognizing that they may all cause the same general syndrome was a valuable contribution. Formerly each of the approximately fifty causes was thought to give rise to a separate entity such as "hemoglobinuric nephrosis", "crush syndrome", "sublimate kidney", etc. The recognition of acute renal failure as a syndrome which may result from any serious injury to the organism is of great importance. The common denominator will be discussed later.

Reinhardt in 1852 listed the causes of "acute Bright's disease" as cholera, acute exanthemata, typhus, other febrile diseases and extensive wounds. (2) He thought the immediate cause of kidney failure was obstruction of the tubules by casts. Cohnheim (3) and Ziegler (4) agreed with Reinhardt but added toxemia of pregnancy as a cause. Osler added toxins and believed them to be the primary cause in most of the previously mentioned disorders. (5) Senator in 1899 emphasized two groups of etiologic factors, (a) infectious diseases and (b) toxins and trauma. (6) Jeghers and Bakst in 1938 made clear the fact that the condition was not a primary disease of the kidneys and that there was usually no pre-existing renal disease. (10) Bywaters and his colleagues

working during the Battle of Britain described the "crush syndrome" (11, 12, 13) and advanced the concept of lower nephron destruction. Although the pathogenesis was not defined by Bywaters he believed the difficulty was closely associated with myoglobin damage to the kidney and stated that anoxia could not be a cause since that damaged the upper nephron. (14, 15, 16) Mallory, however, in 1947 stated that hemoglobinuric nephrosis was associated with damage throughout the renal tubule and occurred especially after shock. (21) Shock had already been implicated by Moon (18) in 1942 and he later emphasized the importance of shock in 1947 and 1948. (19, 20) Oliver stated rather flatly in 1951 that the "ischemic episode" was the one common denominator in acute renal failure. (37)

Moon (42) discussed the pathogenesis of acute renal failure in length and concluded that the only common factor in all of the conditions which give rise to renal failure is peripheral circulatory insufficiency, often subclinical. Moon quoted Duncan and Blalock (43) who showed that experimental crushing injuries led to shock and then to oliguria, and Lauson who reported 35 cases of renal failure all associated with shock. (44) Moon discussed the various other factors that had been suggested as causing oliguria. He stated that the explanation of tubule blockage by casts was inadequate because blockage is not always present and in no case does great dilatation occur above the point of alleged blockade. (Reinhardt (2) in 1852 had described dilatation of the lumina above casts of blood cells, epithelium

and pigment, however.) Hypotension is not the sole factor because the blood pressure may have been maintained at normal levels before and during oliguria. Excess elaboration of anti-diuretic hormone has been suggested but Moon dismissed this on the grounds that although ADH may cause oliguria it does not cause proteinuria which often occurs in renal failure. Moon concluded that renal anoxia was the one best explanation for the tubular damage seen in acute renal failure. The next question is that of the genesis of the anoxia and then the question of how anoxic tubular damage causes oliguria.

Trueta (45) hypothesized an arterio-venous shunt that diverted blood flow from the cortex of the kidneys but this was and is disputed by most other authors. Van Slyke (28) showed that an immediate decrease in renal blood flow occurs as part of a systemic reaction to shock. He stated that the only shunt resulted from the decreased head of pressure that reduced the supply of blood to the renal cortices. Maxwell (46) showed by renal clearance studies in man that there was a severe decrease in renal blood flow in shock which resulted in a diffuse cortical ischemia but not necessarily as a result of a shunting mechanism per se. Bleck and his coworkers (47) reported that hypotension from hemorrhage was consistantly followed by renal insufficiency and an oliguria lasting two to three days after the blood pressure was returned to normal levels. Hamilton and Phillips (48, 49) removed the right kidney from a series of dogs and clamped the left renal artery for varying lengths of time.

They found that dogs uniformly survive clamping of two hours duration, some dogs survived 3-4 hour clamping but no dogs survived longer periods of clamping. In dogs subjected to three hours of clamping the greatest mortality occurred in the summer. After removing the clamp the urea clearance remained low for varying lengths of time and the blood urea nitrogen gradually increased proportional to the decrease in urea clearance. The dog either recovered completely in up to a month's time or died in gradually progressive uremia. Teschan stated "...hypotension appears to be a primary etiological factor, though lay in therapy, inadequate blood replacement, increased plasma hemoglobin and other pigments, and severity of the wound may contribute to the extent of renal damage and to hypotension." (24) Oliver, MacDowell and Tracy (37) outlined the pathogenesis of acute renal failure as follows:

1. Crushing injury --> shock --> renal ischemia --> random disruptive tubular damage --> anuria --> uremia --> death.
2. Toxins --> diffuse nephrotoxic proximal tubular damage --> dehydration, potassium poisoning, enteritis, diarrhea --> circulatory collapse --> renal ischemia --> random disruptive tubular damage -- anuria -- uremia ---> death.
3. Moderate poisons -- diffuse nephrotoxic proximal tubular damage ---> oliguria or temporary anuria ----> possible uremia ----> regeneration ----> recovery.

It oan be seen from he foregoin& outline that the one oonmon factor in renal failure is renal ischemia. Oliver pointed out that moderate poisoning damaged only the epithelial cells of the proxinal tubule while the basement membrane remained intact but when ischemia was also a factor the basement membrane throughout the length of the tubule was disrupted and renal failure ensued. Kolff (55) strongly emphasized the ischemic episode and made clear that the most important point in prevention of renal failure was the constant maintenance of adequate blood pressure.

Although it is generally agreed that hypotension may be an important factor in the etiology of renal failure it is also apparent that other factors are probably involved. The experiments of Hamilton and Phillips (48, 49) indicate that the brief instances of hypotension so often seen in human patients would probably not be sufficient in themselves to cause renal failure since absolute loss of a11 blood flow in the kidneys of dogs for up to three hours did not uniformly lead to renal failure. Of interest in this light is a report by Newrman and Pocock (50) that in a series of kidney transplants, the kidney which had been ischemic longest survived longest. This was probably based on a report by Hume (51) and factors other than ischemia entered in.

Kolff suggested that unidentified substances may be re-leased from hemolyzed blood or from injured or ischmic parts and contribute to renal failure. (35) Rice, et al (52, 53) suggested that electrolyte imbalance inself may contribute to renal failure. They found a close correlation between electrolyte imbalance before

death and evidence of tubular degeneration an autopsy. Since no histologic studies were carried out during the course of the disease leading to death no conclusions can be drawn as to which came first, the tubular degeneration or the electrolyte imbalance. Oliver (37) did mention the contribution of potassium intoxication to renal failure in relation to the action of nephrotoxins, however. Pigment casts and other casts, as though they may not block all of the tubules could play an important role in contributing to localized areas of ischemia in the kidney tubules. (37) Edema of the kidney may result in a longer period of ischemia in the kidney than elsewhere. (38)

The mechanism of oliguria in renal failure is no better understood than the etiology of the tubular degeneration. Phillips and Hamilton (48, 49) determined glomerular and tubular function after varying periods of ischemia, measuring PAH and Creatinine clearances. They found that renal blood flow in all cases quickly resumed at nearly pre-ischemic rates after release of the clamp and that PAH and creatinine extraction were not markedly affected after 20 or sixty minutes of ischemia. Two hours of ischemia, however, reduced creatinine extraction in three experiments to 63, 26 and 9 per cent of pre-ischemic values and PAH extraction in four experiments to 37, 14, 11 and 10 per cent. It appeared that functional and histologic effects of the two hour ischemia resulted in tubular damage which then resulted in decreased PAH excretion by the tubules and increased tubular reabsorption or leakage of creatinine from the glomerular filtrate.

This evidence supported the view of Bywaters (14) and Lucke (17) that after shock, uremia is the result of tubular reabsorption of excretory products. This view has been supported by Van Slyke (28) and Homer Smith (54).

In conclusion it may be said that the one common factor in all of the conditions which may give rise to acute renal failure is the renal ischemic episode. It is also apparent that hypotension, in itself, unless very severe may not cause renal failure. It may be that yet unidentified substances in the circulation may play a part or it may be that the kidney itself is excessively sensitive to relatively minor episodes of hypotension associated with severe insults to the organism as a whole. It appears that the tubular degeneration which results from the circulatory insufficiency and anoxia may lead to tubular reabsorption of excretory products and thence to oliguria and retention of solutes.

PATHOLOGY

Reinhardt (2) gave one of the earliest descriptions of the pathology of acute renal failure. He described a large, soft, pale kidney with hyperemic pyramids and a capsule which stripped easily. He described microscopic findings of swollen and vacuolated epithelial cells which contained granules. The tubules were filled with casts of blood cells, epithelial cells and pigments that caused obstruction and dilatation of the lumina. This description was adequate as far as it went. Until the advent of discussions pertaining to the site and description of changes occurring within the tubule this description was all that was necessary.

The following discussion concerns the controversy regarding the site of the tubular lesion. Bywaters and his group (14, 16) described destructive lesions in the distal tubule almost entirely and denied damage of a disruptive nature to the proximal tubule. On this basis they ruled out anoxia as a cause of renal shutdown. Mallory, however, in 1947 described damage throughout the renal tubule resulting from hemoglobinemia and shock (21) and Moon in 1948 also described damage in all segments of the renal tubule. (20) Lucke had attached the term "lower nephron nephrosis" to the condition (17) and the popularity of that term along with the significance of the work of Bywaters obscured the work of others which tended to disprove their theories. (18, 19, 20, 21) McManus in 1949 and 1950 stated bluntly that the term "lower nephron nephrosis" was a misnomer. (55, 56) He tested for the presence of alkaline

phosphatase in different segments of microdissected tubules and found that in ischemic renal insufficiency the greatest changes occurred in the proximal tubules. McManus stated further (56) "The epithelium of the proximal convoluted tubules is remarkable in not showing any colloid droplets in the cells. This is in the face of the constant proteinuria which these cases show during life. It will be recalled that athrocytosis, a process by which protein in the tubule lumen is recovered, is a constant feature of normal epithelium in the presence of proteinuria. The absence of colloid droplets in the "crush" lesions suggests strongly that the epithelium is functionally not intact" and "The reduction of alkaline phosphatase in the kidney generally, and its patchy loss in some proximal convoluted tubules is an excellent indication of damage to the tubules. The diffuseness of involvement and the fact that proximal tubules are involved is against the terminology 'lower nephron nephrosis.'" Bleek and his coworkers (47, 57) concurred in this finding after careful microscopic studies.

Some of the most significant work in regard to the site and nature of the lesion was done by Oliver and his group. (37) The technique used was rather complicated and time consuming but precise in its results. (36) It involved digestion of the connective tissue of the kidney and microdissection of the tubules, special preparation of the tubule and photomicrographic studies of the tubule in toto. This method gave a longitudinal section of the tubule in question and there

could be no mistake as to where a lesion occurred. Oliver contended that the concept of damage only to the lower nephron arose from inadequate technique in examination of the kidney. This group stated that the common structural lesion in all cases of acute renal insufficiency is a tubular nephropathy characterized by entirely random disruption along the entire nephron. There is, however, a difference in the lesion seen in the toxic nephropathies and the nephropathy that occurs as an aftermath of trauma, shock, etc. Toxic nephropathies are characterized by degenerative changes in the epithelial cells of the proximal tubule. The basement membrane is not involved and regeneration occurs in uncomplicated cases. The complication of severe systemic reaction to the toxin in the form of severe dehydration, shock or other conditions leading to ischemia of the kidney results in a random disruption of the basement membrane of the nephron ("tubulorhexis") as well as degeneration of the epithelial cells. This concept was amplified by Oliver in 1954. (38) In the nephrotoxic lesion the intact basement membrane affords the supporting surface of a tube which needs only to be relined with a new epithelium. In the tubulorhexis lesion the entire tubular wall must be rebuilt and there is a great gap to be spanned by proliferating tissues that must be exactly oriented if the continuity of the tubule is to be re-established. In addition reaction around the lesion results in the intrusion of granulation tissue upon the developing tubule with obliteration of the lumen.

As a result complete repair of tubulorhexic lesions is an exceptional occurrence. The older views that regeneration does occur were based on histologic sections which showed regenerating cells but did not show whether the cells were regenerating in an organized fashion to re-establish tubular continuity. (38)

Ischemic damage to the kidney is random not only in regard to the parts of the individual nephron but also in regard to all of the nephrons of the kidney. Consequently only a few or many nephrons may be involved depending, evidently, on the severity of the ischemic episode. Fortunately the kidney has a large reserve and if the patient and the unaffected areas of the kidney are supported through the oliguric phase the patient can survive even though affected tubules do not regenerate functionally. This fact probably lays the basis for the clinical observation made by Stock (39) that "...urinary suppression is usually a self-limited disease when due to such causes as shock, intravascular hemolysis, post-partum eclampsia or poisoning by a variety of agents."

The pathology of the kidney during the diuretic phase has been discussed by Oliver. (38) He states that the kidney, far from being normal during diuresis, is functionally immature. Serial studies made on dissected tubules in laboratory animals after nephrotoxic damage indicate that diuresis occurs during a stage when the tubule cells are flattened and lacking in metachondrial rodlets and hence enzymes. Oliver makes the point

that morphologic reconstuction of nephrons alone is not enough; functionally mature cells are necessary for control of urinary output.

In conclusion the chief pathologic changes in renal failure are degeneration of epithelial cells of the proximal tubule as a result of nephrotoxins and random disruption of the basement membrane of the entire renal tubule in renal failure resulting from ischemia. Regeneration usually occurs in the former case but seldom in the latter. Recovery depends on the fact that all tubules are not usually effected by ischemia. Diuresis after the oliguric phase is a sign of regenerating but immature renal tubular cells.

DIAGNOSIS AND CLINICAL COURSE

Before any treatment can be instituted in the serious condition of oliguria resulting from acute tubular necrosis, less serious causes of oliguria must be ruled out. Mereney discussed this in relation to indications for transfer of oliguric combat casualties to the Renal Insufficiency Center. Mereney and his group recognized the less serious causes of oliguria as follows: (22)

1. Reflex oliguria: Oliguria that follows operation injury may not be truly reflex but it lasts only a few hours. Kolff does not believe this type of oliguria occurs at all. (35)

2. Hypotension: In oliguria from hypotension restoration of blood pressure brings an end to the condition. Mereney transfered no patients with a systolic blood pressure under 100 mm. Hg. to the Center.

3. Dehydration: Dehydration must be severe to produce oliguria. The urine has a high specific gravity. Mereney used a specific gravity of 1.030 as the dividing line but Teschan used both a specific gravity of 1.030 and a diuresis after administering a load of water. (24) He gave 1000 cc. of 5 per cent glucose in water intravenously in an hour. Mereney feels the latter test is dangerous and contraindicated.

4. Obstruction: This may be demonstrated by catheterization of the bladder but pyelograms may be necessary in obstruction of the ureters.

Acute renal insufficiency caused by tubular necrosis is marked by a severe oliguria with retention of fluid and solutes that lasts an indefinite period and is followed by a diuresis if the patient survives the oliguric phase. The symptoms during oliguria depend on the severity of the retention and the symptoms during diuresis depend on the severity of the fluid and electrolyte depletion.

The most significant changes are in the blood electrolytes. One of the most important is hyperkalemia which is also reflected in ECG changes. Serum potassium values may reach high values before symptoms occur and hyperkalemia is asymptomatic long after ECG changes are manifest. (22, 23, 24, 34) Mercney discussed the ECG changes in detail. These are best seen in the precordial leads. Briefly, he described the characteristic changes in hyperkalemia as follows. (22) The first change noted is peaking of the T wave at about 6 MEq/Liter. Beyond this value the changes are usually not wholly characteristic of pure hyperkalemia because there is usually an associated hypocalcemia which contributes to the ECG changes. The ECG patterns will be described as they occur with the combined effects of hyperkalemia and hypocalcemia since pure hyperkalemia is rarely seen. Peaking of the T wave is most marked at about 7 MEq/L. At 8 MEq/L. there is an increase in the angle between the S and ST segments and the ST segment encroaches on the horizontal component until it is gradually obliterated. The changes above 8 MEq/L. are progressive and involve, in order, depression of the P wave,

depression and rounding of the T wave and an increase in the RS angle with widening of the QRS until a smooth biphasic wave similar to a sine wave is produced. The QRS changes may occur much earlier and are largely contingent on the calcium level. They signal a fall in plasma calcium and may occur rapidly. QRS changes and especially the development of the sine wave pattern are of grave significance and indicate severe myocardial toxicity.

Tetany rarely occurs from depression of plasma calcium. The lowest value reported by Stock (39) was 7 Mg. per cent and by Moreney (22, 23) 5.9 mg. per cent. The chief danger is in intensifying the potassium intoxication.

Elevation of non-protein nitrogen may reach high levels. Moreney stated that uremia of less than 250 mg. per cent NPN is asymptomatic but at that level symptoms may appear abruptly. (22) The first symptom to appear is usually hiccups, followed by lethargy. It usually takes from five to eight days to reach that level of NPN. Stock (39) stated that the highest level seen in a patient who survived was 450 mg. per cent but in the reports of Smith (25) and Teschan (24) as well as Moreney (22) higher values were recorded in patients who survived. Stock had one patient who was anuric for fifty days because of bilateral ureteral obstruction and developed a BUN of only 230 mg. per cent. The major symptoms in this patient were lethargy and irrationality terminally. (39) Metabolic acidosis which occurs with protein catabolism and anion retention contributes to lethargy.

Bicarbonate values have been recorded as low as 15.6 MEq/L. by Kohn and Kiley (58) and a carbon dioxide content as low as 17 volumes per cent was recorded by Stock. (39)

Fluid retention is a severe problem, especially in the patient overhydrated by treatment. (59) Pulmonary edema is a major cause of death in renal failure.(22, 23, 39, 60) Alwall reports sixteen cases of uremia from renal failure in which chest X-rays revealed changes of the type described as "uremic lung" or "fluid lung." (61) In Alwall's clinic radiographic studies of the lung and abdomen are routine on all new cases of oliguria. He claims that they afford valuable information concerning the degree of fluid retention and he looks for pulmonary edema, retroperitoneal edema and peritoneal effusion. Pulmonary edema is further complicated by myocardial failure from potassium intoxication and hypocalcemia. Cerebral edema has been implicated in five cases of convulsions reported by Stock. (39) Hamburger and Mathe from fluid volume studies stated that there is definitely a tendency to an increase in the total body water contributed to in large part by an increased production of water. This effects an increase in intracellular fluid while the extracellular fluid seems to decrease. (62) These findings conflict with previous theories (34, 35) and remain to be further evaluated. (See discussion at the end of the Hamburger and Mathe paper.)

Hyponatremia and hypochloremia are usually reported in renal failure. The actual causes are not definitely known.

It has been predicated that they may be caused by one or two mechanisms. It may be that the absolute increase in total body water simply dilutes the sodium and chloride. In this case the hyponatremia and hypochloremia may be only relative, the total quantities in the body not being actually decreased. It has also been suggested that sodium is entering intracellular fluid along with increased intracellular water.(62) In either case, during oliguria there is no absolute hyponatremia. Hypochloremia may exist absolutely depending in large part on the amount of vomiting done by the patient but is usually also relative.

Anemia, leucopenia and a depressed hemoglobin are fairly constant findings in renal failure. Smith and his group (25) reported these as regular and progressive findings. Kohn and Kiley (58) reported hematocrits ranging as low as 24, hemoglobins as low as 5 Gm. per cent, leucopenia in the range of 2000 to 3000 wbc per cubic millimeter and comparable reductions in the red blood cell count. These findings can be consistant with marrow depression or hemodilution. It is generally agreed that uremia causes marrow depression but not so acutely as in these cases. It is likely that hemodilution plays a large part. This coupled with the finding of depressed plasma sodium and chloride without readily apparent explanation has made controversial the findings of Hamburger and Mathe. (62)

Anemia, even if relative, contributes to the general weakness of these patients and, when added to the electrolyte changes and uremia, is a severe complication. Treatment is

difficult and may contribute further to the progression of the disease. Transfusion with whole blood may be dangerous both because of the high potassium content of such blood if not absolutely fresh (22, 23, 24, 25) and because of the danger of contributing to pulmonary edema. (25) Lucke reports a dramatic complication from transfusion. (17) A woman with acute renal suppression and an oliguria of 480 cc. of urine per day and a severe anemia was transfused with 2500 cc. of a hemoglobin solution since type specific blood was not available. Her oliguria promptly approached anuria with an output of about ten milliliters per day. She died three days later. The autopsy report described pigment casts in the lower nephron.

Leucopenia has serious import in the decreased resistance of the patient to infections. Even during the Korean conflict, when antibiotics of proven value were readily available, one of the chief causes of death was overwhelming infection. (25) Presence of peritoneal fluid, pleural fluid or general edema complicates this picture by providing a rich culture medium for pathogens. (22) It must also be remembered that a patient with renal failure usually has suffered a severe wound that may be grossly infected. This was often true in Korea. (22, 24)

Hypertension usually does not develop during the course of renal failure but may present a serious complication if present before renal failure. Actually, hypertension, when found, usually pre-existed the renal failure which presents as an end result of the renal disease that caused the hypertension.

In such cases cerebral edema and myocardial failure are particularly likely to occur. (35)

The usual causes of death in the oliguric phase of renal failure are infection, pulmonary edema, congestive heart failure, cerebral edema and combinations of these. (39) Complications of treatment such as digitalis intoxication and hemolytic transfusions reactions may contribute to death. Death usually results from a combination of the above entities, only occasionally from any one of them alone. (59, 59)

Diuresis is a signal of returning renal function but it does not signify that the kidney has recovered. (38) It must be emphasized that the diuresis which occurs is pathologic in nature and there is the ever-present risk of electrolyte depletion as contrasted with the oliguric phase. In the diuretic phase hypokalemia is a serious problem as are hyponatremia and continuing acidosis, largely a result of loss of fixed base. Serious complications of this phase may result from a too rigid maintenance of "normal" serum electrolyte patterns and too liberal use of digitalis during oliguria.

The excessive use of agents designed to lower the serum potassium may backfire if diuresis suddenly occurs and the appearance of hypercalcemia and hypokalemia may be manifested by an extremely irritable myocardium. If the patient is digitalized at the time the result may be fatal. (22, 58)

Uremia may continue to progress during the first few days of the diuresis. The cause of this is not known. (35)

TREATMENT

I. Introduction

Acute renal failure may be a self-limited condition as pointed out by Stock (39), Card (59) and Kolff (55). Stock emphasized that the prognosis depends on the general powers of recuperation of the patient. He stated "The conclusion seems warranted that urinary suppression relatively infrequently causes death unless the patient's health is otherwise jeopardized. This is supported by comparison of the ages of surviving and fatal groups." In Stock's series of 22 patients the average age was 44.7 years. In the group of eleven survivors, the average age was 35.4 years and in the group of eleven fatalities the average age was 53.9 years. In the group of nine patients over fifty years of age only one survived but in the group of thirteen patients under fifty years of age only three died. Stock pointed out that the coexistance of underlying disease in the elderly patient with urinary suppression accounted for most of the deaths in that group. His concept of therapy was conservative and only aimed at support of the patient through the episode of renal suppression. Teschan (24) and Smith (25) agreed on this point except that their therapy tended toward the more radical. Their statistics showed that prior to the use of the artificial kidney in maintaining proper blood chemistry the mortality rate ran from 80 to 90 per cent in combat casualties but after this form of treatment was instituted the mortality rate dropped off to 53 per cent with the mortality directly related to the extent of underlying wounds.

Oliver's work (37, 38) in the pathology of renal failure supports the concept of supportive therapy in that disease. His group has pointed out that the kidney will regenerate and regain function depending on the degree of damage. Hence treatment is best directed toward correction of the underlying illness and support of the patient during the episode of renal failure.

I will discuss the treatment of renal failure in four parts: 1) conservative management, 2) treatment by lavage, 3) treatment with the arificial kidney and 4) general supportive treatment. None of these forms of treatment are specific in nature and none are directed toward hurrying the kidney back into function.

Before the discussion of presently accepted modes of treatment, some controversial and experimental methods of therapy will be briefly discussed.

Renal decapsulation, hypothetically effective by relieving pressure from edema and relieving vasospasm, will not be discussed except to mention that there is no evidence that there is any value in such a procedure. (35, 39, 65) Stock (39) suggested that it is instituted too late to be of benefit. With Oliver's evidence of the nature of renal failure (37, 38) such a procedure would appear to have little value after oliguria has been established and may be damaging because of the operative trauma involved.

Exsanguinotransfusion has a place in conditions of massive intravascular hemolysis (35) but is of little value

after the onset of solute retention. McManus (56) suggested that injured tubules in the failing kidney are not able to handle any added effort such as required by the excretion of hemoglobin and may be further damaged. For this reason the removal of hemoglobin resulting from transfusion reaction or other causes of intravascular hemolysis would seem to be of great importance to the preservation of undamaged tubules.

High spinal anesthesia has been advocated (63) but evidently belongs in the same category as renal decapsulation. Kolff reports cases of renal failure occurring after high spinals. (55)

The transplantation of a homologous kidney has been attempted in cases of intractable renal failure or loss of both kidneys to other disease. Hume (51) and Hawn (64) discussed this procedure. The results have been generally disappointing. Temporary support of homeostasis may be achieved through transplantation of a kidney to the thigh. In a kidney so transplanted a long enough period of survival was achieved to pull a patient through a severe oliguric episode. (51) Hume (51) reported one case where the NPN was held at 40 mg. per cent after transplantation of a kidney to the thigh when it was 170 mg. per cent before transplantation. In all cases the transplanted kidney succumbed to one disorder or another. In the case which survived the longest, infection finally caused failure of the transplant. In general, if a patient can be made to survive by means of such a procedure, he can be supported by the methods discussed below.

II. Conservative management of renal failure

In conservative treatment an effort is made to avoid overhydration and dehydration, to correct marked deviation from normal of sodium, chloride, potassium and acid-base balance by controlling the patient's input rigidly. Conservative treatment includes efforts to prevent or correct complications such as infection and myocardial failure. This form of therapy forms the base upon which the more radical procedures may be superimposed. Some workers believe that conservative treatment is the only form of therapy to be considered and that more radical procedures have no place. (39, 59, 60, 65, 66) This divergence of opinion probably results from the type of case handled, the degree of personal experience and the facilities available for special forms of treatment. In any case it is apparent that conservative treatment may be sufficient in most cases of renal failure but in severe, rapidly progressive cases, the conservative treatment may actually be the radical from the standpoint of results.

Conservative treatment shall be discussed from the standpoint of fluid balance, electrolyte balance, protein catabolism, acidosis, caloric intake and general supportive measures aimed particularly at correcting anemia, combatting infection and preventing myocardial failure.

1. Fluid balance - At one time attempts were made to induce diuresis by infusing large amounts of fluids (17) but overhydration is now recognized as one of the more dangerous complications of renal failure. (24, 25, 35, 59, 60, 61)

Authorities now generally agree that the quantity of fluids administered to a patient with oliguria should not exceed the insensible loss plus the quantity of urine formed and the loss from wounds, vomiting, etc. This amounts to about 700 cc. per day input (35) or 600-800 cc. per day (25). Stock (39), following the line of reasoning covered in his definition of oliguria (q.v.), limited intake to 750 cc. per day plus any extraneous loss. He made the point that in a thirsting 70 Kg. man with an intake of 100 grams of carbohydrate a day 250 cc. are required to provide obligatory urinary output plus 500 cc. for insensible fluid loss, sparing preformed body water. Any fluid in excess of this amount, barring extraneous loss, must be excreted in the urine. Smith (25) preferred to underhydrate his patients and attempted to obtain a steady weight loss through loss of preformed body water in insensible perspiration. Meroney (22, 23) agreed with Smith on this point.

Fluid is best given orally but vomiting is a problem in most cases. Bull (66) filtered the vomitus and returned it to the patient's stomach via a gastric tube. Most workers attempt to institute oral feedings as soon as possible.

Meroney (22) warned of a problem in ambulatory patients especially. These patients become thirsty with fluid restriction but neither the oliguria nor the thirst is an indication of fluid need. The patients under Meroney's care became very clever about sneaking extra water and would go to great lengths to obtain it. He advised maintaining vigilance and taking care not to leave any

source of water available to the patient. He recorded instances of patient's drinking from flower vases, toilet bowls, urinals and stealing ice from ice bags.

The amount of water prescribed per day must contain all nutrients to be administered that day. (22)

2. Electrolyte balance -

A. Potassium retention: Stock (39) tended to minimize the danger of potassium intoxication and stated that in his series no ECG changes were noted attributable to high levels of potassium. The highest value he found was 7.4 MEq/L. but in three cases of sudden death no ECG or potassium values were available. Because he did not find hyperkalemia of serious degree, Stock made no attempts to correct abnormally high potassium levels. This approach to renal failure is unusual.

Several methods have been used to combat hyperkalemia. As emergency treatment of severe hyperkalemia, Smith and his group (25) used hypertonic sodium chloride (200-400 cc. of a 3-5% solution) intravenously if sodium values were also low. This, according to the authors, is only temporarily effective and probably works by forcing potassium back into the cells. Moroney (22,23) varied the procedure by the use of sodium bicarbonate in doses of 50-100 cc. of a 7.5% solution, thereby relieving both acidosis and hyperkalemia.

The use of hypertonic glucose with insulin intravenously has been mentioned often.(22, 25, 35) Smith (25) used 50% glucose in water with one unit of regular insulin per two to three grams of glucose. Moroney (22) pointed out that

hypertonic glucose must be given continuously or sharp spikes of hyperglycemia followed by periods of hypoglycemia occur. The latter result in potassium extrusion from cells associated with glycolysis. It is well known that glucose transport across cell membranes is associated with potassium transport in the same direction.

The oral or rectal administration of sodium cycle carboxylic exchange resins which exchange sodium ions for potassium ions has been mentioned by several authors. (22, 25, 35) Smith (25) used it only to attempt to control potassium levels after hemodialysis. He used 25 grams of the resin as a ten per cent suspension in water twice a day by retention enemas or in divided doses orally with laxatives. The results of this treatment were disappointing but Smith pointed out that associated abdominal wounds may have contributed to failure. Meroney stated that resins given as retention enemas often gave rise to fecal impactions with attendant complications. Kolff (35) used thirty to sixty grams per day in divided doses orally with laxatives and reported variable results. It is probable that resins are most useful as an adjunct to more radical procedures to be discussed later. (25)

Myocardial intoxication from hyperkalemia may require the use of digitalis. There is danger here, in that the sudden onset of diuresis may result in extreme myocardial irritability.

During the diuretic phase of renal failure potassium may have to be replaced. (22, 25, 35) Smith stated that quantitative replacement of electrolytes is not necessary in this phase.

Kolff used potassium chloride, gluconate or bicarbonate, depending on the acid-base balance for choice of the anion.

B. Hyponatremia: This is not usually a serious problem (25, 35) and usually can be corrected by therapy directed toward correction of other problems, i.e. hyperkalemia, acidosis.

C. Hypocalcemia: Meroney (22) obtained dramatic ECG improvement with intravenous solutions of 10% calcium gluconate in amounts up to 60 cc. He used this particular solution only when the ECG suggested abnormalities amenable to calcium replacement. General calcium replacement is taken care of in his general electrolyte replacement formula (see below). Kolff (35) gave one gram of calcium gluconate intravenously per day as well as aluminum hydroxide by mouth to bind phosphates.

3. Acidosis and uremia: Acidosis is related both to anion retention and to ketosis resulting from increased protein catabolism. The former is handled by base replacement in the general intravenous fluids. Kolff (35) rarely used sodium bicarbonate and only when the blood bicarbonate level was less than 12 MEq/Liter. (33, 34, 35)

Protein catabolism is reduced through the use of carbohydrates. Smith (25) quoted Gamble (41) as stating that 100 grams of carbohydrate per day prevents ketosis in fifty per cent of fasting men but increasing the dose to 200 grams per day produced no further anti-ketogenic effect. As a consequence Smith gave his patients at least 100 grams of glucose as a 15% solution

of glucose in water or, if necessary, up to a 50% solution by intravenous cannula. Kolff (35) suggested the use of 40% glucose or invert sugar by cardiac catheter or 20% invert sugar plus insulin intravenously. He also suggested that 10% glucose plus hyaluronidase may be used subcutaneously. The latter may be dangerous, however, in that the combination of a hypertonic solution and hyaluronidase may cause contraction of the circulating fluid volume by sequestration of water at the site of administration.

Borst (66) has discussed the dietary management of oliguric patients. He stated that in normal people a diet containing practically no protein or potassium and providing an amount of carbohydrate and fat not wholly sufficient to meet caloric requirements reduces the daily protein catabolism in three days to six grams of nitrogen and in 14 days to less than four grams. In patients with uremia, the effects were the same. Borst pointed out that infection causes much higher rates of protein catabolism and must be prevented. He showed that if infection is prevented anuric patients maintained on a proper diet will not have a rise in blood urea nitrogen for at least three weeks. Bull (65) further developed this concept and suggested a diet for oliguric or anuric patients. He suggests the following formula by gastric gavage.

Glucose .....400 grams
Peanut oil .....100 grams
Acacia, quantity sufficient to emulsify
Water to one liter.

This diet provides 2500 calories per day. All vomitus is

collected, filtered through lint, and returned by the stomach tube. Bull has had good results from this regimen. He reported a series of eleven cases of renal failure with three fatalities. (65) Before the diet was started he found the daily increase in BUN ranged from 35 to 60 mg. per cent in the eleven patients. After the diet was instituted he found the daily increase was only eight to 26 mg. per cent in eight of the eleven patients. Three patients died before therapy was started. From a control study of patients with gastric ulcer but no renal failure Bull estimated the daily rise in BUN on this diet would have averaged 17.7 mg. per cent for the first week and 10.1 mg. per cent during the second week if renal shutdown had been present. The average daily increase in BUN in his anuric patients not on the diet was 50 mg. per cent. Borst (66) found that Bull's diet, by preventing tissue catabolism, also tended to retard the rise in serum potassium. Fat emulsions now available may also be useful given by gastric drip. (35) Kolff has worked out several diets for oliguric patients. (31, 32, 35)

4. Anemia: Anemia is best corrected by the administration of type specific packed red blood cells. (25, 35) Blood transfusion may be dangerous because of the fluid volume involved. It is important that the preparation be fresh because of the tendency toward high potassium content in the older specimens of either packed red blood cells or whole blood. (22, 35)

5. Infections: Antibiotics are indicated prophylactically. (25, 35) Kolff (35) stated that erythromycin is tolerated

the best by oliguric patients and warned that streptomycin may be dangerous because of retention and neurotoxicity.

Meroney and Herndon (22) have presented a prescription for general electrolyte replacement and control, caloric intake and acid-base balance. It is designed as a basic intravenous fluid and is presented here as such.

Calcium gluconate 10% ..... 100 cc.
Sodium bicarbonate 7.5% ..... 50 cc.
Glucose 25% in water ..... 400 cc.
Insulin (regular) ..... 50 units
Isotonic saline or M/6 sodium lactate, quantity sufficient to bring total to equal patient's output.

This formula may be varied to fit individual cases. All authors emphasize the advantages of oral feeding as soon as possible. It is important, however, to closely calculate input and to control it throughout. Constant attention is absolutely necessary.

III. Treatment by lavage

Lavage techniques utilize body membranes as dialyzing surfaces. A "rinsing" or dialyzing fluid is washed through a body space (such as the peritoneal cavity or the intestinal tract) which is separated from the blood stream by semi-permeable body membranes. The content of the rinsing fluid depends on the content of the patient's blood. If the patient has a high serum potassium and it is desired to lower it then the rinsing fluid is made up with low or no potassium and that ion will move from the blood stream into the rinsing solution and be removed from the body. Conversely the rinsing solution may be made hypertonic

in comparison with the blood concentration of some other substance and that material will move into the blood stream.

Peritoneal lavage is apparently the best of the lavage techniques for handling renal failure. (30, 35) It has the advantage of being simple, of requiring no special apparatus and of being effective in the control of blood chemistry. This technique is not new, dating back at least to 1938 when Wear and Rhoads described it separately. (67, 68) It has since been advocated by Abbott (69), Frank (70), Fine (71), Fenn (72), Grollman (29) and Kolff (30, 33, 35). The main difference in method lies in the use of intermittent lavage (29) or in continuous lavage (35, 71). The principle is the same in either case as is the general technique which will be described below.

Grollman (29) presented a series of totally nephrectomized dogs which were maintained in electrolyte and nitrogen balance over periods of thirty to sixty-one days. Lavage was carried out twice a day for a period of two hours each time. Blood chemistry was determined a few hours in advance of each lavaging so that the constitution of the rinsing solution could be chosen. In addition to lavage, the dogs were maintained on a high carbohydrate, low protein diet similar to that proposed by Bull (65) and water intake was strictly limited in accordance with the concepts discussed in the preceding section. Grollman also treated five patients who were in the terminal phases of diseases with renal failure. Three patients had arteriolonephrosclerosis with hypertension and two had long standing chronic nephritis.

These patients were handled with continuous lavage in an heroic effort to improve their blood chemistry relationships. Hypertension was consistently improved in so far as diastolic pressures were concerned and in three out of four cases systolic pressures were significantly reduced after lavage. The BUN, which ran from 142 mg. per cent to 312 mg. per cent before lavage, was reduced to a range of from 87 mg. per cent to 204 mg. per cent after lavage. Serum potassium ranged from 5.0 to 7.8 MEq/L. before lavage and from 3.8 to 4.6 MEq/L. after lavage. Duration of lavage in these patients varied from sixteen to forty-eight hours. Grollman did not encounter any difficulties with bacterial contamination of the peritoneal cavity though he recognized the danger. He advocated the routine addition of penicillin or other suitable antibiotics to the lavaging fluid. Fenn (72) reported that he was able to maintain the NPN at an average of 160 to 200 mg. per cent with continuous lavage for as long as twenty-four days in a terminally oliguric patient. He also advocated the addition of antibiotics to the dialyzing fluid. The apparatus used by Fenn is illustrated in Figure 1. It is similar to that used by Grollman (29) and Kolff (30, 35) except that the latter does not use suction.

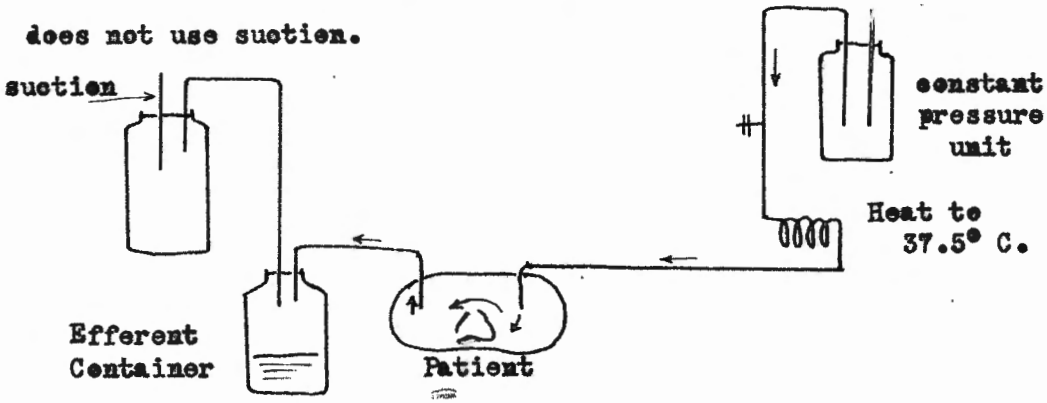

FIGURE 1

Kolff (35) has described the procedure of peritoneal lavage in some detail. The bladder must be emptied before a trocar is inserted under local anesthesia through the left abdominal wall at a point corresponding to McBurney's point. A snugly fitting plastic or rubber tube is inserted through the trocar and the trocar is withdrawn. One and a half or two liters of dialyzing solution (see below) are instilled into the peritoneal cavity. If intermittent lavage is to be used this fluid may be withdrawn by way of a second cannula inserted into the right side after two hours. If continuous lavage is utilized the second trocar is introduced immediately after distending the abdomen with the rinsing fluid and drainage is instituted as illustrated in Figure 1 with or without suction.

Kolff also discussed the composition of the rinsing fluid. (35) He warned that it must be sterile and suggested the use of 25 mg. of oxytetracycline per liter of rinsing fluid. Kolff suggested preparing small amounts of sterilized stock solutions that can be added to sterile water to gain final solutions for administration. These stock solutions have the following composition.

Solution A		Solution B	
KCl	4.5 gm.	$NaHCO_3$	84.0 gm.
$CaCl_2$	11.1 gm.	Na_2HPO_4	5.7 gm.
$MgCl_2 6HOH$ ..	12.2 gm.	NaOH	9.6 gm.
NaCl	237.5 gm.	Water	1500.0 ml.
Glucose	40.0 gm.		
Lactic acid (USP 85%)	27.1 ml.		
Water	1500.0 ml.		

Solution C	Solution D
5.85 gm. per cent NaCl (1 MEq/milliliter)	50 gm. per cent glucose/water

All solutions are autoclaved before the final solution is made.

The electrolyte composition of a solution made up by taking 75 milliliters each of solutions A and B and adding sterile water up to two liters is as follows.

Sodium	134.5 MEq/L.	Chloride	111.0 MEq/L.
Potassium	1.5 "	Bicarbonate	24.0 "
Calcium	5.0 "	Phosphate	2.0 "
Magnesium	3.0 "	Lactate	7.0 "
	144.0 MEq/L.		144.0 MEq/L.

If a higher sodium content is desired, appropriate amounts of solution C are added. For higher glucose concentrations solution D is added in desired quantity.

After peritoneal lavage one or two liters of rinsing fluid which cannot be recovered are trapped in the peritoneal cavity. The more fluid trapped, the higher the tonicity of the rinsing fluid must be so not to cause diffusion of water from the peritoneal cavity into the circulating fluid. Increasing the glucose concentration is a convenient method of achieving greater tonicity. Pain caused by hypertonic glucose may be alleviated by the addition of 50 milligrams of procaine per liter of dialysis fluid. (35)

Kolff discussed the complications of peritoneal lavage including perforation of distended bowel by the trocar and peritonitis, both chemical and bacterial. Kolff believed he avoided peritonitis in his patients by use of antibiotics and shorter periods of dialysis. Patients commonly complain of distention and discomfort for several days after lavage.

Kolff listed as good risks for peritoneal lavage patients who are dehydrated so that fluid absorption is tolerated and

patients with little omental fat so that technical difficulties are not encountered. He warns that peritoneal lavage is a "useful but unpredictable procedure that should not be performed by untrained nurses, inexperienced interns, or a resident whose time is taken up with the care of other patients. Peritoneal lavage has saved the lives of several patients; but it also has brought great distress to others and it has proved fatal in some cases in which the technique was not rationally and judiciously employed." (35)

IV. The artificial kidney

The principle of the artificial kidney is the same as that for peritoneal lavage except that the patient's blood is withdrawn from his body and rinsed, then returned. Although the concept of the artificial kidney is not new (according to Kolff (35) it was first introduced by Abel, Rowntree and Turner in 1912) it was not widely used until the Korean war.(22, 23, 24, 25) It has received rather more extensive civilian use in Europe. (61, 73)

Use of the artificial kidney requires complex equipment, a trained team and definite indications because the procedure is not without danger. These points will be discussed separately below.

The type of artificial kidney is not important, according to Kolff, as long as it is efficient. (35) He believes the rotating type to be the most efficient. It is diagrammed in Figure 2. (35)

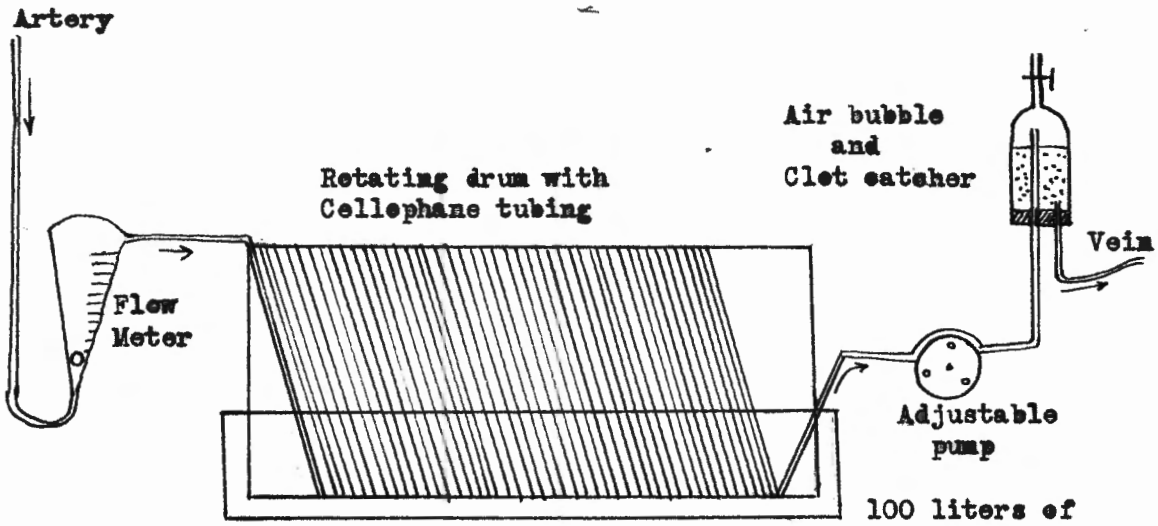

FIGURE 2

The apparatus suggested by Fishman (74) is essentially the same with some modifications as shown in Figure 3.

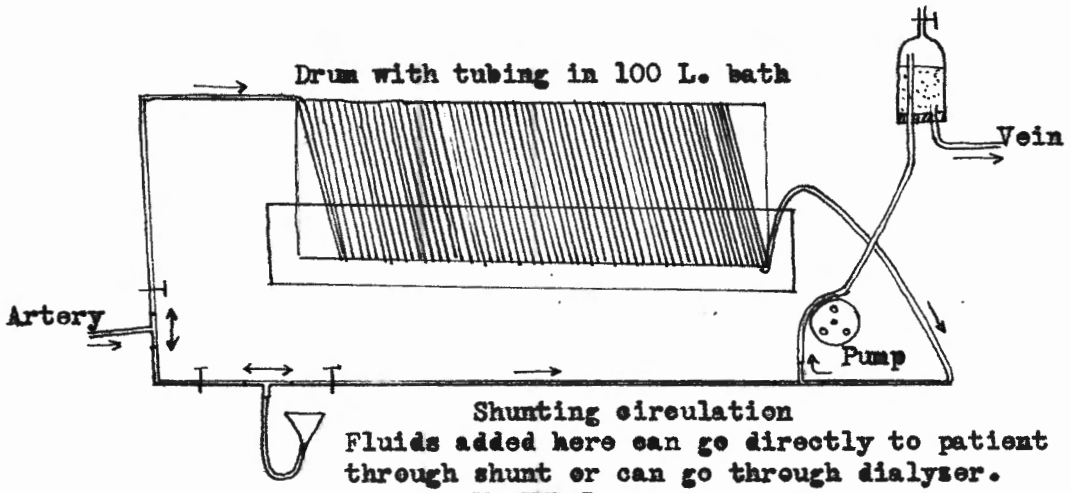

FIGURE 3

This is the general type used in Korea by the Renal Insufficiency Center. (22, 23, 24, 25)

Alwall (61, 73) used what he called the "ultrafilter-dialyser" as diagrammed in Figure 4. (61)

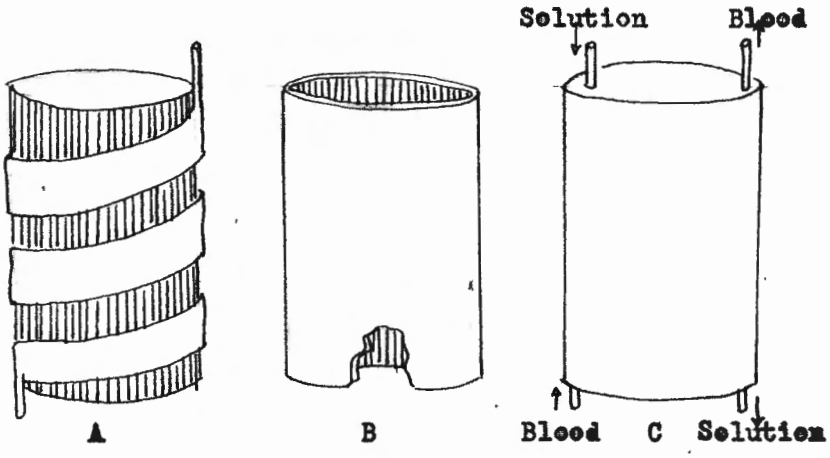

Figure 4

Part 'A' of Figure 4 represents the inner cylinder of Alwall's dialyzer which is grooved on the outside and wrapped with cellophane tubing. 'B' is the outer cylinder which is grooved on the inside and fits around the inner cylinder. 'C' is the assembled dialyzer with ends fitted on. Rinsing fluid flows in the fluting between the two cylinders, thus flowing over the cellophane tubing.

A minimum team for operating an artificial kidney according to most authorities (22, 25, 35) includes a technician to handle the apparatus, a laboratory technician to perform immediate laboratory determinations, a nurse and an experienced physician supervising the entire procedure. These members are, as stated, the minimum and they should be thoroughly trained in the use of the artificial kidney. Kolff believed they should comprise a specialized team with little or no other duties. This precludes the organization of such a team in any but large medical centers.

Indications for the use of kidney as listed by Smith (25) and used in Korea are clinical judgement concerning the progress of the patient, serum potassium greater than 7.5 MEq/Liter, ECG evidence of myocardial intoxication and symptomatic uremia associated with hyperkalemia. Kolff (35) generally agrees with these criteria but stated that if the team is readily available early use of the artificial kidney greatly alleviates the later course of oliguria. For the latter reason he tends to use the artificial kidney before the above criteria are established. Fishman (74) agrees with this view point and Alwall (61) used the kidney whenever evidence of pulmonary edema was present.

The only absolute contraindication to the use of the artificial kidney according to Kolff (35) is active bleeding because of the necessity of heparinization of the patient (see below). This was not a serious problem in Korea. (22, 23, 25)

Complications which arise in the use of the artificial kidney are few if the procedure is handled correctly. (35) Heparinization of elderly patients with arteriosclerotic vascular disease is dangerous according to Fishman (74) and according to him is the chief complication. Kohn and Kiley listed hemorrhage related to heparinization, elevation of blood pressure, cardiac arrhythmias, net gains or losses in fluid volume and blood loss. (58)

Heparinization is necessary in order to prevent clotting of the blood within the tubing of the dialyzer. (30, 33, 73) The total amount of heparin needs not exceed 150 milligrams

according to Kolff. (35) He has not found it necessary to use an antidote for heparin in his work but suggests protamine sulfate (1 mg. per 1.5 mg. heparin) is the need should arise.

The efficiency of the artificial kidney varies somewhat with the type of machine used. Kolff reported urea clearance in the rotating type at a flow rate of 200 ml. per minute as 170 ml. per minute and at the same flow rate the stationary type gave a clearance of 125 ml. per minute. (35) High clearances of urea are desirable because the clearance of most of the other solutes is lower. With urea clearance as a basis for comparison, the clearance of uric acid is only 45%, clearance of inorganic phosphate and sulfate is 32% each and the clearance of phenol red is only 11%. (75) Smith (25) reported that after dialysis the potassium was regularly lowered to 4.5 to 5.0 MEq/L. and the BUN to 90 to 100 mg. per cent, regardless of original values of these substances depending on length of dialysis. The best evidence for the efficiency of the artificial kidney is found in the mortality statistics of Smith however. This group used the Kolff type of artificial kidney. The mortality rate of their patients on conservative treatment was about the same as reported during the second World War or 80 to 90 per cent. It dropped off to 53 per cent after they began using extra-corporeal dialysis. (25) The fact that the mortality rate was so high on conservative treatment was a result of the severity of the wounds in their patients. All of their patients were classified as "severely wounded" which, in Korea, signified the danger of early death

of a patient if he were not immediately transported to an area where more or less definitive major operations could and would be carried out. (22)

The dialyzing fluid suggested by Kolff (35) is similar to that he used for peritoneal lavage. The fluid is always adjusted according to the electrolyte pattern of the patient's blood. Potassium content may be cut down or entirely eliminated from the fluid. Calcium, in contrast with Fishman (74) is retained in the rinsing fluid and no mention is made of difficulties with precipitate formation. For the latter reason Fishman gives calcium directly intravenously instead of allowing it to circulate through the dialyzing circulation. It is important not to overload the patient with sodium even if the blood level appears to be low to avoid aggravating or causing pulmonary edema, hypertension or cardiac failure. (35)

Kolff has also pointed out that the volume of rinsing fluid must be large enough and must be continuously changed in order to prevent excessive back diffusion of retention products. (35)

In summary, the artificial kidney is an excellent means for supporting a patient with renal failure. It requires special apparatus and specially trained workers, however, and should be used only if such are available.

V. General supportive measures

These measures have been partially covered in the section on conservative treatment. They involve treatment of pulmonary edema, myocardial failure, respiratory depression, infection,

convulsions, hypertension, bronchial obstruction from retained secretions, vomiting, abdominal distention and psychoses. Most of these are treated as they would be in any disorder but the treatment of some deserves special mention in regard to their occurrence in renal failure.

Pulmonary edema deserves special consideration because of the high incidence of its occurrence and the high mortality rate associated with it. Kolff suggests the following regimen in the treatment of acute pulmonary edema and warns that it must be instituted immediately. (35) For the latter reason he agreed with Alwall (61) that X-ray examination of the chest should be carried out routinely. Kolff suggested (1) venesection with removal of 300 to 500 ml. of blood with careful control of the blood pressure, (2) morphine sulfate, 10 to 15 mg. slowly intravenously (beware if cerebral edema is also present), (3) hypotensive drugs if the blood pressure is elevated (see below), (4) immediate digitalization and (5) intermittent positive pressure breathing with oxygen and detergents. Removal of ascitic and pleural fluid has been suggested to increase ventilatory space. Pulmonary edema, if severe, is in itself an indication for more radical treatment of solute retention by use of the artificial kidney (61) or lavage (29).

Respiratory depression may reach the point of Cheyne-Stokes breathing, in which morphine is contraindicated. In such cases the administration of aminophylline, 250 to 500 mg. intravenously was suggested by Kolff. (35)

Obstruction of the respiratory passages is a major complication that may result in fatal bronchopneumonia. Therefore, sedatives and codeine have been considered contra-indicated. Small doses of morphine accomplish the same pain relief as codeine without the complication of depression of the cough reflex. (35) Morphine is twenty times as potent in relieving pain as codeine but only three times as potent in depressing the cough center. (76) Frequent aspiration of secretions may be necessary and early tracheotomy may greatly facilitate such aspiration if it is needed frequently. (25, 35)

Restlessness, vomiting, twitching, confusion and psychoses may all be alleviated in part by chlorpromazine. (35) For vomiting 25 mg. of chlorpromazine given by deep intramuscular injection one half hour before meals is usually effective but the dose may be doubled if necessary. This treatment may lead to near hibernation but this is not undesirable in preventing convulsions or psychoses if they are impending. Psychoses and restlessness may also be treated with paraldehyde (2 to 5 ml. deep intramuscular) with the advantage that it is excreted by the lungs. (76) If pulmonary edema is impending morphine is preferred but it must be emphasized here that convulsions may result from the administration of morphine in the presence of cerebral edema. (76) Unfortunately pulmonary edema and cerebral edema are frequently associated. (61)

Hypertension may be present as an underlying disease in patients with acute renal failure or it may appear as a complication

of treatment with the artificial kidney. The rapid elevation in blood pressure may in itself lead to coma, convulsions and paresis from cerebral vasoconstriction or cerebral edema. (77) In the treatment of hypertension Kyser (77) as well as Kolff (35) suggest the use of ansolysen (pentapyrrolidinium) or hexamethonium intravenously in intermittent doses. Kyser suggests 0.1 ml. (2.5 mg.) of hexamethonium intravenously every three to five minutes until the desired drop in blood pressure is attained. Hydralazine (Apresoline, hydrazinophthalazine) may be a valuable drug in the treatment of underlying hypertension since it apparently does not decrease renal blood flow and according to some workers (78) it actually increases it. Chao (79) stated that the drug was usually ineffective when used alone but may be combined with reserpine with good results. The dose of hydralazine is usually given as 25 mg. four times a day with meals and with weekly increases of 10 to 25 mg. a dose until the required effects are seen or until the total daily dose reaches 500 mg. (79, 80, 81) Larger doses should not be used for any period of time since there is evidence that prolonged use leads to the development of collagen disease. (81) Reserpine has several other advantages in that it tends to slow the tachycardia which may result from hydralazine (82) and which makes hydralazine contraindicated in coronary artery disease (79); it is useful in preventing intestinal stasis which may occur in the course of renal failure or from hexamethonium or ansolysen (83) and tends to prevent the restlessness and psychoses which develop in uremia. It should not be used in the depressed patient, however. (83)

Abdominal distention may be treated more effectively with anticholinesterase drugs such as neostigmine (prostigmine). Freis (81, 84) and Chao (79) stated that ganglionic blocking agents such as hexamethonium or ansolysen should never be used without the adjunctive use of such drugs. Freis and Chao both suggested the use of 15 to 30 mg. of neostigmine in the morning and a laxative before retiring if the former is not effective. Kolff (35) used one milliliter of prostigmine in a dilution of 1:2000 or 1:4000 subcutaneously every four hours if necessary. Prostigmine may be used in this manner one half hour before the use of an enema. (35)

In general summary of the treatment of renal failure, it may be said that therapy is entirely supportive. General medical treatment is directed toward the comfort of the patient and specific measures are taken to maintain the blood chemistry in a state compatible with life. It has been shown that renal failure is essentially self-limited and the object of the treatment is to keep the patient alive and as comfortable as possible during the lack of function of the kidney. This therapy is basically conservative with control of input, including diet. In serious cases and if circumstances permit, more radical treatment may be superimposed on conservative methods. The latter treatment involves dialysis, either in the form of peritoneal lavage or extracorporeal dialysis with the artificial kidney. Modern forms of treatment have cut the mortality rate in renal failure to the point that death is, in most cases, caused by underlying disease processes.

SUMMARY

Acute renal failure has been recognized as an entity since it was first described by Bright in 1827 but it did not assume its present significance until the second World War. This emphasized the relation of acute renal failure to trauma. Steady progress has been made in understanding renal failure since that time and a unified concept of its pathogenesis has been formed. Therapy has reached the point where the majority of deaths associated with renal failure result from underlying disease conditions rather than from renal failure, per se. The purpose of this paper was to present the current concepts of renal failure from the point of view of pathogenesis, pathology and treatment.

Acute renal failure has been defined as acute failure of the kidney to clear the plasma of normal metabolites with resultant solute retention. Oliguria has been defined as an output of urine by the kidney inadequate to prevent solute retention. It has usually been defined as a daily output of urine less than 500 milliliters. Diuresis has been defined as a daily output of urine greater than one liter after a period of oliguria.

Acute renal failure results either from the action of specific toxins on the renal tubule cells or from severe trauma to the body in general which causes a period of renal ischemia. The ischemic episode is the one unique feature of all the diverse conditions which may lead to renal failure. The multiplicity of

terms formerly describing the condition are superfluous. It is apparent that the usual degree of hypotension associated with most of the traumatic episodes leading to renal failure is insufficient to cause renal failure. It is probable that there are other factors associated with trauma which cause the kidney to be more susceptible to a temporary ischemia.

The pathology of renal failure involves two types of damage. Specific nephrotoxins affect only the epithelial cells of the proximal tubule and regeneration occurs. Post-traumatic renal failure, or that renal failure caused by an ischemic episode results in both damage to the cells and random disruption of the entire renal tubule basement membrane. Lower nephron nephrosis is a misnomer which resulted from inadequate histological technique in examining the kidney. Acute tubular necrosis or tubulorhexis are suggested as better terms. In acute tubular necrosis regeneration does not occur functionally because of disruption of the basement membrane of the tubules. Recovery in such cases depends on the functional reserve of the kidney and the fact that individual nephrons are randomly affected leaving many undamaged. The diuretic phase of renal failure of either the nephrotoxic or tubulorhexic type is marked by beginning regeneration but functional immaturity of tubular cells with resultant impaired resorptive powers.

The diagnosis of acute renal failure depends on ruling out other causes of oliguria such as reflex oliguria, hypotension, dehydration and obstruction to the renal outflow tract.

The clinical course of acute renal failure depends on the period and degree of oliguria. Solute retention, especially the retention of potassium contributes to the seriousness and symptomatology of the illness. Potassium retention has its most serious consequence in myocardial toxicity. Fluid retention has its consequences, in most severe form, in pulmonary and cerebral edema. Other serious consequences of oliguria include hypocalcemia, pancytopenia, infection, toxic effects of retention of the products of nitrogen catabolism and the effects of metabolic acidosis.

Treatment of renal failure is entirely supportive since the failure is usually self-limited and since once failure has occurred there is no way to hurry repair of the kidney. Treatment may be entirely conservative and directed toward the control of homeostasis by control of input. If conservative treatment is inadequate, dialysis in the form of peritoneal lavage or the artificial kidney may be employed. The over-all treatment is still based on controlled input, however, and dialysis is adjunctive to it. Both peritoneal lavage and extracorporeal dialysis are specialized procedures. The latter requires a specially trained team and special apparatus. General supportive measures involve specific treatment of pulmonary edema, hypertension, convulsions and psychoses as well as other complications when they occur.

It is the opinion of this writer that most cases of renal failure from whatever cause can be handled by means of the conservative treatment discussed in this paper. However, it is also my opinion that dialysis techniques are valuable adjuncts and may be necessary in order to salvage more difficult or refractory cases. No large general hospital should be without the facilities for peritoneal lavage at least. This is especially true in hospitals in which major operations are carried out on patients in older age groups since the incidence of underlying disease complicating oliguria is high in these groups. The artificial kidney is a valuable aid but the complexities of its use and the necessity for trained and constantly prepared personel preclude its use in all but the largest treatment centers. With modern methods of treatment renal failure should cause death in a small percentage of patients.

CONCLUSIONS

1. Acute renal failure is usually associated with severe trauma or the effects of specific nephrotoxins.
2. Temporary ischemia is the unifying pathogenetic factor in all the diverse causes of renal failure except nephrotoxins.
3. The chief pathologic changes in renal failure are degeneration of epithelial cells of the proximal tubule as a result of nephrotoxins and random disruption of the basement membrane of the entire renal tubule in renal failure resulting from ischemia. Recovery depends on the fact that all tubules are not usually effected by ischemia. Diuresis after the oliguric phase is a sign of regenerating but immature tubular cells.
4. Diagnosis involves ruling out conditions other than ischemia or toxins that may cause oliguria.
5. The clinical course depends on the extent and duration of oliguria and the severity of underlying disease or injury.
6. Treatment is aimed at support of the patient through the period of renal failure and recovery by attempting to maintain proper blood chemistry relationships. Treatment may be entirely conservative by controlling the dietary, fluid and electrolyte input of the patient or it may be more radical involving dialysis either by means of peritoneal lavage or by the use of the artificial kidney.
7. It may be stated that renal failure need no longer be fatal as it has so often been following severe trauma, operation, other insults to the organism in general or the action of

nephrotoxins. The limiting factor in the treatment of oliguria is the extent of underlying illness, although in a small percentage of cases the kidney may be damaged so severely that it has no functioning nephrons left.

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