

DIALYSIS, BILATERAL NEPHRECTOMY, TRANSPLANTATION AND THEIR INFLUENCE ON HYPERTENSION

The basic principle of all artificial kidneys currently used is that a membrane is required for dialysis, usually of cellophane⁽⁶⁾.

While the blood is in the cellophane tubing, and rinsing fluid outside, three things take place:

1. Dialysis - small molecules such as urea, creatinine and other retention products move through the pores of the membrane, are diluted, and are washed away.
2. Equilibration of electrolytes - Electrolytes pass either way through the membrane, and when the composition of the rinsing fluid is correct this will result in a normal composition of the patient's blood plasma, in regard to the electrolytes.
3. Ultrafiltration - Since the blood is under pressure, water passes through the membrane into the rinsing fluid compartment.

The three functions of the artificial kidney can be observed with the treatment of any patient in acute renal failure. During each treatment with the artificial kidney there is a sharp decrease in the blood urea concentration, the creatinine, and in other retention products. With each treatment of the artificial kidney there is a rise towards the normal of the bicarbonate, and normalization of other electrolytes. As much as one litre of ultrafiltrate can be removed per hour, and it seems that some of this fluid comes, first of all, from the patient's lungs, which is a great help in the treatment of patients with pulmonary oedema.

The treatment of patients in chronic renal failure with the artificial kidney⁽⁷⁾ became practical when Scribner⁽⁸⁾ and coworkers in Seattle, on the West Coast of the United States, developed their indwelling cannulas. One cannula is inserted into an artery and it is connected with a shunt to a cannula that is inserted into a vein. Whenever a patient needs treatment with the artificial kidney the shunt is disconnected and the arterial and the venous cannulas are then connected to the inflow and the outflow tubes of the artificial kidney. The blood flow through the shunt when the kidney is not in use is large enough to prevent clotting, and not large enough to embarrass the heart as a large arteriovenous shunt would do.

One of our patients, a businessman, comes to the Cleveland Clinic twice each week. He has no renal function of his own and has been sustained with more than 224 dialyses for more than two years. He does his work and supports his family.

It is my estimate that there are between 60,000 and 90,000 persons with chronic renal failure in the United States who need treatment with the artificial kidney. If not treated with dialysis they will die in uraemia. Only a fraction of those are actually being treated. In some communities committees have been set up, first a medical committee and then a lay committee, to select patients, that is, to decide who is going to live and who is going to die. The first question that the medical committee always asks about the patient is, "Is this an emotionally mature adult?" However, patients in chronic uremia are mostly unhappy, miserable, sometimes comatose, and sometimes psychotic. All of these states are reversible. I am against committees of any sort to select patients! Practically every

patient in chronic renal failure can be improved, and most patients can be restored so as to lead an enjoyable existence.

I have said that patients in chronic renal failure can be maintained with the artificial kidney, but quite often the blood pressure causes a serious problem⁽⁹⁾. Every time a patient is treated with the artificial kidney fluid is removed by ultrafiltration as is noticed by an acute decrease in body weight. Sodium is removed at the same time. While this is done both the systolic and diastolic arterial pressures drop in most patients. When a patient is gradually dehydrated, the blood pressure, in the course of many months and many dialyses, gradually goes down to a more normal level. However, small aberrations of the self-restricted diet may result in serious hypertension; often the blood pressure oscillates between hypertension and orthostatic hypotension.

Sometimes the blood pressure in patients in chronic renal failure, even when they are well maintained with an artificial kidney and are sub-dehydrated, is so irregular that normal life is not possible⁽⁹⁾.

For example, in one man there was an erratic high blood pressure. Notwithstanding treatment with the artificial kidney, and despite our attempts to dehydrate him, his heart shadow remained large, he was in cardiac failure and he continued to have eyeground changes. We took both kidneys out. After bilateral nephrectomy this patient's blood pressure became nearly normal almost immediately. His heart shadow became small and his pulmonary oedema cleared up.

Looking at a short period only of the renoprival state, however, would give a false impression, because after bilateral nephrectomy the blood pressure can still become high. The blood pressure in the renoprival state is extremely sensitive to salt and overhydration. So, I did not say that after bilateral nephrectomy the blood pressure always becomes normal - I do say that after bilateral nephrectomy a severe or malignant hypertension can be more easily treated.

We have listed a series of 10 patients with renal hypertension who underwent bilateral nephrectomy whom we have classified according to their eyeground changes. In 6 of the 10 it was easier to treat the blood pressure after bilateral nephrectomy. However, there were patients, usually with less severe hypertension, in whom bilateral nephrectomy did not seem to make much change in the blood pressure. Before and after bilateral nephrectomy it behaved very much the same.

We sent some of the kidneys of these patients to Dr. Harry Goldblatt and his collaborator, Dr. Erwin Haas. They determined the renin content in the kidneys that had been removed. High renin content occurred generally in the kidneys of patients in whom the blood pressure became more easily tractable after bilateral nephrectomy⁽⁹⁾. I know that these data are not statistically significant, but life would be dull indeed if we could speak only in statistical terms.

Fortunately, we do not only take out kidneys, but, following the example of the pioneers such as Doctors John P. Merrill⁽¹⁰⁾, Michael F. A. Woodruff⁽¹¹⁾, Jean Hamburger⁽¹²⁾, and others^(13,14), we are also transplanting kidneys^(15,16). The next case history is a typical example of the behaviour of the blood pressure after bilateral nephrectomy and, after successful (so far) transplantation. The patient, a man, had been known to be hypertensive since 1960. He had had malignant hypertension.

His blood pressure stayed high, although it was controlled with drugs. In 1962 he became increasingly uremic and finally, in 1963, he needed treatment with the artificial kidney. Although his blood urea concentration decreased and he felt very much better, his blood pressure remained as high as it was before. Then, he underwent bilateral nephrectomy and there was a prompt reduction of his blood pressure, which, however began to rise again when he became overhydrated, as was evident from the increase in body weight.

After transplantation of a kidney from his brother, the blood pressure soon became normal, and it has remained normal now for 17 months without anti hypertensive drugs, and without diet or salt restriction. This man is working full time as a travelling salesman, with a territory that covers three states. He has not missed a day of work for more than a year.

A similar course we have seen in other patients too. In some, severe or malignant hypertension is not sufficiently treatable with the artificial kidney. The hypertension is more easily controlled after bilateral nephrectomy, and the blood pressure becomes normal after renal transplantation. One of these patients works 10 hours a day, chopping frozen fish in a food market, and he intends to go back to college on a part-time basis this fall. He is now 15 months post-transplantation of a kidney from his father.

In a biopsy specimen of his kidney, 4½ months after transplantation, we saw good parenchyma, but the same biopsy revealed an arteriole in which there was a type of thickening that has been described in France and in England⁽¹⁷⁾, and which we consider a vascular sign of rejection. This was a reason for giving this patient increased doses of immunosuppressive drugs.

Which drugs? Azathioprine (Imuran), Actinomycin-C, Prednisone! Furthermore, we perform on most of our patients thymectomy⁽¹⁸⁾ and splenectomy⁽¹⁹⁾, for which there is as yet no real justification; appendectomy may be performed since the appendix is an analog of the bursa of Fabricius in birds. In some cases we irradiate the transplanted kidney^(13,14), but never the patient himself. Bilateral nephrectomy is also done. It is done not to suppress the immune reaction, but to eliminate the ravages of severe hypertension, further, in the hope of preventing the original disease from being transmitted to the transplanted kidney and of eliminating a source of infection.

In our first patient to receive a kidney from a live donor, we had considerable difficulties⁽¹⁵⁾.

The dosage of Imuran is determined by the amount of protein in the urine on the one hand, and the level of the white blood cell count on the other hand⁽¹⁵⁾. When the white blood cell count is low, you cannot give Imuran even if you want to. This situation occurred in our first patient. She had several episodes of rejection, proved by cellular infiltration in the renal biopsy specimen. Since we could not give enough Imuran we had to give large doses of corticosteroids which resulted in a moon-face. The blood pressure of this patient followed the pattern described above. First, malignant hypertension that was intractable, notwithstanding multiple dialyses and an attempt at dehydration.

After bilateral nephrectomy the blood pressure was easy to manage. Pulmonary oedema disappeared and the eyeground changes improved.

After transplantation of a kidney from her mother, there first was an episode of hypertension, then the blood pressure dropped down to normal levels, but in the course of the next 11 months there were several episodes of hypertension, undoubtedly due to rejection, which we could not sufficiently control. Finally, after 11 months she again had malignant hypertension and convulsions. A renal biopsy specimen showed extreme thickening of the walls of the arteries in the transplanted kidney, which undoubtedly acted as so many Goldblatt clamps. The transplanted kidney was removed and the blood pressure again became manageable. You will realize that we have now completed the cycle.

I would like to clarify the just-mentioned cycle in this diagram (Figure 1). I like to think of renal hypertension as having a renal component and a renoprival component⁽⁹⁾. When you do bilateral nephrectomy the renal component is, of course, eliminated, but the renoprival component is still present. In the resultant state you have a blood pressure that is sensitive to salt and water intake. After a successful kidney transplantation the renoprival hypertension becomes normal. If, however, the kidney is rejected (the rejection may have a humoral, cellular, and a vascular manifestation) the renal hypertension will return.

Of course, we try to treat rejection with Imuran and other drugs. If we succeed, there is a return to the normotensive state. However, if too much damage was done by the vascular location of rejection, there is a return to a state of renal hypertension, this time provoked by the transplanted kidney, and all we can do is to remove that kidney. You can transplant a second kidney and start the cycle all over again.

In the patient just mentioned, it took 11 months to complete the entire cycle, but in many of our patients we already know for certain that it will take longer to traverse the cycle. Indeed, we have several patients who have no hypertension after 14 and 15 months. The longer the cycle takes to be completed the more worthwhile will be transplantation.

The possibility of giving a patient a second transplanted kidney becomes a reality, since we are now using cadaver kidneys.

A patient, coming home from a church meeting, drove into a telephone pole, lacerated a kidney and the kidney was removed. After it had been taken out it proved that he had only an aplastic kidney on the other side. He was referred to us and was treated with the artificial kidney. On August 24, 1963, we had a cadaver kidney for him. It was taken from a deceased patient who had had cardiac arrest and acute tubular necrosis after a heart operation. The recipient of the cadaver kidney needed three more treatments with the artificial kidney before his transplanted kidney functioned sufficiently. A renal biopsy specimen taken 7 days after transplantation showed some evidence that acute tubular necrosis was still present. Immunosuppression caused no difficulties.

A slide is shown of the man with his happy family 11 months after transplantation of a cadaver kidney. He is able to work full time as a laborer in a small city in Pennsylvania. It is now more than a year post-transplantation and the patient never had hypertension since he had no renal disease; but the next patient did have renal disease and hypertension when he came to us.

A 54-year-old man came to us in severe uremia, with malignant hypertension, convulsions, coma for 5 days, cardiac failure and pericarditis.

He was maintained with the artificial kidney for one year. During that year he had a period during which he had cardiac tamponade, needed construction of a pleuropericardial window, an empyema developed which formed a fistula three times. Although he enjoyed life during his better periods, the blood pressure remained a terrible problem. Often he had such severe orthostatic hypotension that he had to be taken to the artificial kidney room on a stretcher. Finally, we had a cadaver kidney for him and he received a transplant. He needed three more treatments with the artificial kidney before the cadaver kidney functioned satisfactorily. After that he underwent bilateral nephrectomy. After removal of his own kidneys the blood pressure became normal and it has stayed normal for 7 months. Recently, he has shown some symptoms of rejection, and consequently the blood pressure has increased, but no higher than 140/90 mm. of mercury.

I have two pictures of the patient. One shows him with a grey tie at the time when he had been maintained for 6 months with the artificial kidney. He looks well and he enjoyed life. The other one, however, shows him a year later, and that was 6 months after kidney transplantation. Now you recognize that there is a twinkle in his eye!

How do we preserve cadaver kidneys? The procedure is as follows:

1. The donor is pronounced dead by his personal physician.
2. Infusion of low-molecular dextran, heparin, and closed chest cardiac massage and artificial respiration, which are continued until the kidneys are removed.
3. Flush and cool the kidney.
4. Keep it in a hyperbaric oxygen tank under 3 atmospheres of pressure and keep it cold.
5. Implant it.
6. Dialyze the patient until the transplanted kidney has recovered function. It will go through all the various phases of acute tubular necrosis, including the anuric phase, period of opening up, and the diuretic phase.

The reasons for failure in our cadaver kidney transplants have been:

1. Nonviable kidneys, when we have not recognized that the kidney was dead at the time of transplantation.
2. Surgical difficulties, leaking ureters, bleeding from the renal surface after accidental decapsulation.
3. Necrosis of the transplanted ureter.
4. Infection.

You will notice that overt rejection is not on the list. As a matter of fact, in none of our patients have we considered acute rejection to be the cause of death.

I am sure that I could not leave this meeting without presenting some of our statistics.

As of August 20, 1964, we had attempted kidney transplantation in 35 patients. Fourteen kidneys were from living donors and 21 were from cadaver donors. Seventeen patients have functioning transplants, 7 from living and 10 from cadaver donors. Three patients have had their transplanted kidneys removed and are now sustained by dialysis.

Of the functioning transplanted kidneys on August 20, 1964, 6 have functioned for from 12 to 15 months, 6 from 4 to 10 months and 6 from 1 to 3 months.

In regard to the cadaver kidney transplants, also as of August 20, 1964, one transplanted kidney functioned for 12 months, four for from 7 to 10 months, and five for from 1 to 2 months.

We are using more and more cadaver kidneys and fewer kidneys from living donors. This, I hope, indicates the trend.

In conclusion:

Artificial kidneys are most useful to prepare patients in chronic renal failure for renal transplantation and to maintain them until the transplanted kidney functions. Transplantation of kidneys from cadavers is practical, even several hours after death of the donor. Hypertension, arterio-sclerosis, and age, need not be deterrents to transplantation in a patient with otherwise fatal uremia.

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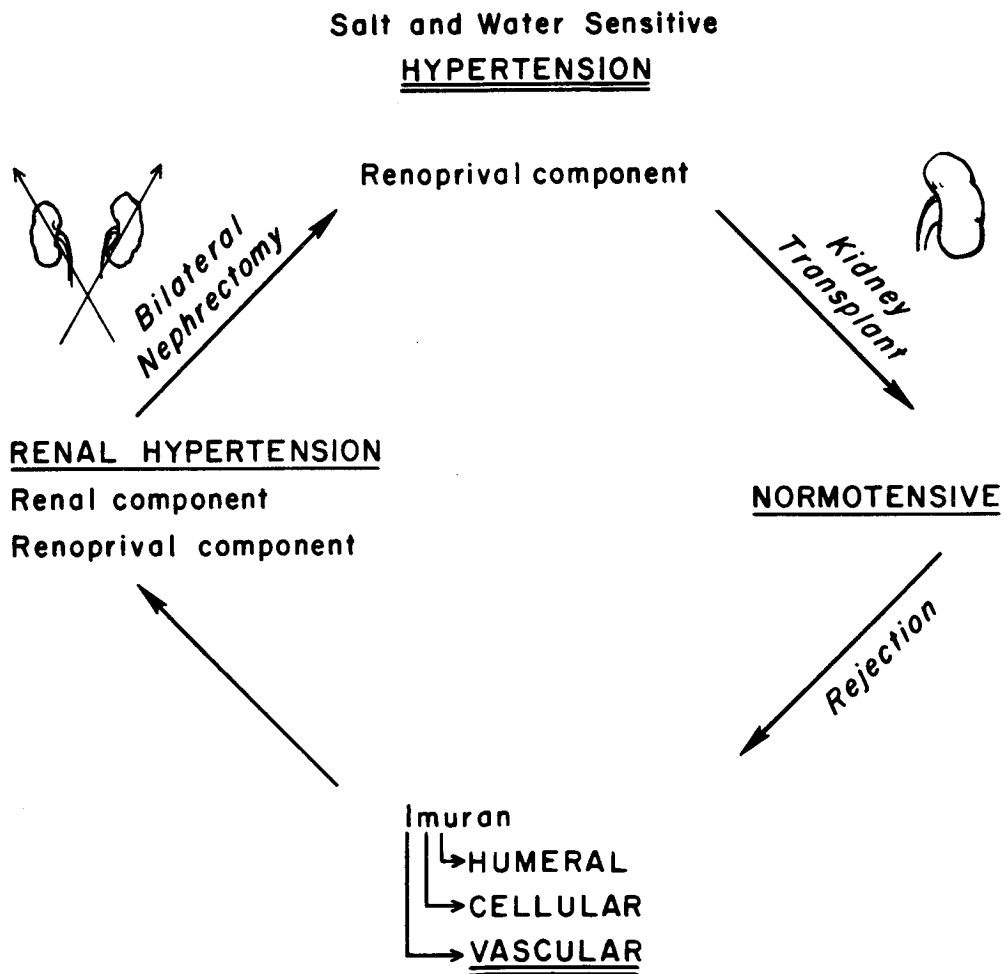


Figure 1.