Magnesium transport in normal and uremic patients

The kinetics of radiomagnesium exchange in normal and uremic subjects was studied by administering high specific activity $^{28}$Mg intravenously and utilizing conventional and analogue and digital computer techniques of data analysis. In normal subjects the extracellular magnesium exchanged with 2 magnesium pools. A third tissue magnesium pool of intermediate size was also present. Urinary excretion of $^{28}$Mg averaged 10.4% dose/72 h in the normal subjects and their urine specific activity was maintained at levels which were 23-40% higher than those of the plasma. In uremic patients with hypermagnesemia, the extracellular magnesium was increased. The fractional coefficients for influx into the two bi-directionally exchangeable tissue magnesium pools and the unidirectionally exchangeable tissue magnesium pool were decreased by 60%. Therefore, despite hypermagnesemia, the sizes and flux rate of these pools were normal. Urinary excretion of $^{28}$Mg was reduced to 44% of normal and urine specific activities were 19-26% higher than those of the plasma. These data suggest that one tissue magnesium pool, because of a finite influx rate, but a negligibly small fractional efflux rate, is capable of maintaining a specific activity above that of the plasma, and conventionally calculated exchangeable body pools of magnesium may not provide a true estimate of magnesium exchangeability. The urinary data further suggests the presence of a magnesium fraction with this characteristic in renal tubular cells. In hypermagnesemic uremia, an excessive intracellular accumulation of magnesium does not occur since the cellular structures involved in magnesium transport have the ability to reduce the fractional rate of cellular influx of magnesium upon exposure to an elevated extracellular concentration of magnesium. Studies of experimental hypermagnesemia suggest that this is a physiologic response to hypermagnesemia which is not impaired in the uremic state.

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Hemodialysis in Methyprylon Poisoning

A patient who had ingested 30 g of Methyprylon was treated with extracorporeal hemodialysis and forced diuresis. The patient recovered and renal and dialysis clearances were studied. During a three-hour period of high urine flow (16.7 ml per min) the renal clearance of methyprylon was 10.7 ml/min. In the following 12 h period with a urine flow of 1.9 ml, the clearance was 2.4 ml/min. In the first two hours of dialysis (which immediately followed the period of high urine flow) the clearance of methyprylon was 50 ml/min, giving a clearance ratio renal: dialyzer of 1:4.66. These clearance values are comparable to those reported for secobarbital. As the serum level fell, the dialyzer clearance fell to between 20 and 30 ml/min. The serum level was halved in seven hours initially and was not halved.
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again in the following seven and one half hours. The authors indicate that this data demonstrates that methyprylon is dialyzable. The biological halftime of this compound in patients seriously poisoned is greater than the four hours previously reported.

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Erythropoiesis in patients with renal failure undergoing chronic dialysis

Erythropoiesis was evaluated in sixteen patients with advanced renal failure undergoing dialysis. Some patients were maintained with the artificial kidney for as long as six years. These patients had a mean hematocrit of 24%, maintained, when necessary, by transfusion. The patients were studied by standard hematologic methods as well as the measurement of red cell survival and ferrokinetics. The average red cell iron turnover was 0.44 mg/100 ml of whole blood per day, as compared with the normal value of 0.6 mg. In 14 of 16 patients, no plasma erythro-poietin activity could be detected. Mean red cell life span was half the normal value, a degree of hemolysis that could easily be met by the normal bone marrow. The anemia could be ascribed primarily to defective erythropoietin, resulting in impaired erythroid bone marrow release. Ten patients had evidence of iron overload as manifested by an increase in plasma iron, increased non-erythroid iron turnover, and increased liver uptake of radioactive iron from transferrin. Five patients were restudied one to three years later, and erythropoietic function had doubled. In four of these patients iron overload receded with increased red cell production. The authors conclude that these observations indicate a gradual improvement in erythropoiesis in the patient with extreme renal disease supported by dialysis.

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Megaloblastic hematopoiesis in uremia and in patients on long-term hemo-dialysis

Bone marrow aspirates and serum folic acid and vitamin B12 levels were measured in patients with chronic renal failure, some of whom were being maintained on intermittent hemodialysis. It was found that serum folate was low in several of the patients with chronic renal failure not severe enough to require dialytic treatment. In only one of ten patients who were being maintained with the artificial kidney was the serum folate acid clearly in the normal range. Serum Vitamin B12 on the other hand was normal or high in all cases. Bone marrow examination in those who were being maintained by dialysis revealed varying degrees of megaloblasto-sis, which was shown to improve in the erythroid series but to persist in the granu-locytes in two cases after six to eight weeks of folate therapy. In vitro studies confirm the dialyzability of folic acid and this, along with low initial values (pre-dialysis), probably accounted for the low serum levels found in these patients. It is recommended that patients on long-term hemodialysis receive folic acid supplementation.

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A hemodynamic evaluation of bilateral nephrectomy and hemodialysis in hypertensive man
Three known hypertensive male patients with end-stage kidney disease were hemodynamically evaluated before and 3-4 weeks after bilateral nephrectomy and pre and post six hours of hemodialysis with the twin coil artificial kidney. Conclusions drawn from this study include: 1) the height of the blood pressure and changes in plasma volume are not necessarily directly related in the early renal-priviledged state. 2) An increase in total peripheral resistance plays an important role in maintaining an elevation of blood pressure after nephrectomy. 3) It could not be documented that bilateral nephrectomy had a beneficial effect on the hypertension of chronic renal failure during the first month of the anephric state. 4) Renin is not involved in maintaining an elevated blood pressure after nephrectomy. 5) An increased sensitivity to ganglionic blockade may be present following nephrectomy if there is a decrease in plasma volume. 6) No evidence was found to support the existence of a cardio-depressor’ substance in uremia. 7) The increase in blood pressure occasionally seen during hemodialysis is probably related to several factors (increased cardiac output, increased TPR). 8) Plasma volume may fall during hemodialysis even though body weight is maintained constant. 9) This type of patient is chronically over-hydrated with an increase in total body water and extracellular fluid. 10) If plasma volume is unchanged across hemodialysis, there is usually no change in cardiac output.

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The effect of rapid hemodialysis on brain tissues and cerebrospinal fluid of dogs


The effects of hemodialysis on cerebral tissue and cerebrospinal fluid constituents and on intracranial pressure were investigated in dogs. It was shown that the potassium content of the cerebral cortical gray matter is decreased in uremic brain. In uremic animals the urea concentration of cerebral tissues was found to be in equilibrium with that of plasma whereas the urea concentration of cerebrospinal fluid was significantly lower. Hemodialysis for 60 min with a twin coil artificial kidney rapidly decreased the urea concentration in the plasma and caused a considerable but slower decrease in the urea content of cerebral tissue. The urea level in cerebrospinal fluid was only slightly altered. Consequently, a significant transient difference between the urea concentration in brain and plasma developed. The difference between the concentration of urea in the cerebrospinal fluid and plasma was always more pronounced and of longer duration after hemodialysis. Swelling of cortical gray matter was demonstrated in 50% of dialyzed uremic animals and of white matter in 75%. A rapid rise in cerebrospinal fluid pressure occurred during dialysis in all cases. Similar effects were observed when a concentration gradient for sodium between plasma and the central nervous system was produced in normal animals by dialysis against a hypo-osmotic, low sodium bath fluid. It was concluded from this study that in experimental uremia, hemodialysis results in increased cerebrospinal fluid pressure owing to an osmotically induced increase in cerebrospinal fluid volume and, to a variable extent, to osmotically induced cerebral tissue swelling. Osmotically induced cerebral swelling was shown to be a different phenomena from cerebral edema associated with trauma. The authors point out that it is not possible to decide on the basis of the experiments described whether the neurological complications which occasionally develop following hemodialysis of uremic patients are related to the cerebral swelling which sometimes occurs or to the consistently demonstrated increase in CSF pressure or to other factors.
Peritoneal dialysis for refractory congestive heart failure
Peritoneal dialyses with hypertonic dextrose dialyzing solutions were used to dehydrate 15 patients with ‘refractory’ congestive heart failure. The clinical improvement which was achieved following this procedure could be related to the degree of excess fluid removal and visceral decongestion. Weight loss occurred in each patient and ranged from 0.9–16.8 kg (2–37 pounds), with an average loss of 5.2 kg (22.5 pounds). There was a uniform decrease in plasma volume averaging 1,105 cc/sq. meter of body surface area. Five patients had cardiac outputs measured, but this parameter did not show any characteristic change. Venous pressure and circulation times decreased in those cases where measured. There were only two complications of dialysis. One patient had subcutaneous dissection of the dialysis fluid, while the other had a ‘positive’ dialysate culture but no clinical signs of peritonitis. Particularly noteworthy was the restoration of diuretic effectiveness following dialysis. This occurred in 12 of the 15 patients. The authors stress that it is not their purpose to advocate widespread use of peritoneal dialysis for the treatment of congestive heart failure, but to point out the efficacy of peritoneal dialysis in removing excess fluid under selected clinical conditions.

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Treatment of chronic renal failure with periodic peritoneal lavage
Twenty-six patients with chronic renal failure, who no longer responded to conservative management, were evaluated for a program of intermittent peritoneal lavage. Dialysis was performed once every three weeks with the use of a multiple-puncture technique. It was possible to maintain 13 of these patients symptom-free and ambulatory for an average period of six months. No serious complications were encountered with the treatment itself. The authors point out that patients with severe renal failure who no longer respond to the usual therapy can be supported by intermittent peritoneal lavage provided some residual renal function is present. In evaluating the groups which did not respond to this form of therapy, the most useful criteria for patient selection appeared to be the urine volume and the time required for regression, i.e. the time elapsed before each patient returned to his previous chemical state. All patients who responded favorably had urine volumes of greater than 500 ml/24 h in the period following peritoneal dialysis. Twelve of the thirteen patients who were able to maintain their post-lavage status for three weeks or more after initial treatment were able to do so in subsequent months. Only one of the three patients who remained under control for two weeks.

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and none of the patients who manifested symptoms after one week were able to do so. The authors feel that this method of intermittent peritoneal dialysis can be an effective way for controlling uremia and its associated symptoms but are careful to point out that it does not change the basic disease process. Five of the thirteen patients had progressive deterioration of renal function while undergoing chronic peritoneal lavage.

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Whole organ preservation. II. Freezing studies
Thirty-eight kidneys were perfused with glycerol and propylene glycol in the highest tolerable concentration. They were frozen at the rate of 1°C per minute and rewarmed by one of three methods. These included (A) immersion in water at +4°C and +20°C. (B) Diathermy warming with two ¼-cylinder glass electrode plates, 5 cm above and below the kidney at 450 W output. (C) Radio frequency heating was performed with a 500 W oven and forced ventilation, and with a 2.0 and 2.5 cm polystyrene foam shell shielding the kidney, to prevent overheating the surface. Kidneys were then retransplanted into the recipient and contra-lateral nephrectomy was performed. Four kidneys were able to support life after nephrectomy, although blood flow and function were markedly diminished. Severe outflow block was followed by uniform hemorrhagic necrosis in the others. The authors conclude that if the considerations applicable to freezing and thawing unicellular and small-bulk systems apply to large organs, slow rewarming must be considered as the most likely cause of these failures. Further evaluation and effective application of freeze-preservation methods for bulky organs must, therefore, depend on the development of more effective techniques of rapid rewarming.

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Renal human homotransplantation. A summary of personal research


Fifty-seven patients with renal failure received renal homografts, three of them requiring two grafts. Living donors who were volunteers and/or relatives of the recipients were used in forty-six transplantations. Cadaver or unrelated donors (requiring a nephrectomy for medical reasons) were used in the fourteen remaining cases. When possible, living donors were submitted to the following tests of suitability: Blood group compatibility—ABO and Rh system compatibility; leukocyte grouping; plasma protein groups—haptoglobin, transferrin and Gm groups; skin grafts—onto the donor; the lymphocyte transfer test; and mixed lymphocyte cultures. Immunosuppression was produced by means of radiation, drugs or both. The most commonly used drugs were 6-mercaptopurine, imuran, cyclophosphamide and azaserin. Prednisone and actinomycin C were used as treatment for ‘transplant crisis’ only. The patients were prepared by irradiation alone in 16 cases, irradiation and drugs in 15, and drugs alone in 26. Satisfactory tolerance was obtained in 39 patients, 29 of whom were in good health, 23 after more than a year, 8 after more than two years, and 2 after more than four years. Pathologic changes occurring in the transplanted kidney of the longer survivors were divided into three major groups: (A) glomerular lesions—noted in five patients between the sixth and twelfth month. (B) Progressive interstitial fibrosis seen in nine patients. (C) Arterial lesions—in one patient a diffuse arteriopathy of the transplanted kidney developed. Tolerance to the transplant was never felt to be complete in these patients as was shown by reversible transplant crisis in the early course of many of them and by the findings of the renal biopsies. A stable and satisfactory situation, allowing cessation of immunosuppressive treatment was only attained in a small percentage of cases.

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Pregnancy following kidney homotransplantation from a non-twin

This communication describes the first successful human pregnancy following transplantation of a kidney from a non-twin donor. The patient was 21 years old and received a renal homotransplant from her mother in February, 1965. Her first post-transplant menstrual period occurred in June of 1965. In September of that year the patient was hospitalized for a routine posttransplant evaluation and was not felt to be pregnant. In February 1966, approximately one year after the transplant, the patient was again admitted to the hospital for follow-up examination and was found to be approximately seven months pregnant. She was receiving 125 mg of azathioprine and 10 mg of prednisone daily. Clinical pelvimetry disclosed a large gynecoid pelvis and no detectable obstruction of the birth canal. The transplanted kidney could not be reached vaginally. The pregnancy was uneventful and in late March, 1966, she vaginally delivered a viable female infant weighing 2610 g. Extensive laboratory and physical examination revealed the infant to be normal.

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Retransplantation after failure of first renal homografts

Nineteen patients whose first renal homograft failed underwent retransplantation and one patient received a third homograft. Eight of the patients were living at the time of this report, five with life sustaining homografts that have been functioning for periods from eleven to twenty-one months. Three patients were being maintained with periodic hemodialysis after failure or the retransplant. Second renal homografts functioned in six of seven patients who lost their first homografts because of technical problems, and four of these patients were still alive with functioning homografts. Second renal homografts were rejected by five of ten patients who lost their first homografts because of rejection of thrombosis of the renal artery; only one of these patients was alive with a functioning homograft. The results tended to support the observation of others that second homografts are more likely to succeed if they are implanted more than forty days after removal of the first homograft than when they are implanted after a shorter interval. The results, however, did not support the contention that second homografts have a better prognosis than the first. From this data it appears that the cause of failure of the first homograft had a more important bearing on the fate of the second

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homograft than did the interval between the removal of the first homograft and implantation of the second. So striking was this finding that the authors are reluctant to recommend retransplantation in patients who have rejected their first homograft.

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Action of furosemide on the clearance of solute free water (Klinisch-pharmakologische Untersuchungen zur Beeinflussung der Clearance freien Wassers durch Furosemid)

From observations made during water diuresis and osmotic diuresis it has been suggested that the application of saluretics may cause a disturbance of osmotic regulation. Since neither form of experimental diuresis corresponds to the fluid retention in pathological states, the effects of a single intravenous injection of 25 mg Furosemide on the free water clearance were studied under clearance conditions during saline infusion in both normal persons and patients with impaired
renal function. It was demonstrated that the application of the saluretic during saline infusion always resulted in a slight increase of the urinary osmotic concentration. In normal persons the maximal fluid excretion after the injection of 25 mg Furosemide averaged 21.3% of the filtered volume, whereas the osmotic clearance increased to 23.6% of the glomerular filtrate. The respective values obtained in patients with impaired renal function were 19.87% for the volume and 29.45% for the osmotic diuresis clearance.

Possible errors in applying principles of water and osmotic diuresis in pharmacological studies of diuretics are discussed. The results also permit a conclusion on the site of action of Furosemide in the nephron.

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Clinical experimental study of the saluretic acting compound Chlosudime-primyl/Klinisch-experimentelle Untersuchungen mit dem Diuretikum Chlosudimeprimyl
In a clinical study we examined the relation between dose and diuretic action as well as the beginning and the duration of the action in normal persons after application of the saluretic compound Chlosudimeprimyl (Brinaldix).
The optimal dosage of Chlosudimeprimyl is around 40 mg per day. A higher dosage is only followed by a slight increase of the natriuresis and diuresis.
The action of Chlosudimeprimyl begins within the first hours after application and reaches its maximum after 12 h. In the following 12 h the saluresis and the diuresis are slightly increased whilst on the second day after application no effect can be observed any longer.
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