New Developments in Hemodialysis for Chronic Renal Failure*

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Introduction

I am going to speak mainly about extracorporeal hemodialysis, that is, dialysis conducted with an artificial kidney as opposed to peritoneal dialysis. I am going to direct the majority of my comments toward the extraordinary technique of the maintenance of life in patients with chronic renal failure. I would like to break my discussion into three general areas: 1) a review of the historical development of the dialyzer, including some remarks on what happens at the membrane level; 2) a look at the results we are getting with this kind of hardware; and 3) a comment on some of the newer experimental dialyzers.

Historical Development

Figure 1 shows a dialyzer credited to Abel in 1913. This is a rather ingenious device for all its simplicity. It is a collection of collodion tubes, marked (C), contained in a cylinder of glass. Blood flowed through the collodion tubes and dialysis fluid through the cylinder surrounding them. This was the first successful extracorporeal hemodialyzer on record.

Figure 2 illustrates a device that is probably the most famous of the artificial kidneys. This was designed by Dr. Willem Kolff in Holland in 1943, 30 years after Abel!s

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Fig. 1—Blood hemodialyzer reported by Abel in 1913.

Fig. 2—The Kolff-Merrill rotating drum dialyzer.
first attempt. It consisted of a drum on which blood-filled tubes of cellophane were wrapped. This tubular cellophane was of the garden variety, food-wrapping sort. The loops were strung over a drum of stainless steel. Dr. Kolff's original, I understand, was made from wooden bed slats and a variety of other makeshift gear that he assembled. This was translated by Dr. Merrill and himself at the Peter Bent Brigham Hospital into the gleaming stainless steel and plexiglass item you see in the figure. The blood leaves the radial artery of the patient. It is taken to the beginning of this helically wound spiral of cellophane. Movement of blood through the spiral is accomplished by the Archimedes screw principle. Eventually the blood is returned, after passing through a bubble trap, into a vein in the patient's arm. The dialysis fluid is in the trough underneath the drum. The drum rotates with its lower third submerged in the dialysate and wets the membrane.

What happens at the membrane level? Figure 3 is a diagrammatic sketch of a cellophane membrane. The white circles represent large molecular-weight solutes, such as protein and the cellular elements, which are retained because they are too large to traverse the membrane. The smaller dark particles, of course, move easily through the pores of the membrane and are trapped in the dialysis fluid. The driving force is diffusion. Dialysis is, in essence, diffusion across a membrane, and is a simple matter of discharging gradients. The toxic solutes, e.g., urea, that are present in the blood in high concentration, are absent in the dialysis fluid and, therefore, move so as to discharge this concentration difference. The solutes that are small in molecular weight, and are desirable to retain in the blood, such as, possibly, sodium, can be placed in the dialysis fluid in physiologic concentrations. As a result of diffusion, abnormalities of serum sodium would asymptotically approach the normal value of the sodium in the dialysis fluid. Dialysis is a great normalizer.

Figure 4 is a photomicrograph of cellophane. You can see that the pores are less orderly. It looks like a haystack run over by a steam roller. The success of cellophane as a dialysis membrane was an empirical triumph. The selection of the membrane was an arbitrary one. Dr. Kolff used this, and it has been used ever since. There have been strong efforts to find better ones, but cellulosic membranes are still the most widely used item for dialysis.

Just to give you a comparison with our divine prototype, in Figure 5 you see on the left the artificial kidney membrane. Cuprophan is one of the best of the cellulosic dialysis membranes. On the right is the glomerular basement membrane. An axiom in dialysis is that the shorter the diffusion path, the more efficiently you can move solutes. If you had your option, you would take the thinnest dialysis membrane available that could tol-
erate the pressure gradient without rupturing. As you can see, we are still far from the natural membrane.

To move back to the historical side, the next development came when a young surgeon in Philadelphia named William Inouye decided that the large, rotating drum dialyzer which is, to put it in perspective, like a small sarcophagus, could be reduced in size, and that this would be an advantage. He wrapped the cellophane tubing up so that it was now a tightly wound spiral separated by a supporting screen. This membrane package fit neatly into an old pressure cooker. Dialysis fluid was then percolated up through the screen. This was later to develop into the twin-coil kidney. Dr. Inouye reported this modification in 1953. Dr. Kolff improved the design and in 1955 came out with his first twin-coil kidney. The circuitry for the twin-coil is presented in Figure 6 and is relatively straightforward. Blood leaves the artery, moves through a blood pump, and goes to the cellophane coil in the inner bucket. Dialysis fluid is pumped over the cellophane membrane, where diffusion occurs. The blood then returns to bubble traps and is returned to the vein.

There are a variety of artificial kidneys that have been developed since the original rotating drum and the development of the twin-coil kidney. The parallel flow plate dialyzers, such as the Skeggs-Leonards and the Kiil, came along after the development of the rotating drum. The next significant development had to do with the deliberate attention paid by Dr. B. H. Scribner in 1960 to the problem of what could be done with the patient in chronic renal failure. Up until then, such devices had been successfully applied to patients with acute renal failure, but that was all. In 1964, W. Quinton reported a device for ready access to the blood vessels of the patient. Clearly, the limiting feature of repeated

Fig. 4—Electron micrograph of cellophane.

Fig. 5—A comparison of Cuprophan and glomerular basement membrane.
dialysis had to do with access to blood vessels. These vessels had to be cut down on surgically and tied off after the procedure. This could be carried out relatively few times. Mr. Quinton addressed himself to the design of a shunt, and Dr. Scribner applied this to the care of patients with chronic renal failure. In Figure 7 we see such a shunt implanted in the forearm. The radial artery is used, and blood returns to the vein running out of the "snuffbox" on the forearm. The loop on the left can be removed, and this, then, provides access to artery and vein. The kidney leads are attached to the shunt. This has worked exceptionally well. Shunts have been left indwelling on single placement without change for as long as a year. The problem that can arise is infection, usually staphylococcal. Such an infection may result in septicemia. More frequently the shunt clots, so you lose your shunt site and have to reimplant higher in the same vessel or in a different area.

In 1964, a variety of workers began to experiment with simplifying dialysis technique to the point where it could be carried out in the home. Drs. Merrill in Boston, Shal­don in England, and Scribner on the West Coast all became interested in home dialysis. They saw in this a technique that was more economical in that the costs incurred for bed charges in a hospital, nursing personnel, etc., could be eliminated. Home dialysis, then, and placement of the shunt in the leg rather than the arm, so that the patient could put himself on the kidney, was the next major development.

In 1966 Dr. M. J. Brescia, going a step beyond Scribner (1965), created an arteriovenous fistula of the vessels that are usually used for the placement of the shunt and, in that way, created a hypertrophied venous tree that could be negotiated with a percutaneous stick using large gauge needles. There are cosmetic benefits as well as the likelihood that the incidence of infection would be reduced and, hence, the incidence of clotting. This has proved to be the case in the trials that have been carried out so far. We have had several patients
with this particular form of fistula. We have had one patient in particular, a lawyer, who has used both of these techniques. He started with the traditional Quinton arteriovenous shunt and moved on to the Brescia fistula. He thinks that, even though it means the pain of a percutaneous stick every time, the latter is by far the method he prefers.

Results

So much for the technique and equipment. I'd like to focus for a moment on what may be more controversial, namely, the results of all of this. I think that there are a number of parameters that have to be looked at fairly closely before assessing whether this technique is a success or a failure.

One guide that is of quite evident importance is the survival rate. Survival figures seem to be quite good, according to the September, 1967 "Report of the Committee on Chronic Kidney Disease" submitted to the Bureau of the Budget.* Of 302 patients followed for up to seven years, survival is 87% at one year, 67% at three years, and 58% at seven years. The number of patients clearly is small, and these figures may change as more patients are added. The cases that are reported at the seven-year mark with 58% survival represent three of the original cases studied by Scribner in 1960. This figure may change radically as we see larger numbers of patients moving through this technique. As far as mortality goes, if we can guarantee seven more years of life for 60% of the people who invest their time, I think this is a handsome success.

Clearly there are other parameters that have to be looked at, not the least of which is the quality of life maintained. Is this the simple preservation of a hopelessly sick person who is not back in the community, or is there real rehabilitation? In trying to make this assessment, which is an exceptionally difficult one, it is important to ask first, "What does the patient have to invest?" and second, "Is the investment worthwhile?"

To any of you who have had close association with chronic dialysis, it is clearly recognized that this is not a simple technique for the patient to undergo. He has to be prepared to put up with a great deal to survive. This is a technique for people who are intelligent and capable, and if they are not both, as well as conscientious about caring for themselves, they quickly die. Two to three times a week they have to invest six to twelve hours on an artificial kidney. If this is done in a kidney center during traditional working hours, this cuts into their day as productive citizens, unless, of course, they are employed in some unusual occupation that permits work at night. Many centers have solved this by providing nighttime dialysis. In home dialysis, hopefully the patient puts himself on the machine at 8:00 in the evening, sleeps quietly through the night, and awakens in the morning to take himself off the kidney. But, nonetheless, this is a significant investment of time. In addition, you are asking your patient to rigorously restrict his fluid intake. In the face of ongoing thirst, this can be exceptionally difficult. Every drop of fluid taken in excess of, say, a 300-400 cc insensible loss per day (most of these patients do not make a significant quantity of urine), has to be taken out with the artificial kidney. You ask your patients to hold down their intake to 500-800 cc of fluid per day, even though they are thirsty. Protein is restricted; potassium is restricted; sodium is restricted; so that attention to diet is probably the most onerous requirement you are asking these patients to fulfill. Your patient investment here is substantial.

It is quite clear from what I say that it is imperative to select the patient from the standpoint of reliability and emotional stability. A staunch psyche is almost prerequisite. In addition, it is important to have strong family support for patient and procedure. So the pa-

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* Prepared by a committee of which Dr. C. W. Gottschalk was Chairman.

Fig. 7—Quinton-Scribner arteriovenous shunt. Stainless steel stabilizers.
tient and family investment is substantial.

What do they get for their investment? Can these people be rehabilitated? Are they back on the firing line? Could they go out and dig a ditch for a living? In general, they cannot. This is a near-normal but not a normal state. The fatigue level of a patient on chronic dialysis is still substantially below normal.

There are ongoing complications that can occur in spite of good dialysis, one of which is neuropathy. Progressive neuropathy of the peripheral sort can provide crippling incapability of the lower extremities. This can rapidly progress even in the face of “adequate” dialysis. The details of why this occurs have yet to be worked out.

Pruritus can be very persistent in some chronic dialysis patients. I was amused when Dr. Setter took me over to view the dialysis unit here at the Medical College of Virginia to see one of the small Chinese carved hand backscratchers lying on the overbed table of one of the chronic dialysis patients. This reminded me of the motto that the medical residents rotating through our service have pasted with adhesive tape over our dialyzer—“Semper pruritus.” Excoriation of the skin with subsequent infection in a patient who does not fight infection well can provide a serious problem.

Anemia is another problem. It is evident that when kidneys are seriously diseased, erythropoietin is present at unmeasurably low levels in the blood; there may be a hemolytic component as well. In addition, the bone marrow does not make red cells normally so that even with good substantial dialysis, these patients do carry a low hemoglobin, usually around 8 gm/100 cc. This may contribute to the fatigue syndrome of the chronic uremic.

Patient rehabilitation is hard to assess. Reports vary enormously depending on whom you read. Most report a reasonable rehabilitation rate (Brown et al., 1962; Gonzalez et al., 1963; Kretchmar et al., 1963; Maher, Freeman and Schreiner, 1965; Rubini, Wolfram and Sokal, 1966; Comty et al., 1966). There are few ditch diggers reported that have done well. You can read the experiences of others, such as Retan, in Detroit, where rehabilitation has been very bad. A lot of the success or failure has to do with the vigor that the investigator or the physician applies to motivate his patients. There is almost a religious atmosphere to the attitudes of the patients trained in the Seattle centers. Dialysis is treated as an end in itself. This becomes a difficult religion to instigate in a patient if there are other programs at the institution which may have a higher priority. This has been difficult for us in our unit with transplantation and chronic dialysis both ongoing. Rehabilitation, then, is a complex function of patient, institution, and professional staff.

Let us move on to another parameter of success. How are we doing numerically? Are we getting ahead? There are a variety of figures given. The most solid come from the “Report of the Committee on Chronic Kidney Disease.” Thirty-five thousand patients per year die of chronic renal failure. Of that group, there are some 7,000 per year who would be good candidates for either dialysis or transplantation. In the last three years there has been an enormous input of effort and money for the setting up of chronic dialysis programs throughout the United States. The USPHS has given grants to establish dialysis units on a trial basis, the Veterans Administration Hospitals have set up a string of hemodialysis units associated with their hospitals, and most university hospitals now have such facilities. All in all, there has been a burgeoning of the hemodialysis effort. How many patients of these 7,000 per year are now on the machines? At this moment, approximately 800. The rather ridiculous logistics of the present situation are apparent. If we are receiving 7,000 patients for care each year, and at the present state of the art are saving only 800, something clearly needs changing.

Moving on to another rather sticky wicket, how about the monetary end? According to the “Report of the Committee on Chronic Kidney Disease,” in-patient chronic dialysis costs, on the average, $14,000 per year per patient. The most economical way to arrange chronic dialysis is at home, but this still costs $5,000 per year, after an initial outlay of about $10,000 for equipment and supplies. This cost of home dialysis in most situations is borne by the patient. Quite clearly, this introduces a selection process into the patient population for chronic dialysis that I am not sure would meet with the best standards of a democratic society. When you realize that an in-patient chronic dialysis slot lasts for at least seven years, if you are doing your job properly, with the annual cost being as high as it is, it is no wonder that most insurance underwriters and hospital administrators blanch when chronic dialysis is proposed. The lives saved-per dollar spent ratio with chronic dialysis leaves a good deal to be desired.

Clearly I feel that this is a dramatic lifesaving technique that the medical profession should be proud to have. It should be broadly available, but in order to make it so there have to be some improvements. One of the improvements is that of cost. Along this line, there was an interesting parenthetical comment injected by a member of the Tokyo Society for Artificial Internal Organs at the 1967 meeting of the American Society for Artificial Internal Organs. This gentleman stood up and said, “Be ware of the Japanese invasion. We are importing cellophane and fiberglass screens and making coils that we will send to the United
States," at a cost, as I recollect, of about $20. This, taken in perspective of the $70 fee that the coil he was describing was then selling for on the American market, shows one important area of improvement that will come along.

New Designs

There are a number of things on the drawing board for the future that I think bear close attention. Moving to one approach in the new design category, Figure 8, with all apologies to Chester Gould and Dick Tracy, was drawn by my colleague, Dr. L. W. Bluemle, and depicts an imaginary miniature dialyzer. It exemplifies one approach to design. This would be to develop a small, wearable, continuously dialyzing system. I think you can project this dream to say that the patient straps a tank of dialysis fluid around his waist in belt fashion and is good for the day. Miniaturization is one approach that the innovators in artificial kidney design have taken. There are two examples of this approach that I would like to show you. One (Fig. 9) is a so-called accordion, push-pull, or tidal flow dialyzer. It is nothing more than an accordion folding of sheet cellophane into a package that would fit neatly in the palm of your hand. This particular configuration permits enormous membrane area to be put in a small package, and, by an appropriate valving mechanism, this rather small membrane package can be used for dialyzing. This was the brainchild of Dr. Bluemle. There are now at least two groups working with this concept.

Another particularly ingenious approach to the problem is the spinning of cellophane capillary fibers. These are hairlike tubes that are made of cellophane. Again, tremendous membrane area can be packed into a very small place. Another approach to the design problem is to come up with a high efficiency dialyzer in order to cut dialysis time to an absolute minimum. Under improved efficiency can come such developments as better membranes and better membrane supports.

A particular approach to a higher efficiency unit has been worked on in our laboratory by Dr. Bluemle and me. Figure 10 at first glance looks rather complicated. It is a device that employs ultrafiltration, not diffusion, as its means for cleansing blood. Diffusion is inherently a slow process. It would be nice to be able to apply some extrinsic force to move toxic solutes out of the body, and we are attempting to use ultrafiltration pressure as just such a force. The figure shows a cross section of such a diafilter, and the inset illustrates the central blood path. In addition, there are two other paths, one on either side of the blood path. The first is under positive pressure (10 PSI), forcing fluid through an ultrafiltration
membrane into the blood; the second, on the other side of the blood path is under negative pressure, drawing the fluid right across the flowing blood stream, carrying with it all solutes that have traversed the ultrafiltration membrane. The success of such a device depends on these two membranes and their properties. The glomerular basement membrane, after all, does this sort of thing very nicely. The glomerulus is not a dialysis membrane; it is an ultrafiltration membrane and, as such, has a very high efficiency. The present design is an attempt to match this efficiency by using simultaneous ultrafiltration and reconstitution of blood. We have suitable ultrafiltration membranes available to us now, and I am sure we are going to see developments of this sort as another important step in increasing efficiency.

References


