EFFECTS OF AN ION EXCHANGE RESIN ARTIFICIAL KIDNEY IN DOGS

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John H. Richardson

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by

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AN ABSTRACT

Submitted to the College of Veterinary Medicine
Michigan State University of Agriculture and
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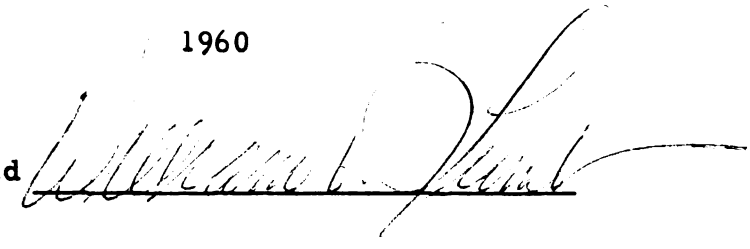
Approved 

JOHN H. RICHARDSON

ABSTRACT

A study was performed to determine the effects of an ion exchange resin artificial kidney in dogs. Bilaterally nephrectomized dogs, dogs with induced nephritis, and normal dogs were subjected to hemoperfusion through a cation exchange resin, Dowex 50W-X8.

The ability to prolong life of nephritic dogs as well as effect on the following were recorded: plasma sodium, potassium, and chloride, hematocrit, non-protein nitrogen, white blood count, and electrocardiogram.

Hemoperfusion was very successful in rapidly lowering plasma potassium values. At the same time it resulted in an elevation of plasma sodium. Non-protein nitrogen was not affected by the resin. Loss of body temperature and infection at the cutdown sites posed a constant problem throughout the course of the perfusions. Repeated collection of blood samples for determinations contributed heavily to anemia, and transfusions were necessary to maintain the hematocrit within the normal range.

The postsurgical life of totally nephrectomized dogs was doubled over that of the controls. The perfused dogs lived an average of 208 hours and the nonperfused controls lived an average of 102 hours. Hemoperfusion was not as effective in prolonging the life of dogs with induced nephritis. The perfused dogs in this group averaged 126 hours postsurgical life while non-treated controls lived an average of 95 hours.

From this study it was concluded that repeated hemoperfusion through Dowex 50W-X8 is of questionable value in the clinical treatment of canine nephritis. Although the procedure was effective in rapidly

lowering elevated plasma potassium values, it had little effect on nitrogenous wastes and proved quite traumatic to the dogs. Oral or rectal use of cation exchange resins as reported in the literature may be of some value in the treatment of canine nephritis characterized by hyperkalemia.

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CHAPTER I

INTRODUCTION

Nephritis is one of the common diseases of dogs past middle age. It is becoming increasingly important in the practice of veterinary medicine since the introduction of new therapeutic and surgical procedures continually extends the life expectancy of domestic pets.

Nephritis in dogs differs from human nephritis principally in location. Glomerulonephritis and pyelonephritis account for the overwhelming majority of cases in man, while interstitial nephritis predominates in dogs (26).

Canine nephritis is considered to be either acute or chronic. Leptospirosis probably causes the most common form of acute nephritis seen by the veterinarian (31). Acute nephritis may also be associated with chemical poisons, such as arsenicals used in the treatment of dirofilariasis, as well as being a result of bacterial toxins.

Chronic nephritis is said to be compensated or noncompensated. Compensated cases of nephritis exhibit an elevated non-protein nitrogen but, on the other hand, do not exhibit clinical symptoms. These dogs may have only 25 percent of the total number of nephrons functioning, but under normal conditions can carry on everyday activity. If, however, undue stress or disease further destroys any of the remaining functional nephrons, the animal is no longer able to compensate, the urea level in the blood becomes excessively elevated, and clinical

symptoms of uremia develop (26). Many cases of so-called acute nephritis are undoubtedly intermittent "flare ups" or periods of decompensation in longstanding cases of chronic compensated nephritis. If the animal can be tided over this period of decompensation and maintained by artificial means until renal repair takes place, it may be able to live a normal life, with certain restrictions on activity and diet.

The paramount finding in nephritis is an increase of urea in the blood and hence the term uremia. This is an unfortunate misnomer, because urea itself is not toxic; however, its level in the blood is used as an indication of the retention of nitrogenous wastes and, thus, renal insufficiency (37).

The blood picture in chronic nephritis usually shows anemia and possibly a mild leukocytosis. Acute renal failure, especially if due to leptospirosis, will reveal a hemogram characterized by extreme leukocytosis, a shift to the left, an increased sedimentation rate and hemoconcentration.

The usual course of renal disease in dogs begins with irregularly intermittent episodes of illness in which polydipsia, polyuria, mild albuminuria, and a few casts are observed. The specific gravity of the urine is low and as the disease progresses, the fixation point of 1.010 is reached. Even when water is withheld, the kidneys are incapable of concentrating urine. Attacks of nephritis may be characterized by depression, vomiting, diarrhea, and occasional convulsions. The mucous membranes are often injected, the pulse bounding, and the skin and coat may show roughness and signs of dehydration.

The electrolyte balance is upset and the over-all loss of electrolytes may be marked. Vomiting contributes to the loss of electrolytes. Inability of the kidney tubules to conserve sodium and excrete hydrogen and ammonium results in a loss of fixed base and the characteristic uremic acidosis. The reduction of electrolytes causes the plasma and interstitial fluids to become hypotonic and the intracellular electrolytes are redistributed to correct this insufficiency. This results in elevated potassium and phosphate values in the plasma and interstitial fluid (37).

An elevated extracellular potassium ion level is toxic to cardiac tissue and is first reflected on the electrocardiogram (ECG) as an increased amplitude of the T wave. As further potassium increases develop, changes in the ECG appear in the following order: depression of the ST segment, intraventricular block, absence of the P wave, and finally cardiac arrest (94). The cardiotoxic effects of the potassium ion may be the ultimate cause of death in terminal cases of nephritis.

The use of an artificial kidney in periods of renal insufficiency would appear to be the answer to the problem. Substitution of artificial organs for natural ones is no longer confined to the research laboratory. Artificial organs are rapidly becoming important aids in the practice of medicine and have gained clinical recognition.

The purpose of this study was to determine if an ion exchange resin artificial kidney would prove effective in the maintenance of a uremic patient until kidney function returned to normal.

CHAPTER II

REVIEW OF THE LITERATURE

A. Introduction

The management of renal failure is well documented in the medical literature. The review presented with this thesis points out many of the different procedures employed both past and present, to restore the homeostatic mechanisms in the uremic patient. Many of these practices are of course outdated and obsolete, but they serve as an indication of the great amount of work which has been done, and the progress which has been made.

B. The Dialyzing Bath Artificial Kidney

The primary purpose of any artificial kidney is the elimination of waste products from the blood. The natural kidney fulfills this function by ultrafiltration and dialysis from the glomeruli, and by specific activities of the tubule cells. The dialyzing bath artificial kidney duplicates the function of the glomerulus (54), in that retention products are eliminated by filtration and dialysis through a semi-permeable membrane. The patient's blood is on one side of the membrane and the dialyzing fluid containing only crystalloids is on the other side. Since the membrane is impermeable to blood colloids and large molecular complexes, only water and crystalloids can pass freely through its pores. The dialyzing fluid need not be sterile since the pore size of the membrane does not permit the passage of bacteria or large viruses (96).

The direction of the movement of crystalloids depends on the difference in concentration on both sides of the membrane. The specific electrolyte concentration in the dialyzing fluid determines the final blood concentration. The more abnormal the patient's plasma values, the greater will be the concentration difference across the membrane and the more rapid the clearance. Urea, creatinine, uric acid, other protein metabolites, phosphates, sulfates and other electrolytes will thus diffuse from the blood into the dialyzing fluid. On the other hand, it is equally possible for the artificial kidney to correct a deficiency in blood electrolytes by maintaining a physiologic concentration of the deficient factor in the dialyzing fluid (54).

In addition to the movement of electrolytes through the membrane, water also moves in both directions. One of the factors which determines rate and direction of the passage of water is the hydrostatic pressure. If this pressure is higher on the blood side of the membrane, ultrafiltration of water from the blood into the rinsing fluid will occur relieving edema. On the other hand, if the hydrostatic pressure of the blood is lowered, water will pass from the rinsing fluid into the blood, thereby restoring fluid balance in the dehydrated patient.

The name "artificial kidney" was coined in 1913 by Able, Rountree, and Turner (1) who pioneered in designing an apparatus for the elimination of waste products from the blood by extracorporeal hemodialysis. Their apparatus was an elaborate one, consisting of collodion tubes which they formed and extruded themselves. These acted as semipermeable membranes and were tied to a system of branching glass tubes with string. The patient's femoral pressure pumped the blood through the apparatus. In order to prevent

coagulation of the blood during its course outside the body they employed hirudin, the active anticoagulant of the leech. The rinsing fluid, into which diffusible substances passed from the blood by way of the collodion membrane, was 0.6 percent sodium chloride. As the apparatus could not be sterilized by heat, it was kept sterile by filling it with thymol between experiments.

Van der Heyde and Morse (87) and Love (44) in 1920 attempted to improve on the collodion membranes of Able and used fish bladders and the intestines of the cat, rabbit, turkey, and chicken. The latter was the best substitute for the more delicate collodion membrane.

According to Merrill (51), Necheles in 1923 constructed an apparatus that used as the semipermeable membrane, Goldschlagerhaut (goldbeater's skin made of animal peritoneum). Tubes of this membrane were placed between nets of wire, which served to prevent expansion. Necheles, too, used hirudin as an anticoagulant. In two experiments with nephrectomized dogs, he observed improvement in apathy after about two-and-a-half hours of dialysis. He noted that the life of a nephrectomized animal was not appreciably prolonged by dialysis, although there was marked improvement in symptoms immediately after the procedure. The improvement, however, was less marked with successive dialysis.

Although Howell (30) isolated heparin in 1918, Lim and Necheles (43) in 1926 were the first to report the use of heparin as an anticoagulant in dialysis. Apparently it did not prove entirely satisfactory however, as hirudin was also used by these workers.

Thalhimer (85) in 1937, devised an apparatus in which the semipermeable membrane was for the first time made of cellophane. This

cellophane membrane was the same seamless sausage casing that is utilized in many apparatuses today. He noted the removal of 700 milligrams of urea nitrogen in a three- to five-hour dialysis. He compared these results to those of exchange transfusion with a normal animal, and finding the latter more satisfactory, concentrated his efforts on this.

Kolff and Berk (39), working in Holland under conditions of the German occupation in 1943, devised what must be considered the first artificial kidney to have met with any degree of clinical success. A cellulose tube was wrapped around a horizontal drum which rotated in 100 liters of rinsing fluid. Propelling forces for the blood were gravity and the patient's arterial pressure. The dialyzing area was large (2.4 meters) in comparison with the small volume of blood (600 milliliters).

A group of Canadian workers, Murray, Delorme, and Thomas (60) reported in 1947 the use of an artificial kidney, similar in design to that used by Able and his co-workers, with the exception that cellulose tubing was employed in place of collodion tubing. The thickness of the cellulose wall interferred with adequate dialysis however.

In 1947 Alwall (2), working in Sweden, reported the use of an artificial kidney in which cellulose tubing was sandwiched between two screens. The tubing was wrapped around a screen and surrounded in turn by a second screen that was fitted very much the way a corset is fitted around a body (51).

Von Garrelts (90) in 1948, obtained a favorable ratio between blood volume in the cellulose tubing and dialyzing surface by winding tubing and wire mesh together into a stationary coil. With this

arrangement the volume of blood in the cellulose tubing was small, the dialyzing area was large, and the unit was compact.

Sterling (83) in 1948 devised a basic filtration unit that consisted of a sheet of cellophane between paired plates forming a chamber. Blood passed through this unit on one side and perfusing fluid on the other. Multiple chambers were held together under pressure to form an artificial kidney which could be autoclaved.

Skeggs and Leonards (78) described, in 1948, an artificial kidney in which blood was contained by flat sheets of cellophane. These in turn were compressed by longitudinally corrugated rubber pads through which the bath fluid flowed in a current counter to that of the blood. Improvements over this original apparatus were reported by these same workers the following year (79) and artificial kidneys of this design are in use in some of the larger clinics and hospitals today (47,98).

An apparatus operating on much the same principle was constructed by Lowsley and Kirwin (45) in 1951. Circular sheets of cellophane were mounted on transparent plastic supports with the blood chambers interspersed between pairs of water chambers. Both parallel and series counter-current flow types were constructed. A disadvantage of this apparatus was that it was disinfected by soaking in cold aqueous urolocide solution prior to use rather than sterilized by steam.

The dialyzer of Rosenak and Saltzman (71), described in 1951, employed cellophane tubing sandwiched between flexible steel chain-linked screens. It employed counter-current flow, and a vein to vein system was used, employing either both femoral veins or one femoral

vein and a double lumen catheter. A pump was used to move the blood through the apparatus.

The reverse of the usual system of dialysis was reported by Guarino and Guarino (25) in 1952. The blood was outside the cellulose tubing and the rinsing fluid was inside. This design had a low clearance and no safeguard against air embolism or against over-hydration of the patient if a leak should develop in the cellulose tubing.

Inouye and Engelberg (34) in 1953 ingeniously used a cheap, disposable plastic screen in a stationary coil that they fitted into a pressure cooker. In 1956, Kolff and Watschinger (40,41) further simplified the idea of Inouye and Engelberg and put the stationary coil into a sealed can, making a dialyzing unit that was cheap, disposable, and could be mass-produced.

The disposable coil kidney, produced by Travenol Laboratories Incorporated (97), and sold commercially, was a result of further developmental work by Kolff. The coil consisted of two cellulose tubes enveloped in fiberglass screens. The coil was wrapped around a central cylinder. In operation, blood flowed through the cellulose tubing, and dialyzing fluid was pumped through the screen. Dialyzing fluid was contained in a 100 liter tank beneath the disposable coil unit. Temperature of the fluid was maintained at 39°C. (102°F.) and 90 percent O_2 plus 10 percent CO_2 was bubbled into it continuously. The dialyzing area was approximately 19,000 square centimeters. Vimtrup (89) in 1928 and Book (6) in 1936 calculated the filtration surface in the human glomerulus. Vimtrup estimated the total filtration surface in both kidneys at 1.5 square meters and Book's calculation was 0.76 square meter. Both these figures are exceeded

by the total filtration surface of the Kolff twin coil kidney. Flow through the apparatus was accomplished by a roller type pump at the rate of 200-400 milliliters of blood per minute. Both dialysis and ultrafiltration were accomplished and in a perfusion of five to six hours' duration, the average amount of urea removed was greater than 70 grams, depending on the initial level of the patient's blood urea.

Of all the different types presented in this history of the development of artificial kidneys, there are three basic types which are in use today: 1) the rotating drum type; 2) the Skeggs-Leonards "sandwich" type; 3) the stationary coil type. The question of which is the most effective substitute for nature's own organ has yet to be answered. In comparing the clinical results of the Twin Disposable Coil (stationary coil) and the Rotating Drum, Schreiner and Berman (75) summarized the relative merits of the machines thusly:

Twin Disposable Coil

1. It is applicable to vein-to-vein flow because of the pump.
2. It permits pressure filtration and water removal in cases of edema.
3. It is always ready for use, sterile, easy to dismantle, and disposable.
4. It has low initial cost.
5. It has a high maintenance cost, with ease in preparation and operation.

The Rotating Drum

1. It has a large available surface area.
2. It has a small dynamic volume-surface area ratio, mainly because it is a low pressure system.
3. It has greater adaptability to the patient's body size.
4. It has high initial cost, low maintenance cost, and low operating noise.

C. Use of Lavage Fluids

In 1922, Putnam (66) studied the passage of crystalloids across the living peritoneal membrane and pointed out the value of this membrane as a dialyzing medium. He observed that water, electrolytes, and urea, as well as other components of the non-protein nitrogen fraction, passed the barrier, while protein was retained. This finding opened the door to the use of lavage fluids for the removal of metabolic wastes.

The principle of the procedure is simple. A lavage solution with electrolyte and osmotic composition similar to that of tissue fluid is introduced into a body cavity. Diffusion takes place across the membrane lining the cavity and equilibrium is established between the lavage solution and the blood. The lavage fluid and the diffused metabolites are then removed by paracentesis.

1. Peritoneal Dialysis

Merrill (52) stated that the peritoneal surfaces of the adult presented an area of about 20,000 square centimeters of semipermeable membranes. This represents a greater area than the total filtration surface of both human kidneys (6,89). According to Odel (62), Ganter in 1923 was apparently the first to take advantage of the observation of Putnam as a therapeutic measure, and irrigated solutions into the peritoneal cavity of rabbits, guinea pigs, and two patients with renal failure.

Darrow (11) in 1935 used peritoneal lavage in a series of studies on changes in distribution of body water accompanying increase and decrease in extracellular electrolytes. Hypertonic and hypotonic solutions of sodium chloride were used to cause a variation

in the electrolyte balance, and glucose was added to the dialyzing fluid to stabilize the total body water while electrolyte depletion took place. Rhoads (68) in 1938 applied this technique in the treatment of experimental and clinical uremia.

In 1946 Fine et al. (20) made experimental and clinical studies of peritoneal lavage with particular regard to proper composition of the injected fluid. They elaborated on the technique previously described in 1938 by Wear (91) in which he employed a continuous perfusion into and out of the peritoneal cavity through two trocars. Fine et al. employed continuous perfusion of the peritoneal cavity for as long as three to four days. They attempted to eliminate the difficulties encountered in the removal of fluid by construction of a stainless steel sump drain with multiple perforations. The effectiveness of this procedure was hindered by obstruction of the inflow and outflow tracts with omentum. The production of flow tracts to the effluent tube decreased the dialyzing area utilized. Bacterial peritonitis accompanied most prolonged procedures in spite of utmost attention to asepsis.

In 1951, Grollman et al. (24) introduced intermittent peritoneal dialysis, a modification of the method previously employed by Darrow (11). A 17-gauge needle, nine centimeters long, was used to introduce the irrigating fluid into the peritoneal cavity of dogs. The solution was allowed to remain in the abdomen for varying periods, and then was siphoned off through the same size needle. Using this technic they were able to keep totally nephrectomized dogs alive for a month or longer, and one dog survived for 69 days. These animals developed hypertension and anemia which were attributed to the absence of renal tissue.

By duplicating the procedure described by Grollman et al. with a few modifications, Houck in 1954 maintained a totally nephrectomized dog for 111 days (29).

Morris and Moyer (56) in 1957 further modified the intermittent peritoneal dialysis technic of Grollman. These workers eliminated antibiotics from the lavage solution because they often produce slight peritoneal irritation. This irritation resulted in fibrin formation which obstructed the peritoneal catheter. Instead, antibiotics were administered by the oral or intramuscular route. A small amount of a nontoxic spreading agent, such as hyaluronidase was added to the lavage fluid.

Kirk (37) reported in 1958 on a technic for intermittent peritoneal dialysis in dogs. The composition of the lavage fluid and the procedure for dialysis was essentially the same as reported in the human literature.

2. Pleural Dialysis

Perfusion of the peritoneal cavity has proven effective in many ways, but a consistent difficulty is the matter of retrieving the entire volume of irrigating fluid which is infused. The usual experience is that perfusate enters the peritoneal cavity easily, but due to obstruction of the catheter, the same quantity is seldom removed after the period of equilibration. Pleural dialysis has been proposed as a reasonable solution to this problem, granting however that the total membrane surface area available for the transfer of metabolites is less in the thoracic cavity than in the abdominal cavity.

According to Shumway (77), Ganter in 1923 noted clinical improvement after replacing 750 milliliters of pleural effusion with normal saline in a uremic human patient.

Seligman et al. (76) in 1946, following an intravenous injection of urea in a dog, irrigated the pleural cavity and obtained a urea clearance of one-third that obtained by peritoneal irrigation. The lung at necropsy was found partially collapsed.

In Shumway's (77) work reported in 1959, dogs were bilaterally nephrectomized and a soft plastic catheter with multiple perforations was introduced into the chest cavity via an intercostal incision. Commencing on the second post operative day 300 milliliters of dialysate per ten kilograms of body weight were infused through the catheter. Two hours were allowed for equilibration and three to four alliquots of dialysate were employed each day. The procedure was successful in removing creatinine and potassium which were the only determinations reported. No difficulty was encountered in recovering the entire volume of perfusate and empyema did not occur in any of the ten dogs but a certain amount of fibrinoid reaction was invariably noted. Fourteen days was the longest period of survival.

3. Intestinal Dialysis

According to Merrill (52), it was observed in 1925 that nephrectomized dogs secreted considerable non-protein nitrogen in their intestinal fluids, and in 1929, significant quantities of nitrogenous substances and chloride were removed from uremic animals by intubation of the duodenum.

Bliss (5) and his co-workers in 1932, noting that nephrectomized dogs eliminated considerable nitrogenous wastes through vomiting,

suggested gastric lavage as a possible treatment for loss of kidney function. They found this method not nearly so effective as peritoneal lavage, however, since the total area of exchange surface was quite limited.

Pendleton and West (65) in 1932 showed that urea and other crystalloids in the blood readily diffused from the blood stream across the wall of the intestine into the lumen. They found that if the urea content of the blood was greater than that of the bowel, diffusion took place through the wall of the intestine until an equilibrium was reached. On the other hand, if the urea content of the bowel was increased, a subsequent rise in blood urea occurred.

Goudsmit (23) in 1941 took advantage of this observation. He passed a modified double lumen small intestinal tube through the stomach and duodenum, and the tip was allowed to proceed well into the upper jejunum. A balloon placed immediately oral to the tip was inflated and a hypertonic solution of sodium sulfate was continually introduced into the jejunum and removed by suction. This procedure was used in two uremic patients and, although the lavage fluid revealed a urea concentration of 75 percent of that of the blood of the patients, no significant change in the concentration of urea in the blood was observed. Nevertheless, these observations by Goudsmit stimulated a wealth of work aimed at removal of nitrogenous wastes from uremic patients by way of the intestinal tract.

In 1947, White and Harkins (92) surgically isolated high intestinal loops in dogs and restored intestinal continuity by end-to-end anastomosis. The blood supply of these isolated segments was left intact and the ends were sutured to the abdominal wall. Twenty-eight days later these dogs were totally nephrectomized and the intestinal

loop was irrigated. The duration of life in the irrigated dogs was not appreciably lengthened over that of the control dogs, probably because of a severe disturbance in the electrolyte pattern of the body fluids. However, it was successful in removing fairly large amounts of urea from the blood.

Seligman et al. (76) in 1946 compared the results of dialyzing different sections of gut in dogs. A constant length of ten inches of duodenum and jejunum, ileum, or colon was used. Exchange was best in the jejunum and duodenum; the ileum was slightly less effective and the colon much less satisfactory. A single attempt in a human subject, using the terminal part of the ileum, gave a urea clearance so low that it was estimated over ten feet of bowel would be required to supply ten percent of maximum normal renal clearance.

In 1951, Twiss and Kolff (86) reported the use of this technique in a patient who survived for forty-six days after the removal of a solitary kidney. Up to twelve grams of urea were removed each day but complications encountered in the technique discouraged its use as a routine therapeutic procedure.

Perfusion of the intact small intestine to remove nitrogenous wastes and electrolytes from uremic patients and animals has been described by numerous workers (48,49,62,70). In general, this was accomplished by the use of double lumen catheters, with the distal opening in the lower ileum and the proximal opening in the duodenum. Dialyzing fluid continually entered the intestine at the proximal opening in the duodenum, and was allowed to flow slowly to the ileum where its progress was halted by an inflated cuff. It was removed by suction through the distal opening.

Continuous lavage of the stomach alone was reported by Vermooten and Hare (88) in 1948 and Kelly and Hill (35) in 1951. Daugherty and his co-workers (12) reported use of the colon as a site for dialysis in 1948. A catheter was inserted into the appendix and the lavage fluid was continually allowed to run by gravity into the appendicostomy tube. The dialysate was retrieved through a rectal tube.

D. Kidney Transplants

Although the artificial kidney has proven satisfactory in the treatment of a great number of cases of acute nephritis, a substitute for the chronically diseased kidney has long been sought. With the marked prevalence of chronic renal disease in humans, transplantation of kidneys from one individual to another has been suggested as a possible treatment where damage to kidney tissue is so extensive that repair is impossible.

According to Merrill (55) Ullmann, in 1902, was the first to carry out renal auto-, homo-, and hetero-transplantation, using prosthetic tubes to make the anastomoses. He made transplants from one dog to another, and from a dog to a goat, placing the kidney in the neck. No details of urinary secretion were published.

In 1908, Carrel (8) transplanted kidneys in both dogs and cats. He observed that the transplanted kidney was infiltrated with plasma cells upon removal after rejection by the recipient. In 1923, Williamson (93) confirmed Carrel's findings that, whereas, autogenous kidney transplants would maintain the life of the animal for months after removal of the other kidney, homologous transplants functioned only for a period of days. He attributed the failure of homologous

kidney transplants to what he called "biological incompatibility" between the donor and the recipient. More recent work in the 1950's by Dempster (15,16) in England substantiated the theory of incompatibility. He showed that the body developed antibodies against the transplanted kidney and these were eventually responsible for destruction of the homograft.

The literature is quite voluminous in its coverage of experimental renal transplants in animals. Most investigators have found that renal homotransplants in the experimental animal function from one to eighteen days. They cease urine secretion at a time when blood flow through the renal vessels can still be demonstrated. Histologically, the kidney which has stopped secreting shows interstitial edema, round cell infiltration, and tubular destruction. The glomeruli remain relatively normal (32).

Renal homotransplantation in the human has been attempted on numerous occasions as a temporary aid to tide the patient over an episode of acute anuria. According to Hume et al. (32), Voronoy in 1936 transplanted a kidney into the groin of a patient with bichloride of mercury poisoning, but the patient died in forty-eight hours and no conclusions could be drawn from his experiment.

Homotransplantation of kidneys received some attention from the United States Atomic Energy Commission in 1946, when it was believed that a significant degree of renal damage would result from incidental exposure to uranium and uranium compounds. Rekers (67) described a surgical procedure for transplantation of a kidney to the neck region of a dog. It was felt that if this kidney could function for at least a short period of time, the kidneys damaged by radiation could recover sufficiently to carry on their function.

The ultimate cause for the failure of homografts to maintain their function for an extended period of time is, in all probability, due to differences in individual tissue specificity. The fact that skin homografts have survived permanently in identical twins (7) led workers to attempt renal homografts in identical twins. Merrill et al. (53) reported the homotransplantation of a healthy kidney from one identical twin to another in 1956. The operative procedure consisted of the following anastomoses: Renal artery end-to-end with hypogastric; renal vein end-to-side with the common iliac; ureter mucosa-to-mucosa anastomosis with the bladder. The homograft had survived for twelve months at the time of the report and renal function was normal, despite the fact that both of the recipient's diseased kidneys were removed. Marked clinical improvement was observed, malignant hypertension disappeared and the patient was able to resume a normal active life.

Further investigation by these same workers reported in 1958 (61) included renal transplants in seven pairs of identical twins. Six of these patients had return of renal function clinically, chemically, and by x-ray. One patient died four months after transplantation when the transplanted kidney became involved with the original disease. One had symptoms of active disease in the transplant at the time of the report. Four others were living and well, the longest three and one-half years after transplantation. One recipient successfully completed a normal pregnancy.

The practice of homografting the human kidney is still in the investigative stage. As Merrill (55) so aptly points out, "before kidney transplantation can be of real therapeutic value, a means must

be found to modify the 'immune' response which results in the rejection of the graft in genetically unrelated individuals".

E. Other Methods in the Treatment of Renal Insufficiency

Many less conventional, and in most cases impractical, procedures have been reported in the management of renal failure. The few which are presented here are not presented because of their effectiveness, but to show the thought and ingenuity expressed by some workers in the search for an adequate treatment for renal failure.

1. Exchange Transfusions

Thalhimer (85), in 1938, used exchange transfusions as a means of lowering blood urea nitrogen. The morning after bilateral nephrectomy, nephrectomized dogs and donor dogs were anesthetized with Nembutal and cannulae were inserted into the femoral artery and vein of each animal. The dogs were heparinized and, using a 50 milliliter glass syringe, 200 milliliters of blood were transferred from the donor into the azotemic one, and then from the azotemic animal to the donor. Samples of blood were obtained from each animal before the transfusion, after 20 exchanges of blood, and after 40 exchanges. There was a marked reduction of blood urea nitrogen in the uremic animals and a corresponding rise in the donor animals. The following day, the blood urea levels of the donor dogs had returned to normal and, when these animals were sacrificed from one to three weeks later, their kidneys were found to be normal both grossly and microscopically.

2. Cross Transfusions

It has been suggested that a parabiotic connection of the blood

streams of a uremic individual and a normal donor may be of therapeutic value. Such a procedure was described in 1940 by Duncan (17) in the treatment of two uremic patients, which resulted in loss of the patient's chemical abnormalities and lack of harm to the donor. In theory, this mode of treatment for uremia had advantages, but the drawbacks were quite obvious. The difficulty of finding a suitable and willing normal partner was of course the most outstanding disadvantage.

3. Replacement Transfusions

Dausset (13) in 1950 and Snapper and Schaeffer (80) in 1951, described the use of replacement transfusions in the treatment of renal failure in humans. The technic entailed the removal of blood from the uremic patient, and its simultaneous replacement with fresh banked blood from normal donors. Up to 41 liters of blood, or several times the total blood volume of the patient was replaced in some of the patients. Improvement in the blood chemical abnormalities was noted. Two obvious disadvantages of this treatment were the difficulty in procurement of large volumes of blood for transfusion and the possibility of transfusion reactions.

4. Cross Dialysis

Krainin (42) in 1952 described a system of cross-dialysis whereby the blood of a uremic subject was cross-dialyzed with that of a subject with normal kidneys. There was no mixing of blood between the two circulations. The apparatus consisted of a stainless steel dialyzing unit, 14 inches in diameter and 3 5/8 inches in height. Two lengths of cellophane tubing were placed against each other and wound as one for eight turns into the hollow section of the unit. With

this procedure, every other turn of the cellophane represented the same circuit, thereby bringing the dialyzing surface of one circuit directly in contact with the other. These units represented approximately 5,600 square centimeters of opposing dialyzing surface for each circuit. The dialyzing chamber was primed with citrated blood and suspended in a water bath at 39°C. The dogs were anesthetized with Nembutal, heparinized, and cannulated in the femoral arteries. The flow of blood was facilitated by the use of a roller-type pump which controlled the flow through both circuits. After leaving the dialyzing chamber the blood flowed through a bubble trap and flow indicator and back into the femoral vein of the uremic subject. The blood circuit from the normal subject followed a similar course. In a series of five dogs made uremic by ligation of the ureters, a significant lowering of non-protein nitrogen was demonstrated. Follow-up dialysis was not performed and the uremic animals survived approximately three days after dialysis, or a total of five days from the time the ureters were ligated.

5. Dialytic Parabiosis

Pavone-Macaluso (64), in 1959, was the first to describe similar experiments performed upon animals of different species, using the same principle but a slightly different technic. His early experiments were made *in vitro*, using various artificial solutions with cellulose tubing and glass cylinders. Further work was done with dogs and goats, using ox plasma or Ringer's solution mixed with Macrodex as a "transferring fluid". When dialytic parabiosis was brought about between a kid and a dog, which was sensitized to the kid's proteins, no signs of anaphylaxis or intolerance were

observed, and the blood pressure was normal throughout. A case report described a woman who developed total anuria following mercury poisoning. She was treated by dialytic parabiosis, using a large sheep as a donor, and diluted plasma as the bath fluid. The disposable unit of a Kolff-Watschinger twin-coil artificial kidney was adapted for this dialysis. There was a significant fall in the patient's blood non-protein nitrogen, and considerable improvement in the abnormal electrolyte pattern. These changes were reflected in the biochemical data of the sheep's blood and the bath fluid. After a diuresis, the patient recovered.

F. Regulation of Diet and Fluid Intake

Regulation of diet and fluid intake is perhaps the most conservative management of renal failure.

According to Holmes (28), in 1958, too much fluid is often given to anuric or oliguric patients in an effort to stimulate diuresis. Fluid intake and output records should be kept and the daily fluid intake should include the previous day's urinary output and other losses, plus an allowance for insensible water loss. The diet prescribed was a low protein, high carbohydrate, high fat diet designed to supply sufficient calories as carbohydrate and fat so that metabolism of protein was kept to a minimum. This tended to prevent a rapid rise in the blood non-protein nitrogen and creatinine. An anabolic agent such as testosterone was also useful in preventing a rapid rise in non-protein nitrogen.

Lubash and Ruben (46), in 1959, reported that adding insulin to hypertonic glucose which is administered intravenously will promote

formation of glycogen and will "cause transfer of potassium within the cell". This effect is transient however. These workers suggested foods containing little potassium such as jello, potatoes, salt-free butter with added sugar, honey, ginger ale, and sweet tea. Fat supplements were also suggested.

Morris (57), in 1959, with reference to animals, emphasized the importance of correct water balance. He contended that an adequate fluid intake encouraged dilution of the urea and a subsequent flushing action through the kidneys. Restriction of the diet to high quality protein such as found in whole egg, cottage cheese, good meat and well-cooked grains was recommended. Common ingredients in commercial dog foods which produce excessive waste nitrogen and therefore should be avoided were meat and bone scraps, dehydrated meat and fish meals, tankage, gelatin, lung, udder, intestine, and most glandular tissue.

Meier (50) in 1958 warned against the use of fluids containing potassium such as Ringer's solution. He stated that the intravenous administration of sodium bicarbonate or sodium lactate controls the acidosis associated with hyperkalemia and at the same time lowers the level of potassium.

Huff and Pearson (31) in 1959 reported a study of a number of nephritic dogs presented to the Angell Memorial Animal Hospital. According to these authors, anuria was not a common symptom in canine nephritis as contrasted to human medicine. Fluid therapy consisted of five percent dextrose solution subcutaneously. B vitamins were administered intramuscularly, and if there was complete anorexia, a protein solution was added to the dextrose. If the subject

could retain food, a high quality protein diet (K/D*) was given four or five times daily. Dogs with severe polyuria were given free choice to water and if vomiting was a problem, water was given in the form of ice cubes.

Guild (26) reported on the management of chronic uremia in dogs in 1959. When dogs fail to excrete deleterious ions, attempts should be made to increase renal function and to decrease the load of deleterious ions. "The first can be attempted by increasing sodium intake by means of bouillion cubes added to feed. The second is attempted through decreased protein intake, either by commercial dog food prepared for this purpose or by home preparations such as meal, potato, and pork fat". He stated that "....fluid requirements have no importance in the management of dogs with chronic uremia".

G. The Use of Cation Exchange Resins

As has been pointed out, dialysis is capable of correcting the over-all syndrome associated with renal insufficiency. Ion exchange resins have little if any effect on fluid balance or the removal of nitrogenous wastes. Their value lies chiefly in their ability to adjust the electrolyte balance by removing toxic ions from the bloodstream and exchanging them for inert or relatively non-toxic ions which are given up by the resin.

The phenomenon of ion exchange is by no means a modern concept. It was observed in 1850 that on treating soil with either ammonium sulfate or ammonium carbonate, most of the ammonia was absorbed and calcium was released into solution. About the turn of

*Hill Packing Co., Topeka, Kansas.

the century, ion exchange resins found their way into industrial use in softening water. Development of synthetic organic exchangers in 1935 led the way to the wide use of ion exchange resins in numerous industrial and commercial processes today (95).

The ion exchange resin particle can be visualized as an elastic, three-dimensional hydrocarbon network to which is attached a large number of ionizable groups. The nature of the ionizable groups attached to the hydrocarbon network determines the chemical behavior of the particular ion exchange resin (95).

Exchange resins used in the treatment of uremia are of three principal types; they may be charged with hydrogen, sodium, or ammonium ions. These ions are exchanged for the toxic potassium ion in the bloodstream.

1. In the Gastrointestinal Tract

Bauman and Eichhorn (3) in 1947 described the fundamental properties of a synthetic cation exchange resin on the basis of their investigation using Dowex 50. Following the report of these workers, it was suggested that ion exchange resins could be of therapeutic value in the treatment of certain cases of uremia.

In 1950, Elkinton (18) and his associates first reported the successful use of cation exchange resins in the treatment of anuric hyperkalemia by oral and rectal administration of the resin. A carboxylic ammonia exchange resin which exchanged ammonium ion for potassium was used by these workers. Significant lowering of serum potassium levels was noted in three patients with renal insufficiency and oliguria or anuria.

In 1953, Evans et al. (19) reported the oral use of a sulphonic resin charged with sodium in the treatment of anuria. It was felt by these workers that sodium was more innocuous than ammonia in the anuric patient, and that exchange with this type of resin was more rapid. The ammonia was thought to raise the already high blood urea level when it was converted to urea in the liver. They found the resin to be more effective when given by mouth than by retention enema. On the other hand, Palmer (63) stated in 1959 that the administration of the resin by retention enema was more effective than its administration in the upper gastrointestinal tract, as it was easier to give larger doses.

Humphrys (33) in 1959 evaluated the effects of oral administration of resins in dogs made uremic by bilateral nephrectomy or ureteral ligation. Beneficial effects were measured by survival time and serum potassium levels. The dogs were divided into various groups as follows: no treatment; water and saline to replace insensible loss; glucose in water to replace insensible loss; cation exchange resin only; high calorie diet only; and high calorie diet plus cation exchange resin. All of the treatments were either fed or administered by stomach tube when voluntary oral ingestion ceased.

The group which received only a few calories in addition to the water survived only slightly longer than the controls which received nothing, or only small amounts of water. All of the control dogs were dead in 97 hours. The addition of a high calorie, non-electrolyte, non-protein diet pushed survival up to seven and a half days. Cation exchange resin in conjunction with the special diet extended survival time to nine and a half days.

Animals which received the high calorie diet developed hyperkalemia more slowly. Those dogs which had the special diet in addition to cation exchange resins had no significant hyperkalemia with the exception of one animal which had severe nausea and "infection". The group which received water and resins without the diet did not exhibit a significant hyperkalemia but survived on the average only slightly longer than the controls. One-half of the animals showed gastrointestinal hemorrhages at necropsy. Nausea was a problem in retention of resin and food, and "severe infection" was a constant occurrence.

The use of cation exchange resins in the gastrointestinal tract as a treatment for hyperkalemia accompanying renal insufficiency is well documented in the literature (4,10,21,38,72,84). The route of administration, dosage, and the basic results are uniformly the same. Resin therapy is considered safe, simple in its application, and relatively effective when employed to reduce elevated potassium levels in the blood.

2. Hemoperfusion

In 1948, Muirhead and Reid (59) suggested the use of ion exchange resins for the removal of nitrogenous wastes from the blood by hemoperfusion through a cation exchange resin. The resin used was nine parts Amberlite IR-100H and one part Deacidite. The resin was placed in glass columns four centimeters in diameter and 50 to 85 centimeters long. In vitro experiments were carried out and urea uptake was measured in synthetic solutions as well as heparinized blood. Six dogs were subjected to perfusion on the fourth day following bilateral nephrectomy. In one dog, 3.5 grams of urea was removed in

a forty-minute perfusion with a flow rate of 70 milliliters per minute.

DeMarchi and Bronniman (14), working in Switzerland in 1951, reported on their experiences with hemoperfusion through a cation exchange resin. Amberlite IR-100 was contained in pyrex columns 55 centimeters long and five centimeters in diameter. The resin was prepared prior to perfusion by treating it with 100 percent sulfuric acid, distilled water, and then Ringer's solution. In vitro experiments resulted in the removal of significant quantities of urea. The technic was used in four human patients with uremia.

Kessler et al. (36) reported in 1953 a study almost identical to that of Muirhead and Reid five years previously. No reference was made to the work of Muirhead and Reid and many findings of the earlier work were duplicated. Approximately 180 grams of Amberlite IR-120 was placed in columns 3.5 x 30.0 centimeters and the columns were sealed, flushed, and sterilized prior to the perfusion. Nephrectomized dogs were perfused through these columns for four to six hours. A fall in plasma potassium, calcium, and magnesium and a rise in plasma sodium occurred during the perfusion. Calcium was replaced in quantities varying from zero to eleven milliequivalents per hour to prevent tetany.

Sorentino (81), working in France, reported in 1956 the use of hemoperfusion through Amberlite in human patients. The effectiveness of potassium removal was especially noted by this worker.

Schecter et al. (74) reported in 1959 on an improved apparatus for performing hemoperfusion through an ion exchange resin. The apparatus, manufactured commercially to the authors' specifications,

was constructed entirely of vinylite, a hemorepellent polyvinyl plastic, which may be readily sterilized by autoclaving. The resin employed was Dowex 50-X8, a sulfonated aromatic hydrocarbon polymer cation exchange resin in the sodium cycle. Fifty grams of resin was supported on nylon bolting cloth filter and encased in seamless plastic columns. Dogs rendered uremic by bilateral nephrectomy were treated with this apparatus. Perfusion for one hour resulted in a marked decrease in plasma potassium. A less significant reduction in blood urea nitrogen concentration was recorded in all seven dogs perfused.

CHAPTER III

MATERIALS AND METHODS

In this study, adult mongrel dogs secured from the Detroit pound were used. Their weights varied from 15 to 40 pounds and they were of both sexes; however, females predominated. Each dog was subjected to a clinical and laboratory examination to insure that only healthy dogs were utilized. The laboratory examination consisted of a white blood count, hematocrit and non-protein nitrogen determination. The dogs in Group II also received a urinalysis and plasma electrolyte analysis prior to the study.

The animals were housed individually in stainless steel cages which were cleaned twice daily and the dogs exercised at that time. A basal diet of dry meal* was fed until such time as they became so sick they refused it. A more palatable commercial canned dog food** was offered to them at this time. In an effort to control vomiting, water was offered in small quantities several times daily rather than free choice.

The perfusion apparatus (Figure I) consisted of five basic parts. The afferent tubing carried blood from the femoral artery of the patient to a glass column containing the ion exchange resin. From here the blood passed through a simple flow meter, then a bubble trap,

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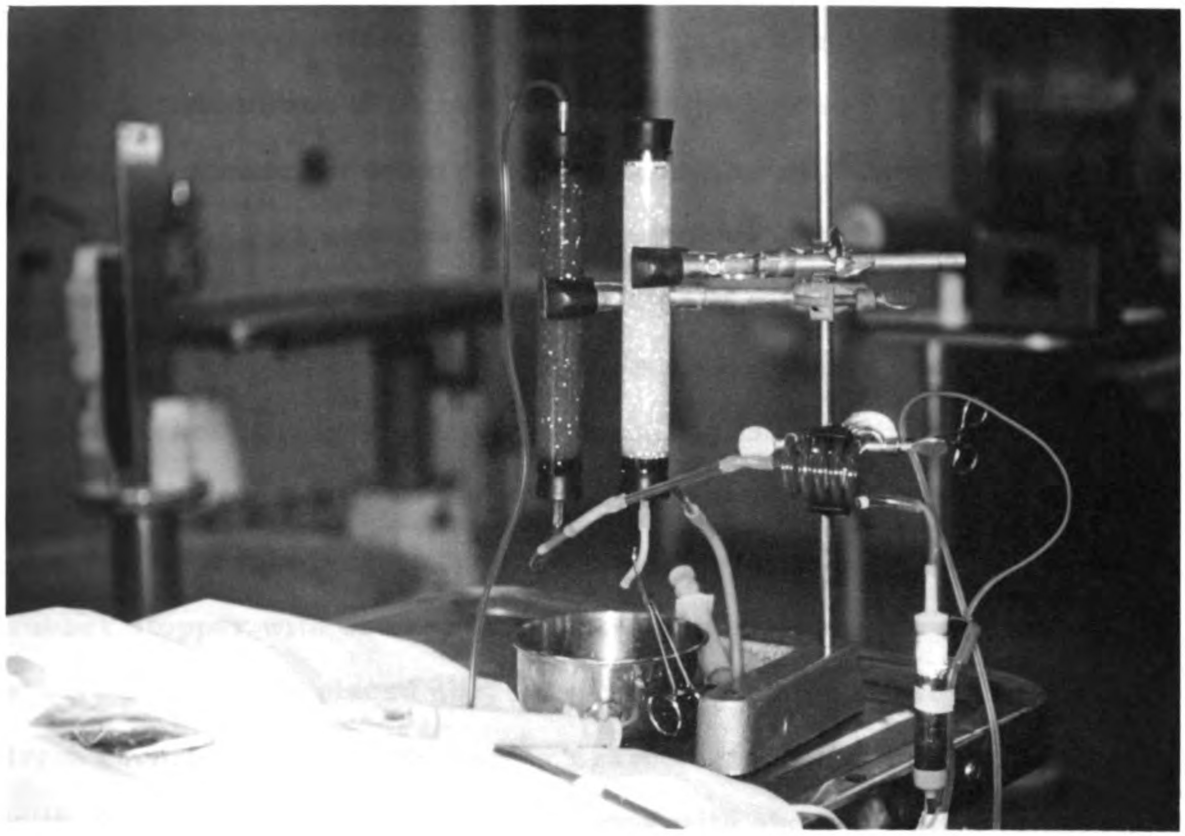
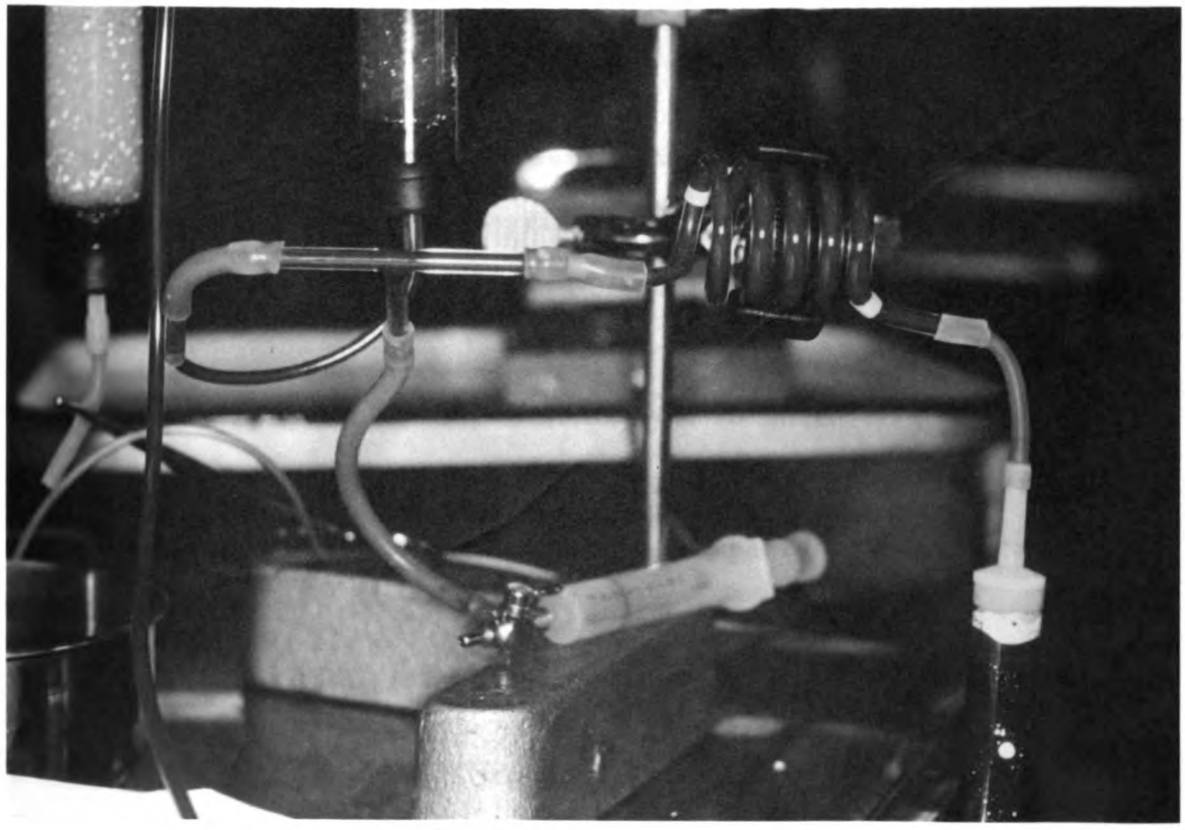
* Fromm Dog Meal, Federal Foods, Inc., Thiensville, Wisconsin.

** Hills Dog Food, Hill Packing Co., Topeka, Kansas.

Figure I. Close-up view of the perfusion apparatus showing the afferent tubing, column of cation exchange resin, flow meter, bubble trap and efferent tubing. A fresh column is primed with heparinized saline and is ready for perfusion.

Figure II. Close-up view of the flow meter. A bubble of air is injected with the syringe and enters the system at the T connection. After passing through the coil, it is caught in the bubble trap. A stopwatch is used to time the bubble as it passes through the coil which is calibrated to have a volume of six milliliters. From these figures the flow rate in milliliters per minute is determined.





and finally back into the femoral vein of the patient via the efferent tubing. The volume of blood contained in the entire apparatus and tubing was measured volumetrically to be fifty milliliters.

The glass columns were eight inches long, 30 millimeters in diameter, and contained approximately 90 milliliters of Dowex 50W-X8 Cation Exchange Resin* in the sodium cycle. Columns twelve inches long containing approximately 150 milliliters of resin were tried at one stage of the study, but the added resistance to flow in columns of this length rendered them impractical. A number six rubber stopper with one hole was used in each end of the column and a wire screen was placed above the bottom stopper to keep the resin from escaping. The units were prepared beforehand by filling them with resin and then washing the columns with about 100 milliliters of distilled water or until the water coming out the bottom was perfectly clear. These units were then autoclaved prior to use.

Rate of flow was determined by the use of a flow meter (Figure II) connected after the resin column. A bubble of air was injected into the system with a syringe proximal to the coil which was calibrated to hold six milliliters of blood. The length of time necessary for the bubble to pass through the coil was measured with a stopwatch. From this value, the flow rate in milliliters per minute was determined at regular time intervals. Using these flow rates, the total volume flow for the duration of the perfusion was determined by interpolation.

A blood administration set with a metal filter** provided the

* Dow Chemical Co., Midland, Michigan

** Abbott Laboratories, North Chicago, Illinois

necessary tubing. The drip chamber, which was connected after the flow meter, served as a bubble trap. The wire filter in the drip chamber insured against any blood clots or resin particles entering the circulation of the dog.

Analytical determinations of various blood constituents were conducted throughout the course of the study.

Hematocrit. The microhematocrit method with an International Microhematocrit centrifuge and an International Microcapillary reader* was used. The results were read directly in volumes percent.

Non-Protein Nitrogen. Nitrogen was determined in a portion of protein-free blood filtrate, using sulphuric acid and hydrogen peroxide for digestion. Ammonia formed was determined colorimetrically after direct nesslerization of the digested mixture. The protein-free filtrate was prepared by Haden's modification of the method of Folin and Wu (27) and the non-protein nitrogen was determined by a modification of the method of Koch and McMeekin (27). The unknown sample was read against a standard solution using a Bausch and Lomb Spectronic 20 Colorimeter.**

Plasma Chloride. The method of Schales and Schales (27) was used. The sample was titrated with standard mercuric nitrate solution at the proper acidity in the presence of diphenylcarbazone indicator. Chlorides present reacted with added mercuric ions to form soluble undissociated mercuric chloride. When an excess of mercuric ion was added, the indicator turned purple.

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* International Equipment Co., Boston, Massachusetts

**Bausch and Lomb Optical Co., Rochester, New York

Plasma Sodium and Potassium. Using a Coleman Model 21 flame photometer* milliequivalents per liter of these ions were read directly from the scale on the instrument.

Electrocardiogram. The three standard limb leads were run, using an Edin Electronic Cardiograph**. Tracings were made both before and after perfusions.

Early experiments were carried out to determine some of the exchange properties of the resin. Although the manufacturer stated the exchange capacity in terms of milliequivalents per volume of resin (95), it was felt that a more accurate evaluation of the exhaustion time of a resin column could be best determined by in vitro experiments using dog blood.

Pooled blood collected by exsanguination of pound dogs was adjusted by the addition of potassium chloride to have a potassium ion content of between five and ten milliequivalents per liter. This blood was passed through the apparatus at three different rates of flow: 100 milliliters per minute; 70 milliliters per minute; and 30 milliliters per minute. Samples were removed at four- or five-minute intervals and potassium ion removal was used as the criterion for evaluation of exhaustion time.

Prior to assembly the flow meter was sterilized by filling with a solution containing chlorhexidine diacetate*** and allowing it to stand for five minutes. After assembly of the apparatus, the entire

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* Coleman Instruments, Inc., Maywood, Illinois

** Edin Co., Inc., Worcester 8, Massachusetts

*** Nolvasan, Fort Dodge Laboratories, Inc., Ft. Dodge, Iowa

system was primed with normal saline containing sodium heparin* at the rate of 10,000 U.S.P. units (90 milligrams) per liter. This coated the tubing and resin with anticoagulant and removed air bubbles which were present. The patient was prepared for perfusion by the intravenous administration of an ultrashort-acting barbiturate, thiamylal sodium.** In an early experiment, a tranquilizer,*** trifluprom azine hydrochloride, and a local anesthetic, hexylcaine hydrochloride**** were tried but general anesthesia was found to be most satisfactory. The skin in the inguinal region was clipped and scrubbed with liquid germicidal detergent.***** A clean but not sterile drape was employed to help keep contamination out of the wound. The femoral artery and vein were exposed as far down the leg as possible, being careful not to disrupt any of the collateral branches.

After the vessels were exposed, sodium heparin was injected into the femoral vein at the rate of one milligram per pound of body weight and allowed time to circulate. The artery was cannulated with a 12- to 14-gauge needle depending on the size of the dog, and the afferent tubing was connected to the needle. After making sure there was no air distal to the bubble trap, the femoral vein was also cannulated with the same size needle and the efferent tubing attached. The cannulae were tied in place with size A nylon suture material. Perfusion was then begun.

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* Panheparin, Abbott Laboratories, N. Chicago, Illinois

** Surital Sodium; Parke, Davis, and Co.; Detroit, Michigan

*** Vetame, E. R. Squibb and Sons, New Brunswick, New Jersey

**** Cyclaine; Merck, Sharp and Dohme; Philadelphia, Pennsylvania

***** Parke, Davis, and Co., Detroit, Michigan

Entry into the vessel was always made distal to a collateral branch if possible. This permitted flow through the vessel between perfusions and helped prevent formation of a blood clot, since clot formation made re-entry into the vessel more difficult in subsequent perfusions.

When a column was considered to be exhausted, as determined by the volume of blood passing through it, it was flushed with normal saline to remove all the red blood cells. Then the next column, which had previously been primed with the saline and heparin solution, was connected and the perfusion continued. This process was repeated as often as necessary, depending on the desired total volume of blood flow. The solutions for priming and flushing the columns were delivered from intravenous administration bottles maintained about five feet above the table (Figure III).

When the perfusion was completed, one cc. of C.G.P. Reinforced* per two pounds of body weight was administered intravenously to replace calcium and magnesium lost to the exchange resin. Protamine sulfate counteracts the action of heparin approximately milligram for milligram. It was given at the conclusion of the perfusion in an amount equal to the heparin administered prior to the perfusion, plus that heparin contained in the saline used to prime each new column. The dogs were also given intramuscular penicillin and dihydrostreptomycin throughout the course of the experiment.

Rectal temperatures were recorded during the perfusion with a Tele-thermometer.** To prevent excessive cooling of the patient,

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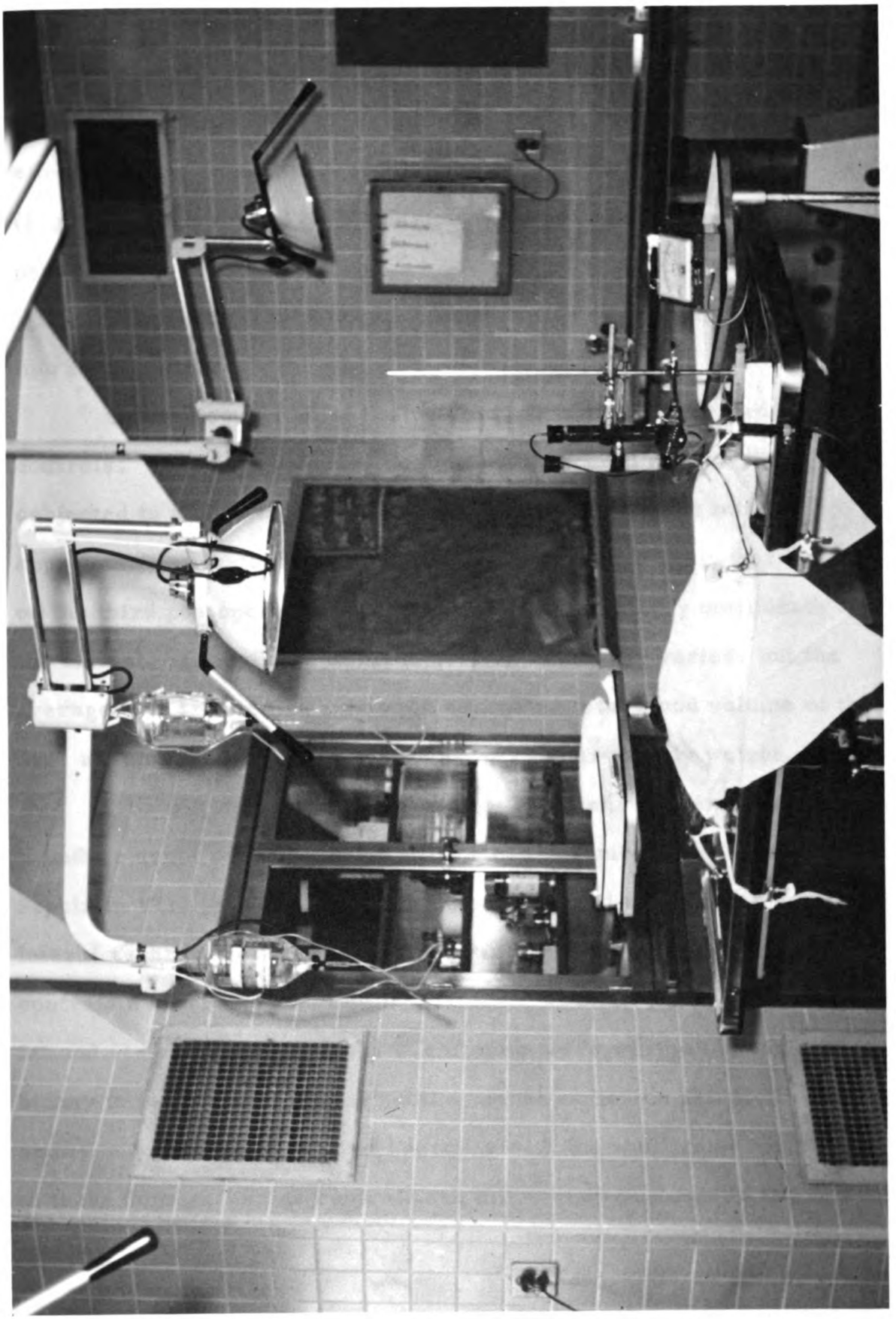
* Calcium 1.08%, Glucose 25%, Phosphorous 0.82%, $MgCl_2$ 3.0%, Haver-Lockhart Laboratories, Kansas City, Missouri

** Yellow Springs Instrument Co., Yellow Springs, Ohio

Figure III. Over-all view of perfusion equipment. Solutions for priming new columns and flushing exhausted columns are suspended over the table.



as was experienced in the first dogs perfused, two different methods were employed. A wrap-on tape*, designed to wrap around water pipes to keep them from freezing in the winter, was taped to the efferent tubing to re-warm the blood as it re-entered the body (Figure IV). A second method employed a heating pad under the patient.

The twenty-seven dogs included in this study were divided into four groups:

Group I consisted of twelve dogs, five of which served as controls. These dogs, under sodium pentobarbital anesthesia, were subjected to a one stage bilateral nephrectomy using the midline approach. Perfusions through columns of exchange resin were begun on the third postoperative day and were continued daily until death of the animal. The volume of blood perfused each day varied, but the average was around five times the estimated total blood volume of the dog, assuming 40 milliliters of blood per pound of body weight.

Group II consisted of seven dogs in which an attempt was made to induce acute nephritis using the method described by Soskin and Saphir in 1932 (82). Under sodium pentobarbital anesthesia, a unilateral nephrectomy was performed through a midline incision. The contralateral kidney was bluntly dissected away from the perirenal fat and strips of gauze soaked in collodion were wrapped around the kidney to form a snug-fitting shell when the collodion dried. Figure V shows one of these kidneys at necropsy with the shell removed. Four of these dogs served as controls and three were perfused in the same manner described in Group I.

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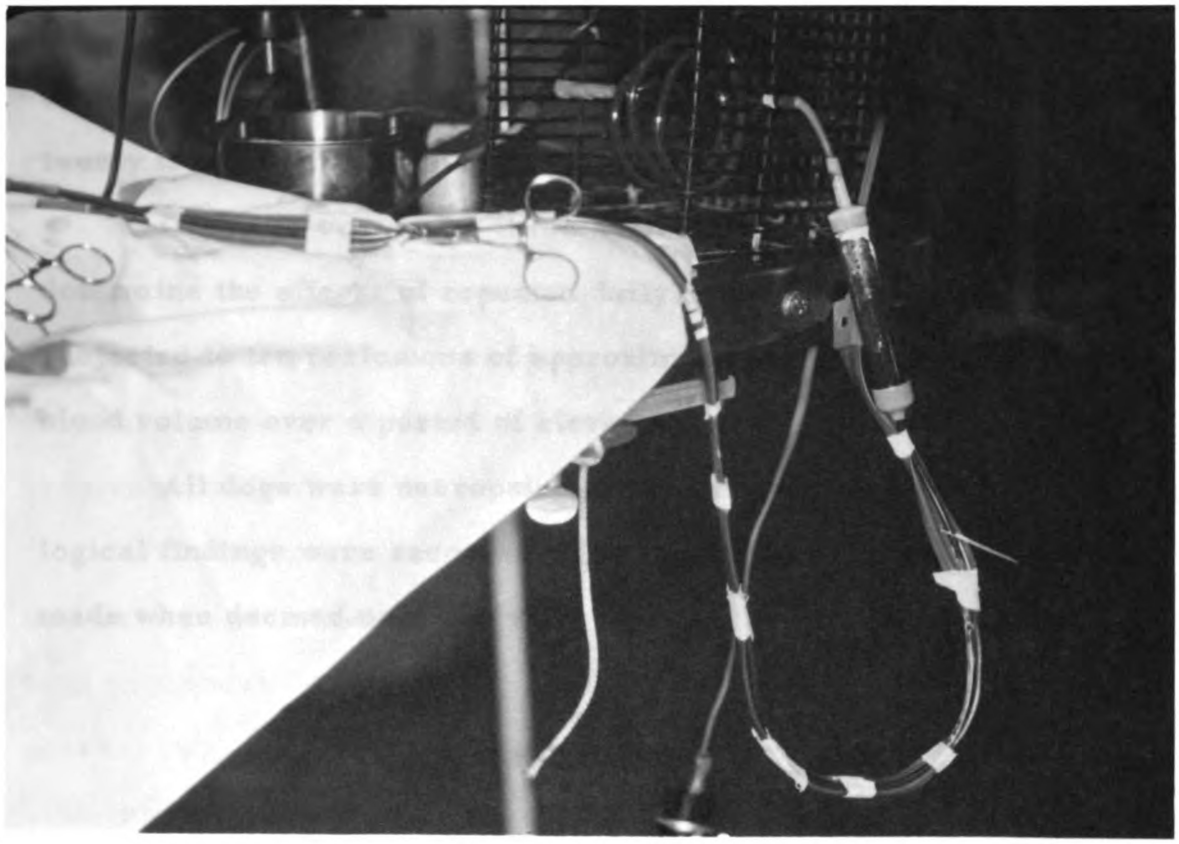
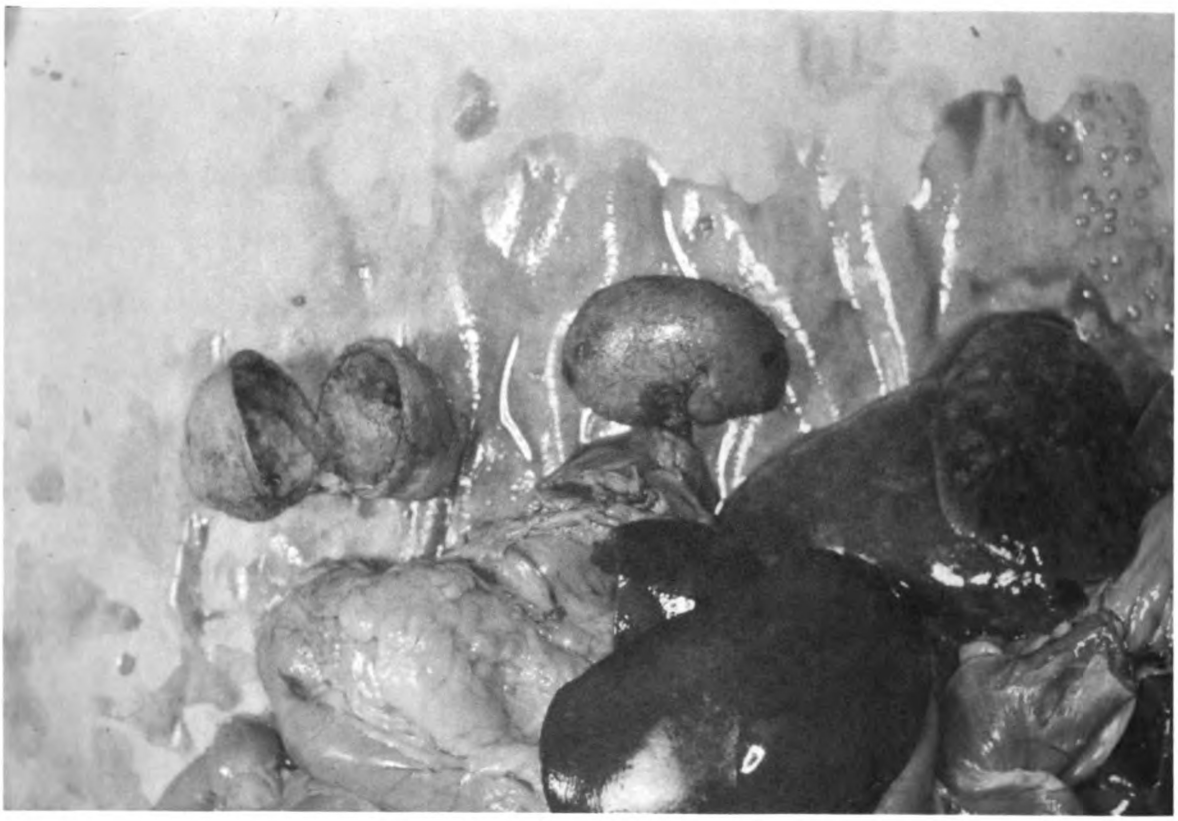
* Wrap-on Co. Manufacturers, 341 W. Superior St., Chicago 10, Illinois.

Figure IV. Close-up view of heating tape secured to the efferent tubing.

Figure V. Kidney with induced nephritis showing the collodion gauze shell removed. Note the pulmonary consolidation in the lung to the right of the kidney.





Five dogs, designated Group III, were used to study the effects of prolonged continuous perfusion. These animals were perfused for twenty times their estimated blood volume or until death occurred.

Group IV containing three normal dogs was used in a study to determine the effects of repeated daily perfusions. These dogs were subjected to ten perfusions of approximately five times their estimated blood volume over a period of eleven days.

All dogs were necropsied at the time of death and gross pathological findings were recorded. Histopathological examinations were made when deemed necessary.

CHAPTER IV

RESULTS

A. General Considerations

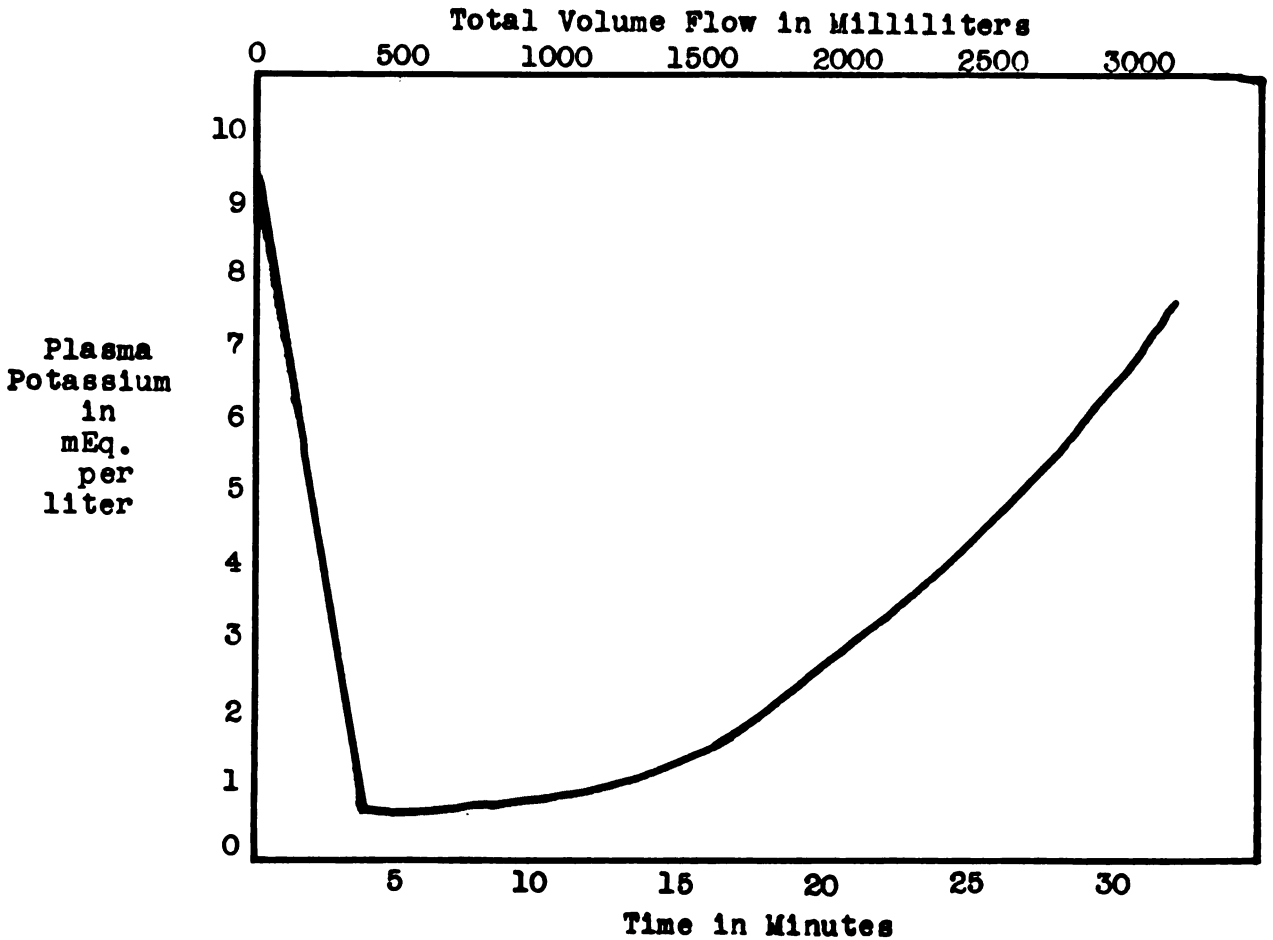
In a study of this nature, the findings are best presented by the tables appearing elsewhere in this chapter. Each group will be considered separately but a few general considerations are in order.

No difficulties were encountered in connection with the apparatus. After the technic was developed, changing resin columns took only about two minutes. The duration of perfusions was dependent upon the size of the dog and rate of flow. Most perfusions took between one and two hours, with the exception of those dogs in Group III which were perfused longer.

B. Determination of Resin Column Exhaustion Time

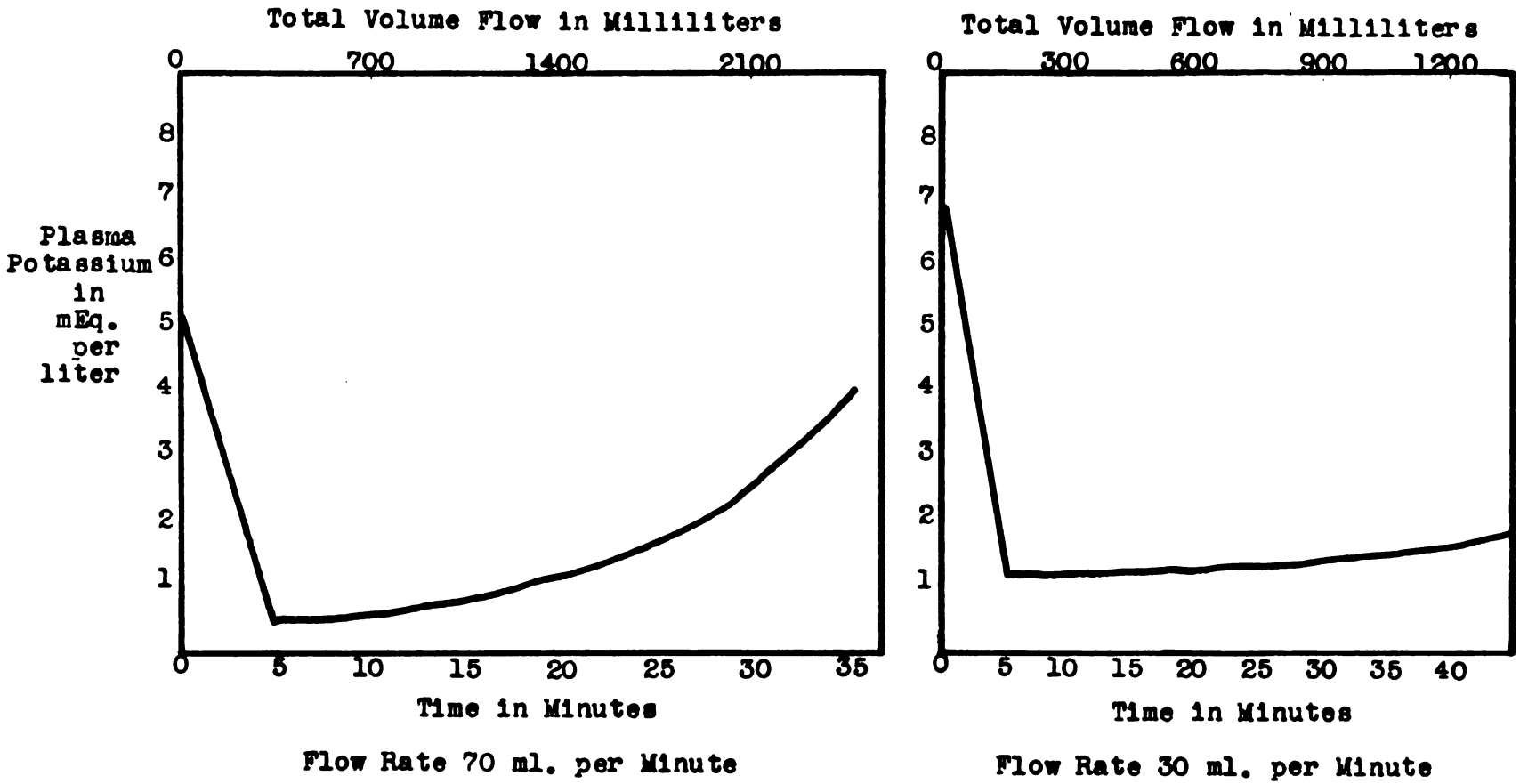
In vitro experiments were carried out to determine the exhaustion time of a column containing 90 milliliters of the resin. As the blood passed through the resin at different rates of flow, samples were drawn at four- or five-minute intervals and tested for potassium ion content. The results of these experiments are shown graphically on pages 46 and 47. Neither the rate of flow nor the length of perfusion, when considered independently affected the exhaustion time. It was the rate times the time, or the total volume flow which determined how often a resin column needed changing. For the purpose

POTASSIUM REMOVAL FROM DOG'S BLOOD IN VITRO
BY DOWEX 50W-X8



Flow Rate 100 ml. per Minute

POTASSIUM REMOVAL FROM DOG'S BLOOD IN VITRO
BY DOWEX 50W-X8



of the experiments which were to follow, the exhaustion time of a resin column of this size was set at 1500 milliliters of blood.

C. Bilaterally Nephrectomized Dogs (Group I)

Table I shows the length of time between surgery and death of dogs in this group. Perfusion doubled the life of totally nephrectomized dogs, the average being 208 hours in treated dogs and 102 hours in untreated controls.

The data obtained from perfusion of nephrectomized dogs is recorded in Table II. Rectal temperatures in all cases were lowered by perfusion. This was minimized in some of the later work by the use of heating tape and heat pads. As the dogs became more toxic and death impended, rectal temperatures below 80°F. were recorded in some dogs.

Hematocrit values fell in both the perfused and control dogs. Transfusions of whole blood were given to most dogs when the hematocrit fell below 30 volumes percent. Plasma sodium increased in perfused dogs. The untreated controls showed little change in plasma sodium content.

The most marked effects of perfusion were in the plasma potassium values. In all dogs this value was well above the normal range when perfusion was initiated on the third postoperative day. Perfusion consistently lowered potassium levels to within normal limits, but the effect was only transient. Excessive plasma potassium levels were present again in all but a few cases twenty-four hours postperfusion. Plasma potassium values above ten milliequivalents per liter proved fatal in all but one case. The potassium value in dog 4 was lowered from above ten milliequivalents per liter to

within the normal range by perfusion on the ninth postoperative day. This dog lived for two more days. Both perfused and nonperfused dogs showed a loss of plasma chloride during the course of the experiment.

The non-protein nitrogen was not appreciably affected by the perfusion. Postperfusion values were essentially the same as preperfusion values in all cases. The rise in non-protein nitrogen was not as rapid however in the perfused dogs as in the nonperfused controls.

White blood cell counts were elevated in both treated dogs and controls. The counts rose steadily in both groups but reached higher values in perfused dogs.

Electrocardiographic changes were much the same as those described in association with hyperkalemia by Winkler (94). Increased amplitude or peaking of the T wave was seen in nearly all dogs, and further progressive changes, such as depression of the ST segment and finally absence of the P wave were seen in dogs which lived longest. Postperfusion tracings revealed some improvement over preperfusion recordings in most cases, however shivering of the dogs waking up from the anesthesia often made postperfusion tracings difficult to read.

A characteristic necropsy finding among perfused dogs was the presence of diffuse and ecchymotic hemorrhages on the gastric and colonic mucosa and serosa. Tissues were icteric and edematous in most of the dogs. Edematous dogs also had fluid of varying amounts in the abdominal cavity. In many cases the heart was dilated and flaccid. Pericardial fluid was not seen. No significant gross lesions were noted in the control dogs.

The appetite of most dogs in this group was fairly good for the first two postsurgical days. Then, as uremic symptoms began to

develop, the food intake of these dogs decreased markedly and the small amount of food that was eaten was often vomited a short time later. After the dogs quit eating, they continued to drink water, in most cases until shortly before they died.

D. Dogs with Induced Nephritis (Group II)

Fourteen dogs were subjected to unilateral nephrectomy and the contralateral kidneys were wrapped in collodion-soaked gauze. Only eight are included in Tables I and III because the other six died within 72 hours following surgery. Three of these six dogs failed to awaken from the anesthetic. Perfusion did not prolong life appreciably. The treated dogs averaged 126 hours and the controls averaged 95 hours after surgery.

The effects of daily perfusion of these dogs are recorded in Table III. The results for most determinations were essentially the same as seen in Group I. Rectal temperature, hematocrit, and plasma chloride all became lower throughout the course of the perfusions. Plasma sodium, non-protein nitrogen, and the white blood count showed an increase.

Plasma potassium values did not show a marked rise in either perfused or nonperfused dogs. Perfusion lowered plasma potassium but in most cases, this value was within the normal range before perfusion was begun. Electrocardiographic tracings did not reveal hyperkalemic changes to the extent seen in the dogs in Group I.

Gross necropsy findings revealed much the same lesions seen in Group I. Gastrointestinal hemorrhages were prominent in both perfused and nonperfused dogs. Approximately half of these dogs showed marked pulmonary consolidation which contributed heavily to

their deaths. Histopathological examination of the wrapped kidneys revealed interstitial nephritis in dogs 12 and 29x. None of the wrapped kidneys in the other dogs showed indications of interstitial nephritis but exhibited parenchymatous degeneration, passive congestion and active hyperemia. The dogs which died within 72 hours revealed no significant gross lesions, nor was the immediate cause of death ascertained.

E. Prolonged Continuous Perfusion of Normal Dogs (Group III)

Prolonged continuous perfusion, the results of which are recorded on Table IV, proved fatal to two of the dogs in this group. Three other dogs survived perfusion of twenty times their estimated blood volume. All the dogs developed hypoxia as evidenced by dark blood flowing through the apparatus. Respiration became slow and shallow; however, heart rate and cardiac output remained about the same until the heart stopped abruptly. As C.G.P. Reinforced was administered to the dogs which survived perfusion, they began panting, respirations became deeper, and the blood was immediately restored to its natural bright red color. Perfusion resulted in a fall in hematocrit and plasma potassium, and a rise in plasma sodium. Rectal temperatures remained about the same due to use of a heat pad. Dogs which survived showed no ill effects from prolonged perfusion.

F. Daily Perfusion of Normal Dogs (Group IV)

Table V shows the effects of daily perfusion on normal dogs. Rectal temperatures remained normal through the use of a heating pad. Hematocrit values fell during the course of the perfusions and

whole blood transfusions were given when the hematocrit fell below 25 volumes percent. Plasma sodium and chloride as well as blood non-protein nitrogen were not affected by the perfusion. Plasma potassium was lowered below the normal range with each perfusion but returned to normal within twenty-four hours. White blood counts rose well above the normal limits and infection at the cutdown site posed a problem.

Dog 34 was weakened considerably during the course of the perfusions and died from too much anesthetic prior to the tenth perfusion. Necropsy revealed no significant lesions which could be attributed to the perfusion. There was complete lack of hemorrhage in any of the abdominal organs. The dog was quite edematous in the hindquarters from infection at the cutdown sites.

Dogs 33 and 35 which survived the perfusions showed a minor weight loss. The cutdown sites healed and there was no impairment of locomotion from ligation of the femoral arteries and veins.

TABLE I

LENGTH OF TIME BETWEEN SURGERY AND DEATH OF THE ANIMAL

GROUP I - BILATERALLY NEPHRECTOMIZED DOGS

Dog Number	Postoperative Life in Hours	
Perfused Dogs		
2	236	
3	139	
4	259	Average
5	209	208
6	209	
19	265	
21	141	
Nonperfused Control Dogs		
18	81	
24	99	Average
25	117	102
26	116	
27	95	

GROUP II - DOGS WITH INDUCED NEPHRITIS

Dog Number	Postoperative Life in Hours	
Perfused Dogs		
8	107	Average
9	192	126
13	80	
Nonperfused Control Dogs		
11	163	
12	68	Average
29	75	95
17	72	

TABLE II

EFFECTS OF DAILY PERFUSION ON BILATERALLY NEPHRECTOMIZED DOGS

GROUP I

Dog No.	Pre-Op.	Post Operative Day - Pre- and Postperfusion Values																	
		1	2	3		4		5		6		7		8		9		10		11	
				Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
		A. Rectal Temperature in Degrees Fahrenheit																	
		1. Perfused Dogs																	
2	-	-	100.6	97.0	93.6	96.0	93.0	98.0	96.5	99.0[a]		96.0	87.8	92.0	89.6	92.0	88.2	93.0	87.2		
3	-	-	-		98.8	97.0	94.8	97.0	91.8												
4	-	-	-	96.2	93.0	97.5	93.5	95.0	91.8	97.8	91.8	97.0	91.8	96.8[a]		95.6	85.6	87.0	78.5	81.0	77.0
5	-	101.7	100.2	99.5	97.5	98.0	95.0	98.8	96.9	97.5	96.2	93.2	95.0[b]	94.5	92.0	95.0					
6[b]	-	-	-	97.0	96.0	97.5	98.0	95.6	95.6	96.0	95.8	95.0	94.6	93.0	92.0						
19[c]	-	-	-	98.0	97.0	98.0	99.0	98.0	94.0	97.5	96.0	97.0	97.5	95.0	93.5	98.0	96.0	92.5	95.0	76.5	87.0
21[c]	-	-	-	98.0	96.0	97.0	95.0	95.0	96.0	96.0											
		2. Nonperfused Control Dogs																	
18	-	-	98.0	98.0															
24	-	-	98.5	98.0		98.2		-											
25	-	-	98.0	98.9		97.6		92.5											
26	-	-	99.4	99.2		97.0		-											
27	-	-	99.0	98.6		91.0													
7	-	-	-	-															
		B. Hematocrit in Volumes Percent																	
		1. Perfused Dogs																	
2	-	-	41	41	37	30	27	24	22	[a]		-	10[d]	29	-	25	-	15	14		
3	-	-	-	-		36	35	36	31												
4	-	-	-	27	27	35	29	30	27	23[d]	33	32	30	[a]		27	25	33	31	33	
5	39	-	-	29	-	31	29	27[d]	30	30[d]	32	30[d]	30	36	32	38					
6	-	-	-	42	43	41	34	35	31	32	30	30[d]	27	27	25	27	27				
19	41	-	35	27	29	27	28	34	29	23	24	20[d]	-	29	25	23[d]	28	22	22	19	21
21	40	-	34	32	33	41	36	33	-	30											
		2. Nonperfused Control Dogs																	
18	42	-	38	40															
24	44	-	45	54		32													
25	43	-	37	46		36		45											
26	44	-	40	34		41		55											
27	49	-	39	30		52													
		C. Plasma Sodium in Milliequivalents Per Liter																	
		1. Perfused Dogs																	
2	-	-	140	153	153	142	155	150	156	[a]		148	148	156	158	150	155	160	162		
3	-	-	-	-		153	156	150	154												
4	-	-	-	144	150	145	148	149	150	150	148	145	134	[a]		154	150	150	150	156	158
5	141	-	-	141	141	148	153	148	150	146	146	156	156	150	148	150					
6	-	-	-	146	150	148	154	154	160	158	161	157	161	161	163	161					
19	156	-	145	140	147	149	154	154	160	150	149	149	151	149	150	153	155	150	154	156	160
21	150	-	135	141	144	147	148	152	150	154											
		2. Nonperfused Control Dogs																	
18	154	-	150	149															
24	149	-	149	150		152													
25	150	-	145	149		147		154											
26	154	-	150	148		150		154											
27	148	-	150	149		150													
7	-	-		157															
		D. Plasma Potassium in Milliequivalents Per Liter																	
		1. Perfused Dogs																	
2	-	-	6.8	8.1	4.4	6.5	3.5	7.1	4.1	[a]		8.3	5.5	7.8	5.3	8.5	5.5	9+1	5.1		
3	-	-	-	-		8.9	6.4	6.7	3.3												
4	-	-	-	8.8	5.2	6.9	3.5	5.9	3.4	6.5	4.4	6.4	4.0	[a]		10+	5.3	9.2	5.3	8.8	8.0
5	4.6	-	-	7.0	3.6	6.8	4.6	5.8	4.1	5.6	3.9	7.2	4.8	7.1	5.8	10+					
6	-	-	-	6.7	3.6	7.7	5.0	6.8	5.5	7.5	4.9	6.6	4.6	7.2	5.2	10+					
19	4.1	-	6.3	7.4	3.7	5.1	3.3	4.9	3.5	4.7	3.5	4.1	3.0	4.9	3.0	4.7	3.0	4.0	4.1	3.7	6.1
21	4.0	-	5.8	7.2	4.0	6.0	5.0	6.9	5.0	7.4											
		2. Nonperfused Control Dogs																	
18	4.3	-	8.5	9.8															
24	4.7	-	6.5	7.5		8.0													
25	4.4	-	5.9	6.7		7.8		9.8											
26	4.2	-	6.3	8.0		9.2		10+											
27	4.0	-	6.4	7.4		10+													
7	-			10+															

[a]Not perfused
[b]Heating tape used
[c]Hot pad used
[d]250 cc. whole blood administered after this determination

TABLE II - (Contd.)

EFFECTS OF DAILY PERFUSION ON BILATERALLY NEPHRECTOMIZED DOGS

GROUP I

Dog No.	Pre-Op.	Post Operative Day - Pre- and Postperfusion Values																			
		1	2	3		4		5		6		7		8		9		10		11	
				Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
		E. Plasma Chlorides in Milliequivalents Per Liter																			
		1. Perfused Dogs																			
2																					
3																					
4																					
5																					
6								113	109	93	101	103	99	102	103	102					
19	111	-	105	105	94	99	100	105	106	94	97	100	96	98	93	95	95	100	100	105	94
21	114	-	87	105	101	102	104	93	94	100											
		2. Nonperfused Control Dogs																			
18	111	-	106	96																	
24	118	-	115	103		97															
25	117	-	107	99		94		89													
26	123	-	114	106		105		87													
27	118	-	105	107		100															
7	-	-	-	135																	
		F. Non-Protein Nitrogen in Milligrams Percent																			
		1. Perfused Dogs																			
2	-	-	144	156	179	227	225	280	288	*		368	400	349	349	371	396	427	427		
3	-	-	-	-		160	139	179	211												
4	-	-	-	148	169	165	152	-	187	306	314	334	349	*		412	392	386	-	326	-
5	39	-	-	206	178	267	178	261	254	275	275	288	288	320	320	422					
6	-	-	-	171	186	229	221	256	269	350	334	416	384	432	480	520					
19	16	-	147	248	224	248	232	328	304	328	320	382	400	346	346	420	392	400	432	432	460
21	17	-	180	312	288	312	336	312	344	400											
		2. Nonperfused Control Dogs																			
18	35	-	190	264																	
24	38	-	-	304		392															
25	38	-	136	224		267		381													
26	40	-	224	221		283		389													
27	38	-	240	267		273															
7	-	-		240																	
		G. Volume Flow in Total Number of Blood Volumes Perfused																			
2		-	-	4.6		4.6		4.9		*		5.0		4.9		5.0		3.3			
3		-	-	-		5.2		6.5													
4		-	-	7.0		6.7		7.0		5.9		7.2		*		7.0		7.3		0.5	
5		-	-	4.8		5.3		5.0		4.8		4.7		1.8							
6		-	-	4.7		4.8		6.8		6.2		6.2		6.7							
19		-	-	7.8		8.1		6.0		6.4		5.9		6.1		5.7		2.5			
21		-	-	4.7		3.4		4.0													
		H. White Blood Count																			
		1. Perfused Dogs																			
2																					
3																					
4												23,400									
5	13,350			11,200						14,300		11,900		16,600		18,300					
6				26,350		30,800		33,350		33,600		39,550		38,850							
19	7,950		17,200	17,150		14,250		20,100		17,900		20,250		25,950		28,050		28,000		6,750	
21	8,550		20,650	9,100		11,850		14,250		16,550											
		2. Nonperfused Control Dogs																			
18	6,650	-	21,000	26,500		-															
24	9,450	-	25,300	-		19,950															
25	11,200	-	25,850	-		16,250		16,950													
26	9,900	-	-	14,950		17,450		10,350													
27	14,350	-	-	20,100		24,650															

*Not perfused

TABLE III

EFFECTS OF DAILY PERFUSION ON DOGS WITH INDUCED NEPHRITIS

GROUP II

Dog No.	Pre-Op.	Post Operative Day - Pre- and Postperfusion Values													
		1	2	3		4		5		6		7		8	
				Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
A. Rectal Temperature in degrees Fahrenheit															
1. Perfused Dogs															
8	-	-	-	96.8	93.0	91.0	89.6								
9	-	-	-	99.0	94.0[b]	97.0	95.0	96.0[a]		92.6	91.0	99.0[a]		97.0	101.0[b]
13	-	100.0	98.0	94.0	96.0[b]										
2. Nonperfused Control Dogs															
12	-	100.0	99.0												
16	-	-	91.0												
29x	-	-	-		-										
17	-	-	98.0		99.0										
11	-	-	-		-		97.0		94.0		91.0				
B. Hematocrit in Volumes Percent															
1. Perfused Dogs															
8	46	-	-	45	45	43	38								
9	43	-	48	50	46	32	27	17[a]		24[c]	21	ad		25	23
13	47	46	45	47	43										
2. Nonperfused Control Dogs															
12	50	44	54												
16	43	45	47												
29x	41	42	32		43										
17	37	47	51		52										
11	42	-	45		45		47		37		34				
C. Plasma Sodium in Milliequivalents Per Liter															
1. Perfused Dogs															
8	150	-	145	142	142	150	154								
9	-	147	165	148	145	148	145	147[a]		152	154	160[a]		145	150
13	156	158	150	150	-										
2. Nonperfused Control Dogs															
12	154	147	145												
16	149	148	145												
29x	149	152	143		129										
17	-	148	148		146										
11	-	154	146		150		154		150		148				
D. Plasma Potassium in Milliequivalents Per Liter															
1. Perfused Dogs															
8	5.4	-	8.1	9.0	6.0	7.3	5.6								
9	-	7.8	8.5	4.2	3.0	3.3	2.7	5.2[a]		3.1	2.4	5.6[a]		2.9	4.0
13	4.9	6.0	8.9	8.4	-										
2. Nonperfused Dogs															
12	4.9	4.6	6.4												
16	5.1	5.6	7.3												
29x	5.4	5.0	5.7		7.2										
17	4.8	5.1	8.2		8.3										
11	-	6.2	5.1		4.1		5.7		5.3		6.8				

[a]Not perfused
[b]Hot pad used
[c]250 cc Whole Blood administered before this determination
[d]150 cc Whole Blood administered after this determination

TABLE III - (Contd.)

EFFECTS OF DAILY PERFUSION ON DOGS WITH INDUCED NEPHRITIS

GROUP II

Dog No.	Pre-Op.	Post Operative Day - Pre- and Postperfusion Values											
		1	2	3		4		5	6		7	8	
				Pre	Post	Pre	Post	Pre / Post	Pre	Post	Pre / Post	Pre	Post
E. Plasma Chlorides in Milliequivalents Per Liter													
1. Perfused Dogs													
8	116	-	107	95	95	98	100						
9	-	124	-	109	-	114	109	*	98	105	*	111	107
13	116	111	107	94	-								
2. Nonperfused Control Dogs													
12	113	111	-										
16	-	111	103										
29x	136	149	103	103									
17	-	111	105	106									
11	-	114	109	-		-		-	-				
F. Non-Protein Nitrogen in Milligrams Percent													
1. Perfused Dogs													
8	38	-	168	283	302	368	280						
9	48	80	187	272	256	224	96	280*	376	357	*	330	355
13	22	47	146	230	288								
2. Nonperfused Control Dogs													
12	22	84	152										
16	25	145	248										
29x	32	47	120	157									
17	27	75	192	248									
11	36	72	178	-		280		304	509				
G. Total Number of Blood Volumes Perfused													
8	-	-	-	6.7		5.9							
9	-	-	-	6.1		6.0		*	5.3		*	5.5	
13	-	-	-	5.7									
H. White Blood Count													
1. Perfused Dogs													
8	13,550	-	-	27,600		25,100							
9	7,150	-	-	24,100		18,350		19,800*	12,250		*	7,200	
13	10,900	24,300	-	33,500									
2. Nonperfused Control Dogs													
12	14,500	24,600											
16	10,150	16,900	28,350										
29x	-	-	-										
17	9,900	28,050	40,150	48,700									
11	10,350	-	-	24,850		18,400		14,250	11,000				

*Not perfused

TABLE IV

EFFECTS OF PROLONGED CONTINUOUS PERFUSION ON NORMAL DOGS

GROUP III

Dog No.	Wt. in Pounds	Estimated Total Blood Volume in ml	Blood Volumes Perfused	Rectal Temp. F. during Perfusion*		Duration of Perfusion	Hemato-crit Volumes Percent		Plasma Sodium mEq/l		Plasma Potassium mEq/l		Remarks
				Pre	Post		Pre	Post	Pre	Post	Pre	Post	
28	19	760	12.9	100.8	-	2hr.40min.	37	54	158	153	3.1	3.4	Died - Hypopnea
29	17	680	20.8	97.0	96.0	5hr. 6min.	35	44	152	150	2.7	2.2	
30	17	680	23.2	96.0	97.0	4hr.51min.	48	39	149	150	3.8	2.6	
31	21	840	22.6	99.0	95.5	4hr.50min.	48	39	150	150	3.1	2.8	
32	20	800	18.8	100.0	-	3hr.44min.	46	46	148	153	2.4	3.8	Died - Hypopnea

*Hot pad used

TABLE V

EFFECTS OF DAILY PERFUSION ON NORMAL DOGS

GROUP IV

Dog No.	Day of Perfusion 1 Pre	1 Post	2 Pre	2 Post	3 Pre	3 Post	4 Pre	4 Post	5 Pre	5 Post	6 Pre	6 Post	7 Pre	7 Post	8 Pre	8 Post	10 Pre	10 Post	11 Pre	11 Post
A. Rectal Temperature in Degrees Fahrenheit[a]																				
33	96.0	94.0	100	98	101	100	101	97	100	100	100	96	100	100	100	100	103	94	100.5	96
34	99.0	101.0	99	97	99	96	101.5	98	100	96	100	97	98	95	100.5	96.5	101	95		-
35	95.0	95.0	98.0	99.0	100	95	100	95	101	99	95	95	95	99	96	100	100	94	100	95
B. Hematocrit in Volumes Percent																				
33	43	37	39	40	49	53	49	47	41	39	41	37	35[b]		28	29	27	32	25	24
34	50	47	40	43	34	33	31	29	32	32	27	26	27	24	25	24[c]	34	39	31[d]	
35	42	39	34	41	33	33	40	34	36	32	29	31	29	26	17	17[c]	21	25	21	26
C. Plasma Sodium in Milliequivalents Per Liter																				
33	152	149	150	149	148	150	149	148	150	148	147	143	149[b]		154	149	146	142	150	148
34	149	147	148	149	156	150	151	150	153	154	147	145	147	145	149	148	149	149	150[d]	
35	149	150	145	148	151	153	154	152	141	143	145	144	145	145	144	144	150	148	150	150
D. Plasma Potassium in Milliequivalents Per Liter																				
33	3.1	3.3	3.1	2.5	4.2	2.6	4.3	2.8	4.4	2.3	3.8	2.4	4.1[b]		4.4	2.6	4.0	2.8	2.7	2.5
34	2.7	3.0	3.4	2.9	4.2	2.7	4.6	2.7	4.4	3.0	3.8	2.5	3.3	2.5	4.2	2.8	4.8	2.7	5.2[d]	
35	2.7	2.5	3.8	2.2	3.7	2.7	4.4	2.9	3.6	3.2	4.4	3.0	4.4	4.3	4.7	3.0	4.1	3.6	5.0	2.8
E. Plasma Chlorides in Milliequivalents Per Liter																				
33	124	119	-		123	120	123	120	122	118	-		-		120	123	-	-	125	126
34	120	124	-		117	119	118	122	123	123	-		-		121	118	-	-	127[d]	
35	123	118	-		119	117	120	116	112	112	-		-		108	106	-	-	117	118
F. Non-Protein Nitrogen in Milligrams Percent																				
33	30		-		-		-		-		-		-		-		-		29	
34	34		-		-		-		-		-		-		-		-		42[d]	
35	36		-		-		-		-		-		-		-		-		38	
G. Total Number of Blood Volumes Perfused																				
33	5.2		4.5		5.4		4.1		5.2		3.3		[b]		5.3		5.4		5.2	
34	5.5		5.4		5.4		7.1		5.0		4.8		4.6		5.6		3.9		d	
35	6.4		7.8		7.0		3.4		7.7		4.1		1.0		6.3		6.3		6.3	
H. White Blood Count																				
33	8,850		-		14,400		-		17,500		-		-		24,450		-		19,950	
34	9,800		-		13,050		-		17,300		-		-		19,950		-		29,800[d]	
35	9,200		-		17,700		-		22,500		-		-		13,850		-		31,750	

[a] Hot pad used
[b] Not perfused
[c] 250 cc. of whole blood administered after this determination
[d] Dog 34 died before perfusion; sample taken postmortem
NOTE: None of the dogs were perfused on the ninth day

CHAPTER V

DISCUSSION

A. General Considerations

One should consider that this treatment was intended for the management of acute nephritis and not designed to maintain a long-standing case of chronic nephritis which is no longer compensated. A limiting factor in its use is the number of perfusions which can be achieved before the accessible vessels are obliterated. By using extreme care one can use the same femoral artery and vein for about seven perfusions over a period of seven days. By this time, blood clots have partially occluded the vessels and collateral circulation has developed to the point that flow through the femoral artery and vein is greatly diminished and perfusion through these vessels is impractical. The best alternative at this point is to use the opposite femoral vessels. Cannulation of the brachial vessels was performed in one dog and the carotid artery and external jugular vein were used in another, but the femoral vessels proved to be the most satisfactory.

The fact that it was necessary to anesthetize the dogs each day proved to be a hardship. Even though an ultra-short-acting anesthetic was used, the dogs spent most of their time sleeping. This affected their nutrient intake throughout the study for, even if they had felt like eating, by the time they woke up sufficiently to eat, it was time for the next perfusion. A feeding at this time was considered inadvisable since vomiting during the perfusion and aspiration of vomitus could lead to greater complications.

Infection at the cutdown site played an important part in the study. All the dogs showed an elevated white blood count if maintained for any length of time. Lack of sufficient personnel so that one could remain scrubbed at all times prohibited the use of strict aseptic technic. The fact that the same operator had to change the columns, administer additional anesthetic, regulate the heat pad, take rectal temperatures, and perform numerous other duties connected with the procedure introduced infection.

Indwelling plastic catheters in the carotid artery and the external jugular vein as described by Rudolph and Paul (73) possibly could have solved many of the problems associated with this study. The catheters were held in place with purse-string sutures and heparin solution was injected into the catheters to keep blood from clotting in them between use. The catheters described by these workers were only one-half as large as required for adequate blood flow for hemoperfusion. Whether or not a larger catheter could be maintained successfully in the vessels is uncertain. The successful use of indwelling catheters of this description would have the following advantages:

1. Introduction of infection would be kept to a minimum.
2. Pain and temporary impairment of function of a rear limb of the patient would be eliminated.
3. A tranquilizer rather than a general anesthetic could be used, and the animal would be conscious a greater amount of the time.
4. The time-consuming cutdown of the vessels prior to each perfusion could be eliminated.

As in clinical nephritis, anemia was a factor in this study. Continual sampling of blood for laboratory determinations, resulting

in gradual exsanguination, was probably the most important consideration. Danowski and Mateer (10) state that the anemia which develops in renal failure could result from any or a combination of the following factors: a) Transfer of interstitial and cell fluid into the circulation with resultant over-expansion of the circulating plasma volume; b) An increased hemolysis of blood cells with or without a positive Coombs test, increased urinary urobilinogen excretion, and a rise in the reticulocytes; c) Decreased red cell survival; d) A terminal depression of erythrocyte production by the bone marrow. Of the reasons for nephritic anemia suggested by these workers, hemolysis of red blood cells undoubtedly contributed to the anemia seen in this study, as evidenced by the degree of icterus seen in the plasma.

The failure of perfusion to lower non-protein nitrogen in this study was somewhat disappointing. Muirhead and Reid (59) using Amberlite, and Schecter and his co-workers (74) using Dowex 50-X8, both reported lowering of blood urea nitrogen by hemoperfusion through ion exchange resins. Although the determination run in this study was total non-protein nitrogen rather than blood urea nitrogen, lowering of this blood constituent was not experienced. It would appear that since the resin has an affinity for the ammonium ion, some lowering of non-protein nitrogen would result from hemoperfusion. Determination of pre- and postperfusion ammonia values was attempted using Conway's microdiffusion technic (9) but the results were so erratic they are not reported. No explanation of how these previous workers achieved a lowering of nitrogenous wastes by hemoperfusion through an ion exchange resin is offered.

Perfusion apparently did have some effect on non-protein nitrogen however. In referring to part F of Table II, it will be noted that following the third postoperative day, when perfusion was begun, the non-protein nitrogen was lower in the perfused dogs than in the nonperfused controls on the corresponding days which followed.

Hemorrhages in the stomach and intestine were a constant finding at necropsy of both the perfused and the nonperfused dogs. The degree of intestinal hemorrhage was greater in the perfused dogs but they lived longer, thereby being subjected to the hemorrhagic factors over a longer period of time. Daily heparinization may have contributed to hemorrhage. Heparinization of the control dogs would have helped to clarify this point. As a means to overcome any ill effects which may result from heparinizing a patient during perfusion, Gordon et al. (22) reported on the use of regional heparinization. Using a roller-type pump in connection with a Kolff stationary coil artificial kidney, heparin was injected into the system at the point where the blood left the patient. Protamine sulfate was regulated by the same apparatus and was injected into the system in amounts equal to the heparin, but at the point where the blood re-entered the patient.

Convulsions are often a symptom of clinical nephritis. Of all the dogs included in this study, only two exhibited convulsions and both of these were controls, one from Group I and one from Group II. None of the perfused dogs showed symptoms suggestive of convulsions.

Loss of body temperature as a result of large volumes of blood circulating outside the body was a problem. The most obvious solution was to place the patient on a heating pad during perfusion. This was very effective in maintaining the body temperature but caused burns

which resulted in enormous sloughs of skin of dogs in Groups III and IV which survived the perfusion. This was not recognized as a problem in Groups I and II since none of these dogs survived. The use of heating tape was probably the most satisfactory method of maintaining body temperature, however it was more time consuming to prepare. No ill effects were noted in connection with the use of the heating tape.

B. Bilaterally Nephrectomized Dogs (Group I)

The survival time of bilaterally nephrectomized dogs varies greatly with the conditions to which the dogs are subjected. In a study of sixteen dogs, Rodbard (69) reported an average survival of 85 hours with a range from 60 to 130 hours. Humphrys' (33) controls were all dead in 97 hours and in the five control dogs reported by Schecter et al. (74), the average life was 93 hours, the range being 85 to 96. The postoperative life of the five controls in this study was 102 hours. This higher figure can be attributed to the fact that perfusion was not begun for 72 hours postnephrectomy, therefore dogs which died before this time were not considered valid controls. Although hemoperfusion of nephrectomized dogs through cation exchange resins is reported in the literature, accounts of repeated perfusions in an attempt to prolong the life of such dogs are not available.

It is interesting to compare the results of this study with those of the study by Humphrys (33). Humphrys' dogs were given resin orally in addition to being fed a high carbohydrate low protein diet. Although his study is not well documented, it would appear his dogs lived an average of nine-and-one-half days after operation, or just slightly over the nine-day average of the dogs subjected to hemoperfusion.

Oral resin therapy was initiated the day following surgery while hemoperfusion was not started until the third postoperative day. Hemoperfusion was not begun in dog 3 until the fourth postoperative day and it is interesting to note that this dog lived the shortest time of any of the perfused dogs. It is felt that force feeding the special diet was a factor in survival time of Humphrys' dogs. The nutrient intake of the perfused dogs was limited to only that food which they ingested by normal means.

C. Dogs with Induced Nephritis (Group II)

This study in which an attempt was made to similate clinical nephritis proved disappointing. Unilateral nephrectomy and wrapping of the contralateral kidney in collodion-soaked gauze produced a toxic reaction. This was much more severe than removal of both kidneys, as evidenced by survival time (Table I).

The reason for rapid death in this group of dogs with induced nephritis is not clear. There may be a toxic factor secreted by the kidney itself, since the dogs in Group I, which had all kidney tissue removed, outlived the dogs in Group II. It is also possible that a traumatic factor was involved if the kidney was bruised severely in the process of applying the collodion shell.

Elevated white blood cell counts were recorded as in Group I. It is not felt that infection was a factor in the rapid death of these dogs.

D. Prolonged Continuous Perfusion of Normal Dogs (Group III)

The question of whether or not prolonged continuous perfusion would prove harmful to normal dogs stimulated the experiment designated Group III. The hypopnea produced by prolonged perfusion leads to much speculation as to its cause. As calcium, magnesium and

potassium were removed from the blood, hypoxia developed. Tetany was not seen in any of the dogs as might be expected in calcium or magnesium depletion. The lowered respiratory rate and shallow respirations apparently were not the effect of anesthetic depression of the medulla, since the plane of anesthesia was kept quite light throughout the perfusion. The actual physiological mechanisms involved in this phenomenon are not clear. The fact that normal respiration and blood color returned with the administration of a solution containing calcium and magnesium indicates that depletion of these ions in the blood was probably the cause.

The fall in hematocrit in dogs which survived can be attributed to the dilution factor since saline solution used to prime and flush the columns was in excess of 600 milliliters. Plasma sodium levels remained about the same while plasma potassium levels showed a decided drop in surviving dogs. The potassium rise in dogs which succumbed during the perfusion goes without explanation.

A gross necropsy on dogs which died during the perfusion revealed no apparent cause of death. A small amount of blood was found in the abdominal cavity of dog 28.

E. Daily Perfusion of Normal Dogs (Group IV)

The outstanding observation in daily perfusion of normal dogs was the fact that it proved quite traumatic. Infection at the cutdown site raised the total white blood cell count well above normal. All dogs showed a minor weight loss but this was due mainly to the fact that they were anesthetized a major portion of the time and unable to eat.

It is interesting to note the anemia exhibited by these dogs. This was probably due to loss of red blood cells through sampling since the plasma was not icteric as in Groups I and II. Other blood changes brought about by daily perfusion were in most cases compensated within the next 24 hours. This is readily explained by the fact that the kidneys were intact and were capable of maintaining normal fluid and electrolyte balance.

F. Special Considerations

Whether hemoperfusion through a cation exchange resin artificial kidney has practical application in the treatment of clinical nephritis still remains to be seen. It was obvious from this study that neither bilateral nephrectomy nor wrapping kidneys in collodion-soaked gauze produces a nephritis identical to that seen in the clinic. It appears that hemoperfusion is effective in rapidly lowering plasma potassium values in nephritis characterized by hyperkalemia. Whether or not potassium retention is a constant finding in canine nephritis is not well documented in the literature. Hyperkalemia is routinely reported in the human literature in connection with oliguria and complete anuria. Oliguria and anuria are uncommon in canine nephritis which is most generally characterized by polyuria. Lubash and Rubin (46) described the late diuretic stage in acute renal failure in humans in which urinary volumes may go as high as ten liters a day. Loss of all electrolytes occurs and hypokalemia results. In this case potassium replacement is in order. If this analogy can be applied to canine nephritis, it is doubtful that hyperkalemia is a consistent finding. Therefore an ion exchange resin artificial kidney of the nature used in this study would not be uniformly effective in treatment of canine nephritis.

On the basis of the experimental data collected in this study and the review of the literature, it would appear that the following practices are most important in the management of canine nephritis.

The uremia-prone dog is best managed by carefully restricting the diet. This should include only those foods which contain a high quality protein that the body can utilize, with a minimum of nitrogenous end product to excrete. High quality proteins that are well utilized by the dog are contained in whole egg, milk, fresh liver, non-tendinous meat and cereals such as whole wheat and soybeans. Poor quality proteins which should be avoided are contained in gelatin, tankage, meat meals, putrified garbage, and table scraps (58). A prescription diet, K/D* is well suited to the feeding of the uremic prone-patient. B-complex vitamin supplements may be added to the diet.

When acute nephritis develops or chronic nephritis becomes decompensated, conservative management should include other procedures in addition to the above dietary restrictions. Fluid and electrolyte therapy is indicated to replace amounts of these constituents lost through vomiting, diarrhea, and diuresis. Vomiting should be controlled by gastric sedatives or tranquilizers, and diarrhea treated with intestinal absorbents. Antibiotics should be used when evidence of primary or secondary infection is present. Packed cell transfusions will correct anemia when the hematocrit falls between 25 and 30 volumes percent. Increased sodium intake in the form of bouillon cubes will increase glomerular filtration rates and excretion of nitrogenous wastes (26). The animal should be kept in nitrogen balance by the administration of solutions containing amino acids. The

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* Hill Packing Co., Topeka, Kansas

oral or rectal use of cation exchange resins would appear to be indicated if hyperkalemia is a symptom.

If all other therapeutic approaches fail, artificial dialysis may be applicable to certain selected cases of renal insufficiency. Peritoneal lavage appears to be the dialysis of choice in veterinary medicine. The cost of equipment and availability of the other methods of dialysis limit their use by the veterinarian. No special equipment or training is required to perform peritoneal lavage and the equipment can be rapidly assembled. After injection of the fluid, the veterinarian can attend to other duties since constant supervision is not required. Either edema or dehydration can be combated by adjusting the concentration of glucose in the dialyzing fluid.

On the other hand, the procedure cannot be employed following recent abdominal operations or in the presence of a peritonitis. Peritoneal adhesions as a result of previous peritonitis may present a hazard in insertion of the needle, and ileus, if present, may be aggravated by admission of the fluid.

CHAPTER VI

SUMMARY AND CONCLUSIONS

A total of eighteen dogs were subjected to hemoperfusion through a cation exchange resin, Dowex 50W-X8. These dogs were divided in groups as follows: Group I, bilaterally nephrectomized dogs; Group II, dogs with induced nephritis; Group III, normal dogs subjected to prolonged continuous perfusion; and Group IV, normal dogs subjected to short daily perfusions.

The postoperative life of the perfused dogs in Group I averaged 208 hours as compared to 102 hours for the controls. The postsurgical life of perfused dogs in Group II averaged 126 hours while non-treated controls averaged 95 hours. Two of the five normal dogs in Group III died as a result of prolonged continuous perfusion. One of the three normal dogs in Group IV which was subjected to short daily perfusions was considerably weakened and died as a result of this debilitation.

Hemoperfusion was successful in rapidly lowering plasma potassium values. At the same time it resulted in an elevation of plasma sodium. Non-protein nitrogen was not affected by the resin. Loss of body temperature and infection at the cutdown sites posed a constant problem throughout the course of the perfusions. Continual drawing of blood samples for determinations contributed heavily to anemia, and transfusions were necessary to maintain the hematocrit within the normal range.

The use of repeated hemoperfusion through Dowex 50W-X8 in the clinical treatment of canine nephritis is of questionable value. On the basis of the literature review and the data collected in this study it would appear that hemoperfusion has only limited application in the management of canine nephritis characterized by hyperkalemia.

In those cases which reveal plasma potassium values in excess of six milliequivalents per liter or show electrocardiographic evidence of potassium retention, hemoperfusion may be employed initially to rapidly lower potassium ion content within the normal range. Maintenance of plasma potassium within the normal range during periods of renal insufficiency could probably be best achieved by oral or rectal administration of the resin. This method appears to be as effective as repeated hemoperfusion and much less traumatic to the patient.

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