

The Treatment of Chronic Uremia

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I will begin by telling a little about the development of chronic dialysis. In 1959 we were working on a system to prevent uremia in acute renal failure. We were trying to develop a system to which we could "hook" the patient for as long as a week, so that we would exactly mimic his normal kidney function during the period of acute renal failure, and make his prognosis that of a patient who had kidneys. The system worked reasonably well. We had to make a lot of modifications, such as using a Skeggs-Leonard dialyzer with low resistance. We used a large deep freeze as a dialysate reservoir because we could not afford to change the bath every few hours. The patient was on continuously. We had to cool the external circuit to control clotting problems and infection. We actually had patients on this system for as long as two weeks. It was important to us that we had this system in operation at the time we first devised the cannulas. (The cannulas were devised by Dr. David Dillard, our surgical consultant, and Mr. Wayne Quinton. It is amazing how well their original design has held. As far as I know, it has not been improved greatly, because the cannulas are still the weakest part of the system.)

General Features of the Cannulas and Shunt

The essential system has a long subcutaneous tunnel with a curve of 180° into each vessel. The tunnel is to prevent infection, and the curve is to stabilize the cannula in the vessel. The system does not clot because one tube is in the artery and one tube is in the vein, and the blood runs through. Of

course, it all depends on teflon for non-clotting. Allwall had tried the idea in 1944 and failed, because he was using glass cannulas and rubber tubing; we had a teflon system exclusively. This is the basic operating principle of the system: when you want to treat a patient, you simply pull off the shunt, connect the tubing to the artificial kidney, and you can dialyze at will. The best evidence I can give that this system works is the first chronic patient ever to receive cannulas. He is Clyde Shields, who now has been five-and-one-half years on dialysis. He has not passed any urine in over five years, and is today in better health than at any time. We had to learn on our first patients how to manage chronic uremia by dialysis. We did not know how much dialysis it would take, we did not know how to take care of the cannulas, and we did not know what complications to expect. Clyde has his present cannulas in his leg. We used up all the arm sites in the first few months because the straight teflon system would last only a few months and not much longer. The new rubber segment has made a great difference in the cannula system. The nurse used to put the heparin into the bloodstream. We no longer do this, but use an infusion pump. Note, though, that the nurse does the entire procedure. In Seattle, dialysis is completely nurse-technician operated on the chronic program, and doctors are not in attendance.

We had our clear plastic Kiil dialyzer built especially to study dialyzer-flow pattern. One of the things that is so important is a better understanding of what is going across these mem-

branes. If we could really understand what the chemicals are that we had to move, and urea is one of them, then we could build better membranes. As far as the technique of dialyzer design, ours is a good one but it is not perfect. There is streaming, and the minute you get streaming in a dialyzer, you lose efficiency. We had this particular version built to study the flow patterns. This Kiil dialyzer is the design of Dr. Frederick Kiil in Oslo. He took the original Skeggs design and modified it so that it was easier to assemble, and more efficient to use. This is the only dialyzer at the present time that has been proven useful in the treatment of chronics, because it is low in resistance, small in blood volume, and easy to assemble. When the blood finally reaches the venous end of the external circuit, the nurse plugs the venous cannula in and the patient is on dialysis.

For some idea of the progress being made in the technology, where we could formerly only treat three patients, we can now take four, thanks to the central pumping system which takes concentrate from a tank, and uses very accurate proportioning pumps. They mix the concentrate with tap water, which is monitored by a conductivity meter, and then the fluid is pumped around the room to the various stations. The whole system is automatic. This then means that we fill this concentrate tank about once a month instead of filling a tank once a day for each patient.

Results of Management by Dialysis

We recently conducted a survey on the current state of dialysis around the world. There are 12 centers that have been in operation for longer than one-and-one-half years. There are seven, and probably more, newer groups just getting started. There have been 95 patients taken into treatment. There have been 28 deaths. What is most important is that 75% of the deaths have occurred during the first year of each program. This underscores the need for adequate preparation, adequate funding, adequate training of personnel, and adequate creation of facilities especially for chronic dialysis. This

also means that a realistic approach to the problem is needed, rather than the helter-skelter one that is so tempting when you are confronted with a dying patient. The other 25% of the deaths were due to what we considered to be natural causes. In other words, the one patient who died in Seattle, died one year after starting the program, of a myocardial infarction. And we certainly do not believe that dialysis is going to prevent myocardial infarction. In fact, these patients having only moderately good control of their blood pressures (some have normal and some have moderate elevation of blood pressures), obviously are going to be more prone to the vascular complications of hypertension than the normal population. But these deaths are the natural ones, and the other deaths can virtually be eliminated with proper training and proper preparation.

The rehabilitation rate should also increase as treatment is started earlier, so you will not be dealing with moribund patients. A lot of the failure to rehabilitate has been due, for instance, to starting with a moribund patient who gets severe neuropathy. This has been the case in our one failure to rehabilitate, and an early start would avoid this. As far as prognosis is concerned, the longest one is our patient who has been five-and-one-half years on dialysis. He is in better health now than he has been at any time.

Limitations of Dialysis in Children

If you take the ideal group, dialysis seems to be contraindicated currently in the adolescent and the child, because we have failed to maintain normal growth and to effect sexual maturity in the one patient we treated in this way in Seattle. This does not mean that, with improved membranes and improved techniques, we will not be able to maintain normal growth. And this will be a very sensitive assay of the adequacy of dialysis. Even when confining ourselves to the age group of 15 to 45, we have about 25 new patients per one million population per year. In the United States, there are about 5,000 new patients per year. If the life expectancy is 10 years, this means there will be a patient population of 50,000.

This is indeed a staggering number of patients. When we think of our present technology, no wonder adequate treatment seems impossible. On the other hand, I think we are just scratching the surface of what is possible technically, and I would like to underscore that by briefly covering some of the advances made since the program began.

Problems and Complications

The first problem we faced was loss of the cannulas. Mr. Quinton correctly diagnosed the reason as due to stiffness in the teflon. The system would not give with the normal rotation of the limb, and we lost the cannulas in a matter of months due to mechanical failure. Infection has occurred, of course, but it is largely due to abuse of the cannulas by the patient, and inability to cooperate in his daily care. Mr. Quinton worked one year to extrude silicone rubber tubing that would not clot, after Dow-Corning said that it could not be done. Now all patients on chronic dialysis have this shock absorber in the system which greatly prolongs the life of the cannulas. The first patient to get this kind of cannula was in the program in Seattle, and, three years later, he has the original set. The usual life of these cannulas extends from a few months to one-and-one-half years, depending, mainly, on how carefully the patient takes care of his cannulated extremity. Certainly, undue activity is the most important factor in determining cannula failure. We think the flexibility primarily accounts for the increased longevity of the cannulas, compared with the old teflon.

In Seattle, as in most centers, dialysis worked like this: it was an operating room procedure that took a lot of work, a lot of people, and was terribly expensive. Chronic dialysis twice a week, using this approach, cost from \$20,000 to \$30,000 per patient per year. But in two years, starting with the basic continuous system I mentioned, we have evolved the Seattle continuous-flow, low-temperature system. We have turned it into a nursing procedure. This makes possible, then, the Seattle community center-type operation (under the direction of John Murray, first, and now Jerry Pendas),

where one nurse dialyses four patients at once. The cost projections and the pattern of operation of chronic dialysis all depend on the basic lessons learned in this center, which was very generously and very wisely funded by the John A. Hartford Foundation in 1962. This center was built in the basement of the nurses' home in Swedish Hospital. It shows what could be done in the community, and that it could be done outside the hospital or in a low cost area. The cost of this type of operation currently is \$100 per dialysis, or \$10,000 per year for two treatments per week, including professional fees. This is really the actual, total cost. Rule off something such as construction and purchase of fixed equipment, and the cost is somewhat less.

We have made considerable progress in understanding the diseases of dialysis. Clearly, all of these diseases, with the exception of peripheral neuropathy, are due to inadequate dialysis. The experience of the older days, where you could not dialyze as much as necessary, or the patients lost weight, vomited, became malnourished, and died, was simply because of inadequate dialysis. Gout, or gouty-like arthritis which is an acute arthritis that is responsive to colchicine and can be reproduced by putting urate in the bath, responds to adequate dialysis. Metastatic calcifications dissolve if you keep the phosphorous low enough with dialysis, and peripheral neuropathy can be stabilized by dialysis. But probably the most important factor in peripheral neuropathy in these patients is the critical illness that may precede the institution of therapy. Invariably, if the patient becomes critically ill at the time you start therapy, in a week or a month he may develop a severe peripheral neuropathy. The degree of severity of this neuropathy varies tremendously from patient to patient, but the clinical picture is constant. There is now an excellent description of this situation in the literature from the Massachusetts General Hospital. The prevention of neuropathy at this stage of our understanding depends largely on starting dialysis or doing the transplant before you are dealing with a moribund patient. We have not yet

defined diseases due to much dialysis, but because our membrane is non-specific, I am sure that some will be defined. Secondary hyperparathyroidism is not a problem, but anemia is a continuing problem. The average requirement, if you rinse your dialyzer properly, is about two units of blood per month. This is an area of obviously great interest. If an erythropoetin could be made available, we might eliminate this. Stanley Sheldon in London believes that more intense dialysis and a higher protein diet will minimize the anemia.

The greatest problem for the patient is controlled hypertension. The real cross these patients must bear is learning to eat a low-salt diet. There is no question that if he can learn a low-salt diet, his blood pressure will be controlled. It takes from three to six months for a patient to really learn to eat a low-salt diet. They cannot cheat. If they eat salt, they gain weight, and it shows up on the scale when they come into the center. Once they learn it, their pressures are controlled either at, or near, the normal level.

The Future of Hemodialysis

With this background, then, I am going to talk briefly about my concept of the future of management of chronic uremia. One point I want to make here is about good conservative care. This is an area which is greatly misunderstood, both by nephrologists and by doctors in general. The most important factor we have found in the management of the chronic is the control of hypertension by means of sodium restriction. All the emphasis in the literature on the management of the chronic has been on the salt-losing crisis and the magic effects that salt has on a patient in uremia. This is not the place to put the emphasis. There is no question that, if a patient is salt-depleted, and his neck veins are flat and his blood pressure is down, that his GFR will drop almost to zero. Salt, then, can have a miraculous, life-saving effect on this patient. But for every one of these, there are 500 patients who are being abused by too much sodium. It is our contention that it is the high blood

pressure induced by sodium overload, rather than the disease itself, that is most often responsible for progression of the renal lesion to the fatal end. And we have diagrammed this idea by showing the maximum and a minimum sodium excretion for a patient having progressive loss of his kidney function over a 30-year period. At some point, he gets both a floor and a ceiling on this ability to handle sodium. The inability to conserve sodium has gotten all the emphasis because a few patients, particularly those with pyelonephritis and polycystic disease, waste sodium. But as of now in our renal clinic, we have about 30 chronics with serum creatinines above 2, and there is only one that is a significant salt waster. The more important problem is that they have an upper limit on their ability to excrete sodium and when they start taking in more than they can handle, their blood pressure rises, they get malignant hypertension, and die. We give every patient a blue book to record his blood pressure, weight, and urine volume, although the urine volume is not really important. Then we teach them the relationship between the amount of salt they eat, the change in their weights, and the change in their blood pressures. We saw a patient in 1960 who had "bad hypertension". The sole maneuver there was to put him on sodium restriction. True, his creatinine bounded around a little. When first started, the creatinine will always go up, which is another thing that has received undue emphasis. As long as it does not go up into the symptomatic range, you should not care. Because, if you are not going to control that blood pressure, experience shows that the man will be dead in a matter of months. Four years later, this patient's creatinine is still stable around 8 and his blood pressure is well controlled on a low salt diet. Occasionally it is well to add small doses of blocking agents, but our experience shows that patients with uremia tolerate these drugs very poorly. If they go into dialysis, they are going to have to go on a low salt diet anyway. We prefer to use the diet as our major therapeutic tool. All of our patients, we feel, would have been dead within

months had their blood pressures not been controlled. So the message is, control blood pressure by any means that you can, and you are likely to get a lot more mileage out of your patient's kidneys and avoid the day when definitive therapy is going to be needed. I am not minimizing the importance of giving salt if the patient is sodium depleted, but this is a very special, rare problem. What I am talking about is the garden-variety, day-to-day management of the patient with renal insufficiency.

The Place of Peritoneal Dialysis

Dr. Fred Bohn has been working in peritoneal dialysis for a number of years, and his monograph is well known. Eighteen months ago, peritoneal dialysis in the management of the chronic was discredited, and rightly so, because peritonitis was the rule. Dr. Bohn devised an automatic cycling machine; which is a completely closed dialysate system. He figured out an experiment to sterilize these big bottles of fluid so that no one has to cycle the machine, thereby eliminating the need of the nurse or family. Now, after having lost one patient with peritonitis, he has a second patient going, and believes it is because of this closed system which maintains sterility. After three months of treating this patient for recurrent peritonitis, he resolved that the indwelling peritoneal access prosthesis was the villain, and to make a successful chronic peritoneal dialysis, he had to insert a peritoneal cannula every week, through a tiny incision that heals from one week to the next. Since he removed the prosthesis, he has not had a bit of trouble with peritonitis. It is on the basis of comparing the patient who loses significant amounts of protein through the peritoneal membrane with our patient on hemodialysis, that we think that a synthetic membrane with a larger pore size is needed.

Hemodialysis in Relation to Transplantation

We are very concerned about the future of dialysis in relation to the real hope in this field, transplantation. There is no question that if you have

a human kidney inside you, working, this is far superior to an artificial one. You are not tied to a machine, you don't have to worry about getting to the center, you don't have to take care of cannulas, and you don't have to eat a low salt diet. But as we see them, here are the facts on the current status of transplantation: Of the identical twins whose operations were performed five years ago, 70% are now dead of recurrent kidney disease. The recurrence rate is 50% in the Boston group. We had a patient with glomerular nephritis who was sent to the Mayo Clinic and transplanted from her mother. Six days after the transplant, the mother's kidney was destroyed by the same disease that originally had destroyed the patient's kidneys. This is a very important case, of course. A question raised is, had this patient been carried for two or three years on chronic dialysis, would this immune activity have abated and would, then, the transplanted kidney have survived? If we get another such patient, we will try a double transplant, probably first from a cadaver, doing it right away, and then waiting two or three years and trying it a second time. Dr. Don Thomas, who is in charge of our transplant program, recently reviewed the latest summary from Dr. Joe Murray's group in Boston. He concluded that the chances of surviving for two years on a transplanted kidney are somewhere between 5 and 20%. The chances of surviving for four years probably are less than 1%.

I can say with some conviction that the chance of surviving four years on chronic dialysis in the current well-run program approaches 100%. The big *if* in the dialysis program is that you must have a coöperative patient. The one thing stressed by all now doing chronic dialysis is, if the patient cannot coöperate, take care of his cannulas, or stay on the low salt diet, then the chronic dialysis is not a very good form of treatment. The amazing thing we have found is that a group of patients who are coöperating seem to pull along the ones who are not, especially during the early days when they are learning about the program. Most patients will coöperate, because

when they begin to feel well and see what salt overload does to them, they learn from bitter experience that it is better to coöperate than to be sick.

I want to make another point that I believe is important because of the neuropathy problem. Despite economics and the intense need right now, the sooner we make a logical transition from good pre-dialysis care into dialysis, and into transplant after dialysis without having a crisis, the sooner our patients are going to be happier. Our new clinic that will be opened at Swedish Hospital has the capacity for 30 new patients. Our patients who now are being treated in town by the various kidney doctors have already visited the center. They know what they are going to get into when the day comes. They have heard about transplants, they are prepared emotionally, and they are getting prepared financially to take on the definitive treatment, long before it will be necessary. This is an ideal that we are far from achieving. When we do achieve it, our patients and doctors will be much happier.

Home Dialysis

So the hope for the future rests on lowering the cost of the present form of treatment (the central pumping system is one example of how we are doing this with the important coöperation of our engineering colleagues), some form of home dialysis, and, of course, the big hope is that we can make real progress in the immunology of transplantation. Now we have a very exciting development, one that I think offers real hope, particularly in the financial area. That is home dialysis. Our first patient on the home program was a young high school girl who is dialysed by our family in her basement. The dialyser is a miniaturized version of our central pumping system that is fully automated. A standard Kiil dialyser is used. We switched from zepharin or formaldehyde to acetic acid, a more effective germicide that is often forgotten. When using acetic acid to sterilize the artificial kidney, some is left in, which the patient readily metabolizes. Then, when ready to dialyze, you simply hook the kidney to the bath

source, acetic acid becomes sodium acetate, and you convert a germicide into a metabolizable substance. Then, as I mentioned, the dialysis fluid is supplied by a miniaturized version of our central pumping system or by a home tank.

We started the patients in an isolated area of the hospital, where the family can be taught a little about what goes on inside an artificial kidney. The family first observes the technique and gradually begins to take over. It takes a surprisingly short time to teach a family to operate a system at home. We totally underrated the motivation of the patient to learn. The family realizes it is their relative's life at stake, and that if they do not learn to run the equipment, they might well lose their relative. They learn much faster than our technicians and nurses who train for our center program.

We are literally just scratching the surface on what is going to be possible in the home program. The cost, which we hope is generous, looks like it is going to be under \$5,000 per year. The breakdown is very encouraging, because such things as equipment, maintenance, and depreciation are the kind of things communities can fund. This leaves \$3,000 or so per year for the patient to pay. The startup costs are around \$8,500 for the first year. This is a very rough figure; we do not have enough experience with home dialysis to know, but at least it is less than half of what our current center type of operation costs. (As of November 1965, there are seven patients on home dialysis in Seattle, and there have been no failures.)

The advantages of home dialysis, in addition to the cost factor, is more intensive dialysis. It can be done in the evening, for example. Instead of spending the evening in the center, they spend the evening at home. When an unattended nighttime dialysis is possible, we have 56 hours a week during the night to dialyze. This would then free all of the patient's waking hours for normal activities. A very important point psychologically, is that the patient himself becomes responsible for the care instead of the institution. There is a real feeling of independence.

Frequent short dialyses are more effective. On twice-weekly dialysis, for a total of 20 hours per week, the patient's creatinine got up to 12. On three times per week, for a total of 18 hours or less time per week, his creatinine got up to 10. So this kind of study projects that the frequent short dialyses are going to keep these patients much healthier than the infrequent, prolonged dialyses can.

One problem is that not everybody is going to be able to go home. We estimate, in our present population of about 20 patients in Seattle, that only half are going to go home. There are going to be other solutions, but the home program is the ultimate one. The center type is perfectly satisfactory if you can afford it, and something in between may be the answer for other patients. Maybe you can get them together in an apartment home—"You dialyze me tonight and I'll dialyze you tomorrow night"—This sounds crazy but it will be necessary if people are going to survive within the economic limits we can provide.