1951

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Donald Charles Niederluecke
University of Nebraska Medical Center

Recommended Citation

Niederluecke, Donald Charles, "Artificial kidney" (1951). *MD Theses*. 1763.
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THE ARTIFICIAL KIDNEY

Donald Charles Niederluecke

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine
College of Medicine, University of Nebraska
January 15, 1951
Omaha, Nebraska

I. Introduction

This paper is intended as a presentation of the artificial kidney and its use in relieving uremia in patients with temporary or reversible renal impairment.

A. The Uremic state.

Uremia is a toxic clinical condition associated with renal insufficiency and the retention in the blood of nitrogenous urinary waste products, and generally accompanied by distrrbance in the acid-base and/or water balance. Its etiology is the inability of the kidneys to rid the body of waste products either through suppression of urine or the inability of the kidney to concentrate as in chronic glomerulonephritis.

The symptoms and signs of uremia are headache, restlessness, muscular twitching, mental distrubances, nausea, vomiting, uriniferous breath and, in some cases, diarrhea. In advanced cases there may be fibrinous pericarditis and necrotizing colitis. In addition there are usually disturbances of the acid-base balance and edema may occur. Edema occurs most frequently as a result of overzealous infusion and in cases associated with hypertension in which there is frequently cerbral edema with convulsions or stupor. (1)

Urema is progressive and unless relieved by spontaneous remission of renal suppression or by theraputic efforts to clear the body of urinary waste products the patient eventually becomes comatose and dies. The renal conditions leading to uremia may be reversible or permanent. It is for the patient with temporary or reversible irrigation, and intestinal lavage are reserved.

B. Renal Kiseases leading to uremia

1. Permanent. Among the most common permanent and progressive renal diseases resulting in death from uremia are found progressive polycystic kidney, bilateral hydronephrosis, chronic glomerulonephritis, malignant nephrosclerosis, chronic pyelonephritis in its last stages and renal tuberculosis when both kidneys have been involved.

2. Temporary conditions which result in uremia are: acute renal shutdown following mismatched transfusions, sulfonamide toxicity, surgery to genitourinary tract, toxemias of pregnancy in some cases, massive burns, and shock. In addition is the large group of degenerative nephroses which may follow massive trauma, mercury or arsenic poisoning, sever toxicity following some cases of diptheria, pneumonia and typhoid fever.

3. The need for an artificial kidney. Certain types of renal failure need not be fatal if the period necessary

for repair may be provided by utilizing an extra renal pathway as a temporary substitute for the normal excretory function of the kidney. Uremia resulting from acute renal damage is frequently fatal because the renal lesion requires more time to heal than the lethal effects of uremia will allos. (2)

Outstanding in this regard are the renal suppressions resulting from mismatched blood transfusions, sulfa drug reactions, toxemias, and the degenerative nephroses, k. e., the break down of tubular epithelium following massive burns, mercury and arsenic poisoning, crush injuries, and massive burns. It has been estimated that the time required for regeneration of tubular epithelium is betwee 5-12 days in most instances, with a resumption of nearly normal kidney function. Ihas been proved clinically that the artificial kidney and peritoneal irrigation are capable of tiding the patient over this period of repair with the absence of uremia until his kidneys are again able to take the responsibility for excretion. It is believed that if the patient is relieved of uremia by artificial means the kidney recovers function more rapidly. If the patients who suffer from these reversible renal dideases could be treated by the artificial kidney for the few days necessary for kidney repair a tremendous number of lives could be saved.

II. History of treatment of uremia by artificial means.

Various methods of temporary compensation for renal failure have been attempted in the past. Chief among these are the artificial kidney, peritoneal irrigation, intestinal irrigation. Of these the first two have been most successful.

A. Peritoneal irrigation.

1. General. Most of the efforts of artificial elimination of uremia artificially have centered about continuous peritoneal irrigation. This is true mainly because of its simplicity when compared to the other methods mentioned.

Briefly, the apparatus consists of a large carboy containing the irrigant from which runs a tube attached to a mushroom catheter inserted in the peritoneal cavity. A perforated stainless steel sump pump such as that used for suction is inserted in the peritoneal cavity on the opposite side of the body and serves to drain the irrigant plus the metabolites picked up into a container placed on the floor.

The solution used is Tyrode's which has been modified by the addition of 2% glucose, penicillin, sulfa, and is Buffered at ph 7.3. The solution used must fulfill three requirements: 1-it must be composed in order to allow products in excess to flow into it; 2-it must prevent necessary constituents from being depleted; and 3- it must be scrupulously sterile. (3)

The hazards of peritoneal irrigation are mainly the development of peritonitis, depletion by the solution of electrolytes necessary to the body, and water intoxication. Bacteria are believed to enter the peritoneal cavity from the skin about the catheters, contaminated irrigant, or contamination of equipment at time carboys are changed. In most cases even with the addition of penicillin and sulfonamides to the irrigating solution it has been possible to culture bacteria from the irrigant as it leaves the peritoneal cavity. In spite of the bacteria present there has rarely resulted a clinically recognizable peritonitis. (4)

III. Case Histories.

Case No. 1. Fifty-four year old white female with carcinoma of the cervix. Became anuric after ureters transplanted to sigmoid colon. NpN 75. Treated eight hours with continuous peritoneal irrigation bringing about fall in NPN to 41 with accompanying improvement in general condition. Portion of small intestine externalized and irrigated for four hours. NPN began to rise and patient was returned to peritoneal irrigation with repeated fall in NPN. Continued on this treatment for six more hours at which time spontaneous diuresis took place and peritoneal irrigation was discontinued. (3)

Case No. 2. Woman with acute renal suppression following mismatched transfusion. Treated conservatively but without remission and with onset of uremia. Patient w was started on peritoneal irrigation and uremic state was slowly abolished. Patient was maintained in this manner for four days until urinary output increased and irrigaion was discontinued. Patient made satisfactory recovery.(2)

Peritoneal irrigation has been proved clinically effective in relieving uremia and allowing the patientto survive the perior of oliguria or anuria until the kidneys regain function. It is impossible to state definitely that the patients successfully treated by this method would have died without use of peritoneal irrigation but similar cases in which peritoneal irrigation was not used would seem to indicate that this is probably true. (4) In most cases peritoneal irrigation has been used as a last resort when conservative measures have failed to bring response. It is believed by the men using this method that results would be better if peritoneal irrigation were used in conjunction with medical treatment instead of waiting until the patient approaches terminal uremia.

Optimum rate of flow has been determined at between

40-60 cc/min. (4) At this rate it is possible to remove 15-20 grams of urea per day. This is equal to the urea production on a normal diet and far exceed that produced on a low protein diet, which is prescribed during treatment either orally or parenterally if the patient is unable to eat. In most cases the patients show improvement within 36-48 hours. The length of time necessary to relieve the uremia depends on the severity and duration of uremia, degree of saturation of extravascular spaces with urinary waste products, and the urea clearance obtained by irrigation (3) When the urea clearance of the recovering kidney has reached 7.5 cc/min irrigation may be discontinued and the patient will not lapse into uremia provided he is maintained on a low protein diet.

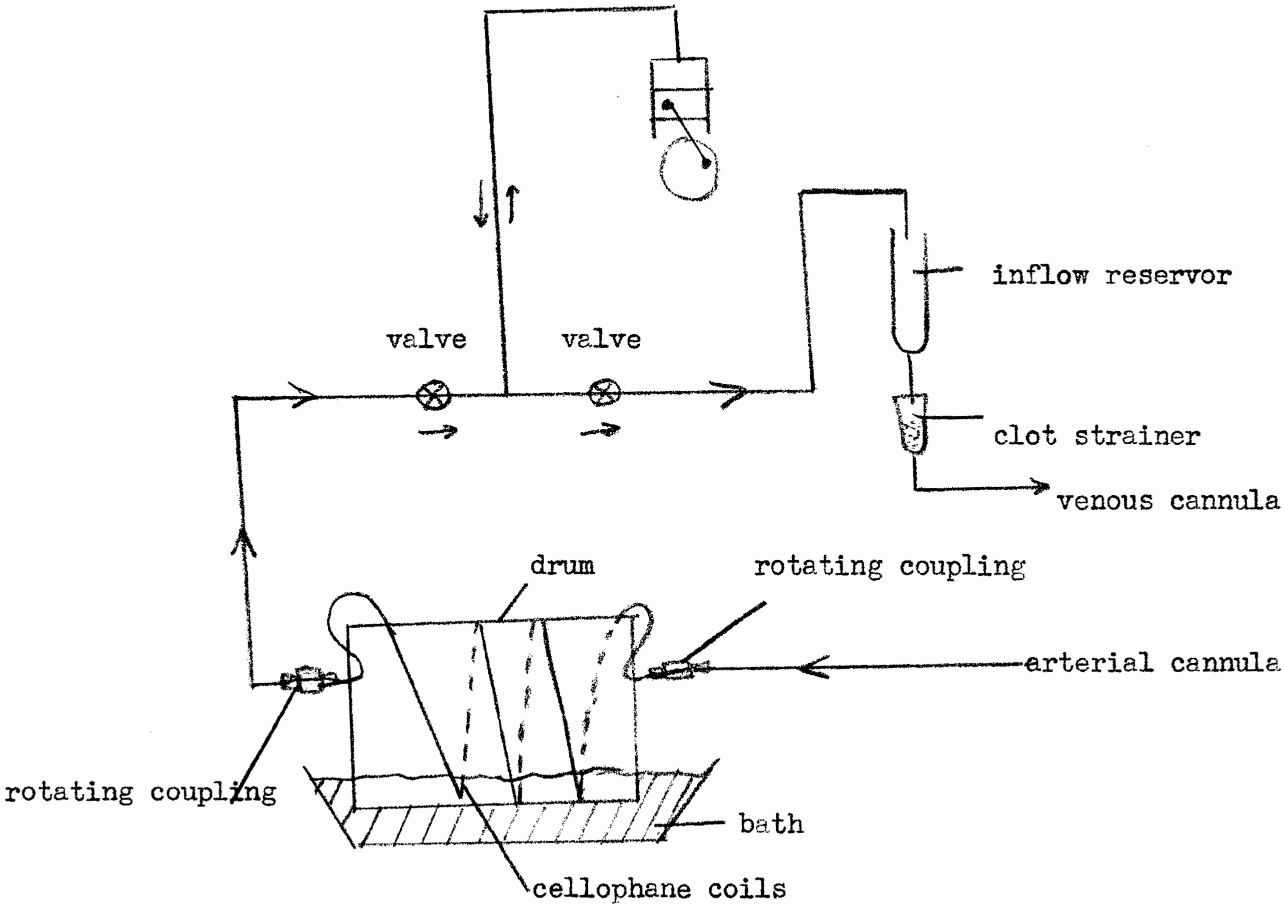
Continuous intestinal lavage. Two methods of treating renal suppression have been devised. One involves surgery in which a double enterostomy is done involving the upper jejunem and the lower illeum which makes almost the entire small intestine available for irrigation. This method offers no advantages over the artificial kidney and carries with it the hazard of surgery on the uremic patient who is a poor surgical risk. The other method which was devised by Maluf involves passing a modified miller abbot tube composed of three portions: 1. a tube for inflating the balloon once it has passed the dupdenum; 2, a tube for passing irrigant into the small intestine; and 3, a tube for drawing fluid from the intestine. Maluf was able to obtain a urea clearance of 34 cc/min. The solution used was a slightly na2 s04. He found that the chlorid loss was approximately 6 grams in an eight hour period and that this amount was easily replaced intravenously. This method has been tried only experimentally on well persons and has never been tried in relieving uremia. (13,14)

C. The Artificial Kidney. Abel, Rowntree, and Turner in 1912 (5) were the first to introduce the artificial kidney in their work on dogs doing what they referred to as "vividialysis". They passed animals blood through a network of celluloidin tubes immersed in a modified Ringer's solution and were able to extract injected drugs from the animal. They were interested mainly in isolating blood constituents and the possiblilities of removing poisons such as salicylates from the blood stream in which overdosage has occurred. They did mention however, that they believed the method had application in the relief of uremia. They experienced difficulties in their work which hindered application of the system to humans. One of the main difficulties and the one which accounted for the deaths of most animals was that anticoagulants were in their infancy and clotting occurred frequently. They reported that hirudin, which was the anticoagulant used was priced at 27.50 per gram and that they frequently used a half or two thirds of a gram in an experiment lasting an afternoon. Because this expense was prohibitve they began grinding leech heads and extracting their own hirudin. They reported that they could buy 1000 of the finest leeches for 20-25 dollars. Another problem was that cellophane tubing was not available commercially and they had to make tubing by pouring a solution of cellulose acetate formed through glass tubes which were rotated until dry and the formed celluloid tubing slipped out. This was somewhat unsatisfactory since the thickness was inconstant and the work very tedious.

It remained for Kolff to develop the first model of the artificial kidney which was satisfactorily used in treating humans. His apparatus consisted of a long cellophane tubing wrapped around a drum immersed in a bath solution of modified Tyrodes solution. All subsequent artificial kidneys have been of the Kolff type withrelatively minor modifications. The modifications have been in the bore of ubing used and in the tubing used to connect the arterial and venous cannulae to the cellophane tubing and in the pumps used to aid the arterial pressure in propelling the blood through the circuit and back to the venous circulation. The solutions used have been essentially the same, most being modifications of Tyrode's solution. One investigator used a marked modification of Kolff's original model in which the blood was passed between two sheets of cellophane surrounded by the dialysate.

Basic design of artificial kidneys of the Kolff type is shown below:

THE ARTIFICIAL KIDNEY



III. The principle of the Artificial Kidney. The principle of all artificial kidneys is dialysis in which the patient's blood is dialyzed by passing it through a long cellophane tube immersed in a bath of dialysate. Constituents which are in higher concentration in the blood than in the dialysate pass into the dialysate. In this manner urinary waste products can be removed. Conversely, constituents which have dropped below normal can be passed into the blood and water can administered or withdrawn. (6)

The design of all artificial kidneys is aimed at achieving a maximum surface area of exposed blood/unit volume, a high diffusion gradient between blood metabolites and dialysate, optimum blood flow, small dead space, and simplicity of construction, sterilization and immediate repair. In order to achieve a large surface area the tubing used is of small diameter and great length. The tubing used is easily sterilized and is only used once to help preclude pyrogen reactions. A high gradient is maintained by using a large volume of dialysate and changing it frequently. Before beginning treatment the tubing is filled with donor blood to obliterate the dead space and prevent lowering of the patients blood volume. The design in most cases is simple and the apparatus is not liable to breakdown. However, replacement parts are on hand before treatment is begun. Blood flow is maintained in most cases by pumps placed in the circuit. Pumps are designed to inflict minimal damage to the blood as it passes through.

IV. Technique of The Artificial Kidney.

A. Avoidance of clotting. One of the major problems of circulating a large volume of blood through an extensive system outside the body is the prevention of clotting. Since the patients who are treated with the artificial kidney frequently have lesions, surgical or otherwise, which may give rise to hemorrhage, prevention of clotting is ideally carried out with a minimum of anticoagulant. Heparin has proved to be the most satisfactory anticoaguland and frequent checks are made on the clottin time. In addition to heparinizing the blood the apparatus is designed to prevent trauma to the circulating blood insofar as is possible. Wuth the replacement of rubber tubing in the circuit by Tygon, an inert, non-wetting vinyl material, clotting has been substantially reduced. Design of the pump is also important in preventing of clots. It must be designed to create a minimum of turbulence and the valves must be of a non-wettable nature. Polished lucite which has been given a silicone coating has proved satisfactory. (6) Donor blood which is used to fill the tubing prior to treatment should be fresh as possible to insure maximum resistence of the blood cells to mechanical trauma. Inevitably some clots will be formed and these must be filtered from the circulating blood before it is returned to the body. In most instances thais has been accomplished by passing the blood through a clot straining chamber filled with silicone coated glass beades of small diameter.

B. Avoidance of hemolysis. The prevention of hemolysis is attempted in the same way as prevention of clotting. In addition care in regulating the osmotic pressure of the dialysate may have some effect. It has been discovered by Vanatta (7) that the glycerine used to maintain pliability in the cellophane tubing contributed significantly to hemolysis. He removed the glycerine by soaking the cellophane tubing in formaldehyde for 24 hours and washing it in distilled water prior to sterilization. This treatment makes the cellophane brittle and it must be hankles with great care to prevent leaks.

C. Pyrogen reactions. Febrile reactions are thought to be usually due to foreign material and a rise chiefly from the following causes: 1, pyrogenic materials in distilled water; 2, impure or improperly or inadequately cleaned equipment. (8) Pyrogenic reactions are kept at a minimum by careful sterilization of all materials and equipment used and the use of disposable tubing. Care is also taken that donor blood used is carefully matched and from a donor free from infection.

D. Leaks. Occasional leaks occur in the cellophane tubing and must be checked for before dialysis is begun. This is done by passing donor blood through the system under some pressure. After dialysis has begun leaks are detected by noting reddening of the bath solution and foaming. Since the pressure within the tubing is al all times higher than that surrounding solution there is no danger of infusion of bath solution into the blood. When leaks occur in the connecters they are replaced by substitutes readily at hand. (6,8)

E. Flow control. Flow has been controlled in most cases by pumps placed in the circuit. Flow control is important since the clearance of metabolites in in direct relationship to the rate of flow through the dialyzing tube. When the rate of flow is raised much in excess of 125 cc/min there is a rise in blood pressure thought to be due either to a too rapid infusion of glucose into the body of the depletion of a vasodepressor substance from the blood at a higher rate than is replaces by the body. (9) Flow control is achieved by the varying speed of the pmp and by adjustable clamps on the arterial and venous sides of the circuit. The cellophane tubing used is somewhat distensible and it is possible for blood to collect in the distal portions. Vanatta (7) found that his results were better if he weighed the patient and the apparatus at intervals with a scale accurate within 10 grams and was able to determine and correct over-loading or depletion of blood volume.

F. Fluid exchange. The problem of fluid balance approached through matching the osmotic pressure of the dialysate with that of the patients serum. Soon before treatment is started the osmotic pressure of the patients serum is determined. This is simply done by use of the freezing point depression method. The osmotic pressure of the bath solution has been predetermined and the difference invalues between the dialysate and the patients serum is corrected for by addition of glucose to the dialysate. By changing the osmotic pressure of the bath solution it is possible to add fluid to the patient or withdraw it. (10)

V. Preparation of the Patient for the Artificial Kidney.

A. General. If time is available before treatment a thorough physical examination should be done and in addition the patient's cardiac condition and fluid balance should be delved into. If time is available an electro-cardiogram is of added benefit in determining heart strain. This is important as it will effect the decision as to the rate of flow advisable.

B. Heparinization. Before treatment is begun it has been satisfactory to give 100- 200 milligrams of heparin and to give 50 0 100 at intervals during dialysis depending on the hourly check of the clotting time. It is best to keep use of heparin at a nimimum since as was mentioned before these patients frequently have lesions which may begin hemorrhaging during treatment. A clotting level of 40% of normal has proved satisfactory. (11)

C. Necessary Preliminary Determinations. Essential preliminary determinations include blood urea nitrogen, Non-Protein nitrogen, Total serum protein, carbon dioxide combining power, total bases, Hematocrit, and clotting time. Hematocrit, carbon dioxide combining power and non-protein nitrogen are done at intervals during dialysis.

D. Technique of attachment. The patient is prepared for attachment by infiltration of procaine at the site of attachment, generally the radial artery of one arm and the brachial vein fo the other. Penicillin is given prophylactically to prevet occurence of infection incident to the cut-down. Attachment is by means of silicone coated glass cannulae. Before tying the radial artery it is advisable to palpate the ulnar artery to preclude ~~of~~ tying off the sole major vessel in the case of anomalous absence of the ulnar artery. Oozing may be prevented cannulating the patient an hour or so before the administration of heparin to allow the wound to dry somewhat. (6)

VI. Efficacy.

Efficacy of the Artificial kidney in removing metabolites from the blood stream are dependent on four main factors: 1, the rate of flow of blood through the apparatus; 2, dialyzing area of the cellophane tubing; 3, load of metabolite in the infused blood; and 4, the diffusion gradient. (12) The area unit valve is made as large as possible by employing fine diameter cellophane tubing and using a great length of tubing coiled around a drum. Because he can obtain a higher load of metabolite and hence a higher diffusion gradient, Murray (10) had used venous blood rater than arterial in his dialysis. This is true in the case of a patient with partially functioning kidneys but not when the patient is anuric. Use of arterial blood has as an advantage the fact that the blood is delivered to the apparatus under arterial pressure making less mechanical pumping necessary and decreasing trauma to the blood. The dialysate is changed at intervals to maintain a high diffusion gradient.

VII. Case Histories.

Most work with the Kolff artificial kidney has been carried on by Merrill who had in April 1950 treated 43 cases of reversible kidney disease with renal suppression and urema, with success in a high percentage of cases and has concluded that the artificial kidney is a valuable contribution to the treatment of renal **disease.** A few sample cases are listed:

Case Histories of Merrill: (6)

Age	Diagnosis	Length of Rx	Result
20	Anuria, type undetermined	6 hrs.	complete recovery
47	Anuria following CCl4 poisoning	5 hrs.	complete recovery
35	ecclampsia following delivery, anuria	12 hrs.	immed. improvement complete recovery
63	renal suppression following sulfathiazole intoxication	17 hrs.	no improve. - died
3	nephrotic syndrome	7 hrs.	transient improve. died - 1 wk. later
43	anuria P.O. nephrectomy	12 hrs.	complete recovery

Case Histories of Fishman (11)

51	anuria following mismatched transfusion	16 hrs.	no improve. - died
35	"" " " " " "	8 Hrs.	immed. improvement
17	anuria, crush syndrome	12 hrs.	immed. improvement ultimate full recov.

Case History of Murray (10)

27	renal suppression following mismatched transfusion	8&5	improvement with eventual recovery

VIII. Summary.

A review of the literature concerning the use of artificial means of treating uremia in patients suffering from acute reversible renal disease with anuria or marked oliguria has been presented.

The various methods of applying such treatment, the artificial kidney, continuous peritonial irrigation, and intestinal lavage have been described and attempt has been made to compare the hazards and advantages associated with each method.

Case histories demonstrating the application of these methods to the uremic patient have been presented.

IX. Conclusion.

Results of the application of the artificial kidney in the timporary relief of uremia during the healing period of acute reversible renal disease would indicate that the methods used offer great promise and could be used beneficially in many cases of acute reversible renal disease which so feequently are fatal before the period of time necessary to resumption of the normal urinary mechanism has elapsed.

At the present time, however, it would seem that peritoneal irrigation offers the best meansof artificial relief of uremia. The apparatus used is simple and inexpensive, and with strict attention to asepsis this method of treatment would be a valuable tool in the hands of the practitioner who is already cognisant of electrolyte and fluid balance in the body.

The artificial kidney before it becomes more commonly must be standardised and produced commercially. The few artificial kidneys in existance have been designed and produced individually and the expense in each case has undoubtedly been great, Also commercial artificial kidneys could be produced in greater numbers and be readily available when needed .

Perhaps a solution would be to have a few of the artificial kidneys on hand in the major medical centers. They could then be transported rapidly along with a man who had had considerable experience in their use and is familiar with the problems confronted.

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