The Development of Nephrology

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(J Postgrad Med 1994; 40(3):109-117)

When Dr Acharya invited me to attend this meeting, she asked me to review the development of nephrology, which each of us had experienced since its beginning. There are many ways in which I could approach this task and no matter which I choose, I will fail to do justice to certain areas and to the individuals who contributed so much to the respective fields. Rather than present you with what I fear would be a boring history of developments and discoveries, I would like you to imagine that you are listening to a modem day Marco Polo, describing a journey through many strange lands, some of which he will have experienced in detail, others he will have visited only transiently and yet others, he will have known only by hearsay. If I dwell more extensively on those areas, where I have had the greatest personal experience, it is because I believe that personal anecdote is always more interesting than second-hand fact, and I will ask your indulgence for not mentioning other areas with which I have been less personally involved.

Nephrology prior to 1960s

I graduated from medical school in 1954 and started my training in the Renal Division of Washington University School of Medicine, under the direction of Dr. Neil Bricker in 1958. At that time, nephrology did not exist as a speciality, although there was a group of individuals around the world, who were interested in various aspects of kidney function, pathology and clinical diseases. The International Society of Nephrology was not founded until 1960 and the American Society of Nephrology did not come in to being until 1966, followed a year later by the Canadian Society of Nephrology. Urology was a well-established speciality and the urologists dealt with stone diseases, urinary tract infections and hematuria and were frequently involved in the investigation of proteinuria and acute and chronic renal failure.

The common problems of nephrology were essentially the same as they are today, but our knowledge of the underlying pathophysiology and our ability to deal with them were significantly less. Dialysis for acute renal failure was considered an experimental therapy and limited to a few centres with special interests in the area. There was no effective treatment for chronic renal failure. The glomerulopathies were poorly understood and renal biopsy was in its infancy. I am sure Dr. Acharya will remember how we classified glornerulopathies into Ellis Type I and Ellis Type II, which was a classification that had so many exceptions to it that it was of very little clinical value. Salt and water metabolism and acid base disorders were in the process of being sorted out but were totally incomprehensible to most practising physicians. Even today, at least in Canada, I find medical students and primary care physicians continue to have great difficulty with these topics. Urinary infections were looked after by all physicians, but the urotogists were consulted about persistent or recurring cases and antibiotics were limited to streptomycin, chloramphenicol, tetracycline, penicillin and sulphonamides. Hypertension was the domain of the general internist and cardiologists, but therapy was limited to thiazide diuretics, reserpine hydralazine and ganglion blocking drugs.

In the early days of nephrology, there was a great deal of interchange between the basic scientists in physiology, and the clinician scientists dealing with patients an interchange which has tended to decrease over the years as nephrology has become more and more specialized and fragmented into specialized areas. You will note that I have omitted renal transplantation from this list. Although the first identical twin transplant had already been performed in the Peter Brent Brigham Hospital in 1955 it was still considered an experimental procedure, limited to a few centres throughout the world.

When I started as a follow, the Renal Division in Washington University had an extensive research program, which was the primary responsibility of the nephrology trainees. At that time we were working on the pathophysiology of chronic renal failure, using a

number of different dog models. The Division provided clinical consultation to the University hospital, but we did not have any patients under our own care, and Dr. Bricker was always concerned that clinical responsibilities should not interfere with the research program. However, a year earlier, he had become involved with a young general surgeon who was interested in providing haemodialysis for acute renal failure, and our Division was in charge of the artificial kidney. We were therefore consulted about all cases of renal failure, both within the hospital and the surrounding region, because we had the only artificial kidney in the mid-west of the United States south of Chicago. The equipment was a Kolff twin coil kidney and, at this point in time, I think it might be interesting to review the development of haemodialysis up to this time.

History of haemodialysis

In 1903 Abet and Rowntree developed a vivid diffusion apparatus using celloidin tubes and successfully dialysed nephrectomized dogs. The first human dialysis was performed by George Haas, in Germany in 1926, again using a celloidin membrane and hirudin from leeches as an anticoagulant. The early attempts at dialysis were hampered by the lack of an adequate anticoagulant, but towards the end of the 1930's, heparin became available and also cellophane, which was marketed for commercial use, just prior to the outbreak of World War II, a young physician called William Kolff, started working on dialysis as a means of treating renal failure. He developed the first workable, artificial kidney shown here. This machine was developed in Nazi occupied Holland, working under extremely difficult conditions and with very limited resources and materials. Of the first 15 patients fie treated, all except one died, and it was not clear whether dialysis had contributed to the recovery of this individual or riot Following World War II Kolff went to Boston where, working with John Merrill, he developed the Kolff-Brigham rotating drum kidney and subsequently, he moved to the Cleveland Clinic where he developed the twin coil dialyzer. In 1946, Murray, Delorman and Thomas developed an artificial kidney in Canada, which was successfully used for patients, and in 1947. Alwall in Sweden was developing his kidney, with which Dr. Acharya is much more familiar than I. In the late 40's, a number of kidneys were developed, including the MeNeil membrane kidney in 1948, and the Skeggs-Leonard plate kidney in the same year. After the war, Kolff gave a number of his machines to different centres around the world. One went to the Hammersmith Hospital in London, where a dialysis program was started by Watters and Joekes, another went to the Mount Sinai Hospital in New York, one went to the Royal Victoria Hospital in Montreal and another went to Professor Borst in Amsterdam, but was never used.

Another went extensively used because of lack of trained personnel. Haemodialysis remained a restricted and quasi-experimental of therapy until 1956 when the Kolff twin coil tank kidney was manufactured and sold commercially, along with the disposable twin coil dialyser and this was the type of machine with which I had my first experience of dialysis. The experience was not reassuring. The dialysis bath was prepared by adding pre-weighed, dried chemicals to a lank of 100 litres, which was filled with warm tap water and maintained at body temperature by a simple block heater. There was no sterility and, after an hour or two, the bath was teeming with micro-organisms. The twin coil was pre-assembled and sterilized, which was a big improvement from other techniques, which had to assemble the membrane layers, but it required a litre of blood to prime it and had a high compliance to pressure changes. It also necessitated a blood perfusion pump and a significant arteriovenous pressure differential across the membrane was developed, which resulted in an uncontrolled ultrafiltration. Access to the circulation was obtained by a cutdown on the radial artery and radial vein. In those days, our criteria for starting haemodialysis were severe hyperkalemia, profound acidosis, symptomatic uremia and a BUN > 200 mg.%. The St. Louis group had only treated a handful of patients before I arrived, and all had died. The first eight patients, with whom I was associated, also died and I vividly remember our first success. This was a 9-year old child who suffered from acute poststreptococcal glomerulonephritis, which had produced total anuria. She had become progressively uraemic and her potassium had risen to 9.6. We all agreed that the child was moribund and needed immediate dialysis if she was to survive. A paediatric surgeon cannulated the femoral vessels and we started dialysis. The ECG was displaying a sine wave pattern and I will

never forget the drama as the ORS interval narrowed and normalized, P waves appeared, the PR interval shortened and the peaked T's gradually returned to normal levels. The child recovered consciousness and subsequent to that, we decided we should dialyse her again in 48 hours. Happily her own kidneys recovered function and she survived to leave hospital.

Evolution of haemodialysis

Following this, we decided that our criteria for dialysis were too stringent, and that early or more frequent dialysis was necessary, a view which was rapidly evolving in all dialysis centres. Three years later, the mortality rate for acute renal failure had fallen to 50% of the patients who were treated by the artificial kidney, but we still had a lot to learn. We still dialysed too late and too infrequently to maintain the patients in a viable condition. There was a young, 28 year old naval technician, who used a fire extinguisher to clean marine engines. In the process, he was exposed to inhalation of large amounts of carbon tetrachloride. He presented to the emergency department at Barne's Hospital in 1959 and was found to be in both hepatic and renal failure. The hepatic disease was relatively mild, but the renal failure persisted. We treated him inadequately, by today's standards. So that he gradually deteriorated and died after 69 clays, from cardiovascular complications. You must realize, that at this time. We had difficulty in maintaining continued access to the circulation. The arteriovenous cannulas could only be kept operating for 1 or 2 dialyses, and it did not take long to use up all the accessible vessels. About this time, we started using saphenous vein access and kept the catheter in the femoral vein, by running an infusion through it, but the catheters were not designed for long-term cannulation and infection and thrombosis were frequent. It was not until 1961 that Scribrier reported the use of the permanent indwelling arteriovenous shunt and chronic haemodialysis became a realistic possibility

Peritoneal dialysis

At this point in time, haemodialysis was restricted to a limited number of major centres and was performed by a team of physicians whose main responsibilities were usually in other areas, it involved a formidable commitment in physician time and financial resources, so that it was not surprising that alternative, simpler forms of management had been sought. Professor Bull, in England, and Professor Borst in Holland, had been strong advocates of protein restriction and dietary management of acute renal, failure. In the 50's, there was considerable debate as to whether haemodialysis actually saved lives. Attempts had been made in the 40's to treat renal failure more simply by using peritoneal lavage. This therapy clearly removed urea and other toxins, but a continuous irrigation process was used and infection almost invariably resulted. Without the appropriate antibiotics, death ensued. The procedure had largely been abandoned until Maxwell and Kleeman re-explored it in the late 50's. They used a closed system, which reduced the risk of infection. The newer plastic catheters were more biocompatible, so that the omentum did not wrap around them and occlude the openings. Most importantly, by this time, we had reasonably effective antibiotics for managing peritonitis. Maxwell and Kleeman had just reported their experience with the technique when in 1959, we admitted a young man with, what we then called, rapidly progressive glomerulonephritis it was recognised that this was going to be a more prolonged illness than the usual acute tubular necrosis, and it was the institutional policy, at that time, not to consider any form of chronic haemodialysis. Someone suggested that we try this new peritoneal dialysis technique, in the hope that we could control the uraemia long enough to permit recovery (it renal function if it were going to occur. I called Cutter Laboratories, who made the peritoneal fluid, the same day, and they arranged for a special shipment of the necessary supplies to be flown in from California to St. Louis. I started the peritoneal dialysis that evening, with significant trepidation. Fortunate1y, we encountered no technical problems and the dialysis ran reasonably smoothly. We were of course, writing our own protocol as we proceeded, and had no one to call on for advice. I stayed up all night doing the exchanges myself and there was a continuous stream of curious physicians, interns, residents, students and nurses coming by to see this marvellous new way of treating renal failure. Peritoneal dialysis quickly became established as a simpler and less expensive alternative to haemodialysis, and in the early 60's, was considered the initial treatment of choice for the management of acute renal failure. It did, however, have limitations. Firstly, it was not feasible in many patients

alter abdominal surgery or in those with multiple abdominal adhesions. Secondly, it frequently tailed to work and we would run fluid into the belly and be unable to get it back. In such cases, there was no alternative except to proceed to haemodialysis, it that treatment was available. Thirdly, in some cases which were highly catabolic. It was not efficient enough to control the uraemic process, and it was not uncommon to treat a patient with both modalities. Finally, there was the problem of continued treatment. We generally found that, after 72 hours, the rate of infection increased rapidly, and the conventional practice was to dialyse peritoneally for 48-hours and then to remove the catheter and reinsert it when the uraemic state had deteriorated to toxic levels. This approach subsequently was applied to the management of more chronic cases, where the routine was to perform peritoneal dialysis for 24 to 48-hours, twice a week. By the mid-60's the treatment for acute renal failure was fairly well established and involved both peritoneal and haemodialysis but the latter was still a restricted form of treatment.

I went to Queen's University in 1961, and at that time, the nearest haemodialysis centre was in Toronto, 156 miles to our west. There was none in Ottawa, the Capital of the country, and the other nearest centre was Montreal, a 186 miles to the east. I was appointed as a Medical Research Council investigator and not as a nephrologist to establish a dialysis facility. That quickly changed however, because the incidence of renal failure has no respect for university job descriptions. I was asked frequently to see patients in renal failure and initially, I started by undertaking peritoneal dialysis and recommending transfer, of those needing haemodialysis, to Toronto. Finally. I was faced one day with a man, who had been severely injured in a truck accident, who was too ill to be moved, and who had a highly catabolic form of acute renal failure. There was a Kolff twin coil kidney in the basement of one of the hospitals in the city. This had been purchased three years earlier, when a young man had died from renal failure, and a charitable group had given the kidney to the hospital without recognizing that it required trained staff to operate it. It had resided in the basement, gathering dust, for the preceding two years, so we decided to resurrect it and try and treat this patient. The chief resident in surgery, who is now a prominent gynaecologist, and I, borrowed a hospital truck and drove across the city to pick up the machine. I spent the next hour or two calculating the necessary weights of the dry chemicals required to produce the appropriate dialysis bath, The pharmacist weighed out the ingredients in little paper bags for us. I can't remember what we used for access catheters, but finally we got everything ready to go, connected the patient and his blood pressure immediately became un-measurable, so we abandoned the procedure and he died shortly thereafter. That was the first haemodialysis attempted in Kingston in 1961. However, two weeks later, we had another patient, a young man of 21, who had skidded on an icy road and rolled his car into a ditch, where he had lain for six hours, He was in severe shock by the time of admission to hospital and had sustained multiple orthopaedic and abdominal injuries. Not surprisingly, he had developed acute tubular necrosis. Initially, we tried to control his renal failure by peritoneal dialysis, but his catabolism was too great and we instituted haemodialysis. His course followed the classical pattern described by Merrill, of an oliguric phase, followed by a subsequent polyuric phase.

We now realize that much of the polyuric phase, that Merrill described, was due to overloading of patients with fluid, during the period of oliguria. Following this, there was no going back, and Kingston now had the necessary mechanisms for treating acute renal failure, but the era of chronic dialysis was just about to start.

The access problem

In 1961, Scribrier reported his success in keeping patients with chronic renal failure alive and functioning by repeated haemodialysis. This achievement was made possible by the Teflon silastic shunt. Two teflon cannulae were inserted into an artery and vein and connected to silastic tubing which was brought out through the skin and joined externally forming a loop which was opened to connect the patient to the dialyser. Anybody who has had to look after these shunts will tell you how much they hated them. They got infected and 'they got blocked and de-clotting shunts was one of the major chores of the early nephrologists. Subsequently, Cimino and Brescia developed the Internal shunt by creating an arteriovenous fistula at the wrist. The fistula delivered a large quantity of blood into the veins, which became enlarged and arterial-

ized. By Inserting needles into the veins it was possible to get an adequate blood flow to provide effective dialysis. For short- term treatments, blood flows of 200/minute are about the minimum and many dialysis centres like to run their blood pumps at 400 ml/minute or more if the fistulas can deliver this rate of flow. Fistulas are now the preferred access for haemodialysis, but they also fail with time, usually because of stenosis at the venous ends. In our institution, we tend to use a large number of brachial fistulas because, in the older patients, the wrist vessels are often inadequate. The alternative to the fistula has been the plastic graft, and a large number of substances including umbilical veins, stripped saphenous veins and bovine arteries were initially used but now, almost universally, the standard graft is the gortex graft used by vascular surgeons. This has become a very frequently performed operation in the United States, but in our centre, we try and avoid grafts as much as possible and only do one or two a year. They usually last about six months, and have a much higher failure and complication rate than fistulas. Ultimately, over time, patients tend to run out of access sites, and when this occurs, we and others have had recourse to permanent, indwelling venous catheters, but like any permanent indwelling line that comes through the skin, there is a significant complication rate from infection, and such infections are usually Staphylococcal septicemia, some of which will be fatal. The maintenance of continued access is the single biggest problem in developing newer and more effective methods of dialysis.

The beginning of chronic dialysis

By the mid sixties the pressures for chronic dialysis were mounting but the resources were not readily available. We started our program by default when the chief of urology removed the remaining kidney from a 45-year-old man who had developed cancer in his second kidney after the first had been removed some years earlier. The transplant group in Montreal had agreed to accept him it he was tree of any malignant disease after 6 months, but needless to say, the cancer recurred before that and we ware not prepared to discontinue dialysis. Two years later we got approval from the Government to open a small 4 bed unit.

During this period we had a urology resident with an engineering background who was interested in dialysis and he and I redesigned the Kolff kidney to run with a continuous flow of dialysis fluid. The machine was produced and marketed by a small local engineering firm but was unable to compete with the major U.S. manufacturers. Our first prototype was produced for only $500.00 and used a milk pail as the dialysis bath. Dr. Ackman, the urology resident, also believed that the patient should be separated from the noise, heat and smell of the dialysis machinery and asked the hospital administration to drill a hole in the wall between two adjacent rooms to permit this. I do not know if you have the same problems in India, but in Canada administrators move very slowly. So one night, Dr. Ackman with my unofficial approval, took a hammer and chisel and cut a hole in the wall himself, This was our first chronic dialysis unit and the picture shows the dialysis machine which we designed and built for $500.00.

The feasibility of chronic dialysis raised enormous problems as to how the treatment was to be provided, who should get it and who should pay for it. It wasn't very long before social and societal pressures were forcing governments, in the west, to provide more and more funds for dialysis. Criteria were finally drawn up, as to who should receive dialysis and in those days, it was felt that it should be restricted to patients between the ages of 15 and 45, who had only renal disease with no significant comorbidity, and who could respond sufficiently well to treatment to be returned to the labour force. It was estimated in the United States and also in a survey which I did of our region, that the approximate incidence would be 33 patients/million in 'this category, and dialysis facilities were planned on that basis. Over the years, in North America, and to a varying extent in other countries, dialysis criteria have been progressively extended to a situation where, at the present time in Canada anybody who can benefit from dialysis, can receive it. This expansion in criteria for selection has resulted in a growth of new dialysis patients at approximately 10 to 12 % per year in Canada, and dialysis facilities go from crisis to crisis in trying to meet the demand.

Subsequent progress in dialysis

By the end of the 60's the basic principles of treatment for acute and chronic renal failure had been reasonably well established and the subsequent decades

have seen more a refinement in technique, an improvement in hardware and a better understanding of pathophysiology of renal failure, rather than any major new breakthroughs.

Various configurations of dialysis membranes were developed and ultimately the hollow fibre dialyser, which provides the maximum surface area for the minimum volume, has been almost universally accepted as the gold standard. There has been a great deal of development in membrane technology and we now have a wide choice of membranes with different permeabilities and better biocompatibility.

It has been increasingly recognized that the biocompatibility of the membranes is important, and amyloidosis has been reported, particularly by French workers, in patients who have been maintained on dialysis for more than seven years. This has been related to problems of biocompatibility, particular with cuprophane membranes. In the past decade, there has been increasing experimentation with high flux dialysis. The French have had the most long-term experience with this, initially using the Rhone-Poulenc polyacrylonitrile membrane, which was highly porous. Because of the high permeability of this membrane, it was necessary to have a pressure control on the outside of the membrane to prevent excessive ultrafiltration and, for this reason, high flux membranes had limited application until the hardware was more universally available. High flux dialysis was poorly tolerated using the standard acetate dialysis bath and this led to a return to the more complex and expensive bicarbonate bath, which we used in the early days. The Americans, particularly, have attempted to reduce dialysis time, using high flux dialysis, but it is now apparent that their survival statistics are worse than those in other countries, and the whole question of high flux dialysis is being re-examined,

Some workers in California and in France have advocated hemofiltration as an alternative to haemodialysis. In this process approximately 20 litres of plasma filtrate are removed three times weekly and replaced with a physiological solution approximating normal plasma in composition. The limitation of this treatment has been the high cost of the replacement fluid and I doubt that hemofiltration will replace dialysis to any extent in the near future, although it has some theoretical advantages.

Other workers have experimented with absorption. This was first undertaken by Yatzidis in Greece in 1964 and followed up by other workers. Passing blood through activated charcoal absorbed most uraemic toxins except urea but it was associated with a number of reactions, and activated the coagulation system and removed platelets. Coated charcoal proved superior and several companies now make charcoal haemoperfusion cartridges. These are of great value in certain forms of poisoning and will remove protein bound and lipid bound toxins which may not be accessible to removal by haemodialysis, These absorbing cartridges, however, are expensive and have not achieved widespread use as a chronic therapy. Absorption was also used in the Redy Kidney to purify the dialysis solution so that a complete treatment could be provided using only 2 litres of dialysis bath instead of the usual 120 litres for a four hour dialysis. Urea was removed by converting it to ammonia using the enzyme urease and then absorbing the ammonium on zirconium phosphate which acts as an ion exchange resin. This kidney was especially useful for home dialysis patients who wished to travel and where the water supply was unsatisfactory.

The third important area of progress has been in the hardware used to provide dialysis. There has been an increasing sophistication in the machinery with safety devices, pressure monitoring, haemoglobin detectors conductivity monitoring and the appropriate alarms and shut- off controls when abnormalities occur. The days when you walked around with a screwdriver and a hammer in your back pocket and the first treatment for a poorly functioning machine was a good kick have long been replaced by the age of electronic technicians.

Transplantation

Now, what about transplantation? I alluded earlier to the initial experiment of renal transplants in identical twins, performed in Boston in 1955. The first cadaver transplant was performed in 1959 by Professor Hamburger in Paris, and in 1976, when I was working at the Necker Hospital, I saw that patient, who was still doing well. There is no question that a successful transplant makes patients feel better and function better than chronic dialysis and in my opinion, is the preferred modality of treatment it it can be obtained. It was widely recognized from the beginning of what I will call the nephrological age, that a perfect renal transplant would

be a much better way of dealing with renal failure than permanent chronic dialysis. The pioneering basic work of Medawar followed by the clinical experiments of Hamburger in Paris. Merrill in Boston, and then the introduction of azathioprine by Calne in Cambridge, lead to effective transplantation.

My initial approach, as a nephrologist heading a renal unit, was that we should not embark on renal transplantation until it had moved from the research domain to standard practice. This became true somewhere in the mid-60's, and we performed our first renal cadaveric transplant in November 1968. One month prior to this, the Chairman of surgery had convened a group of all those, who might be interested in transplantation, and after several meetings, we had decided we were now ready to proceed when a suitable donor became available. Despite everybody's enthusiasm for the procedure, no one was Interested in doing much of the basic work, and I had to write the protocol for the whole procedure including the criteria for the diagnosis of brain death, and even for the surgical technique to be followed. Of course, I had the various experts in the field review the protocol, and correct it where necessary. Our first patient was a young woman who had suffered from membranous glomerulonephritis, with a severe nephrotic syndrome, and this had progressed to renal failure and she was being maintained on our haemodialysis program like many patients, she was doing badly for psychosocial reasons, her marriage was disintegrating and she was demonstrating suicidal tendencies. A patient was admitted following a motor vehicle accident, which had caused severe head injuries. These progressed to a state of irreversible coma and ultimately brain death.

Things did riot run as smoothly then as they do now. I stayed up for 48-hours working with the patient and checking on the donor, and ensuring that those looking after the donor were maintaining appropriate kidney function. Ultimately, patient was pronounced dead by the neurosurgeon and by another independent physician, and the procedure was started. I was in the operating room to perfuse the kidneys as they were harvested and you must remember that this was the first time for all of us and we had not gone and trained in a Centre that had established transplant procedures, although the surgeons had gone to see one or two done. The kidneys perfused beautifully and the vascular surgeons connected one in the right iliac fossa and I still remember the excitement when the clamps were removed and the white kidney became blue and then pink and shortly thereafter urine started dripping out the tree end of the unattached ureter. Fortunately, our first transplant was a success. It was done on the 28th of November, and the patient was home by Christmas. I remember on Christmas Eve driving by her house and leaving her a bottle of champagne. From that time, we have run a small transplant program in Kingston, but our results are comparable to those of other major centres in Canada and the United States. Today we can offer our patients an 80 to 85% chance of a one year survival with a first transplant from a cadaver kidney, but since we have being doing transplants for over 25 years, we are also seeing a return of patients from successful transplants to dialysis after progressive chronic rejection.

It is recognized that the median survival for renal transplants is about 7.5 years and the transplant immunologists feel that this can only be improved by closer matching. At the present time, closer matching involves national programs of tissue typing and organ sharing and have a great number of logistical problems connected with it. Cyclosporine therapy has permitted better short-term results and has lead to loss interest in close tissue matching, which was never as well achieved in North America as it was in Europe.

Future progress of haemodialysis

At this point in time, I believe we are close to the limits in dialysis technology. Not because the technology is limited, but because the human body is. Ideally, haemodialysis should be provided by a slow. Continuous process, mimicking the normal function of the kidneys, but this requires continuous access to the circulation, a problem, which has not yet been solved adequately. We will not improve dialysis by making bigger or faster dialysers. The limiting factor is the body's ability to equilibrate fluid from its multiple compartments. I believe that a tour hour dialysis is the minimum and is probably not adequate. The Seattle group demonstrated early on in the course at dialysis, that it was important to remove middle molecules and that these required a finite dialysis time. It should be recognized that every patient on dialysis is under-dialysed, and any improvements in technology should be directed

towards giving patients more dialysis rather than cutting dialysis time, as has been the practice in the United States, a practice which has lead to one of the worst modality rates in the western world.

The future of peritoneal dialysis

What about long-term peritoneal dialysis? As I mentioned earlier, periteneal dialysis was performed initially with intermittent catheterization and then in 1968, Terickhoff introduced a permanent indwelling catheter. This catheter had been preceded by other indwelling catheters, notably by Palmer in Canada and Pairrier's work. I don't think, has received adequate recognition. A Terickhoff silastic cathiates can be left in place almost indefinitely and pennitted continuous peritoneal dialysis. Prior to that, we had done peritoneat dialysis for 24 hours, in hospital, twice weekly. This is the so- called intermittent peritoneaol dialysis, which is still practised. I regret to say in certain parts of Canada. I believe it is a totally inappropriate form of treatment, because it results in gross under-dialysis and patients slowly deteriorate and die. It may be, alright as an expedient measure to carry a patient for a short period of time, but I do not believe it has any place in long-term management Continuous ambulatory peritoneal dialysis was reported in 1977 thy Popovich, Moncrief and Nolph and subsequently developed by Oreopoulos in Toronto, We put our first patient on CAPD in 1978, and she is still doing well.

The major problems with peritoneal dialysis are the frequency of peritonitis and maintenance of adequate nutrition. In some patients, the peritoneal membranes progressively fail and the process has to be abandoned. Such failure is usually related to repeated bouts of peritonitis. The most important thing for good results, with peritoneal dialysis, is the ability of the patients to comply with the treatment. They must be sufficiently intelligent and motivated to learn the process and carry it out meticulously and they must have a basic minimum of social amenities in their home, such as running water.

It may surprise some of you in the audience to know that, 25 miles north of where I live, we have many individuals living in severe degrees of poverty, who lack these amenities, and we also have a significant number of patients on peritoneal dialysis in Arctic communities where such amenities are difficult to obtain. Not every patient is a candidate for peritoneal dialysis, but for those who can handle it, it often works better than long-term haemodialysis.

Current status of North American ESRD management

So what is the situation concerning dialysis and transplantation today? I speak only from my experience in North America. The standard approach is to try and transplant all young people and get them back into the work force and leading a relatively normal life. We have a growing population who cannot be transplanted, either because they have failed transplantation, or because they have a high co-morbidity, and in our institution we tend to limit transplants to patients younger than 60, although we do not have specific age criteria. It just happens that patients, as they get older, have increasing co-morbidities, which reduce the chance of successful transplantation.

The younger dialysis patients, who are motivated, can usually return to work, but unfortunately, in our country, there is very high unemployment and it is difficult to find work for someone who is labelled as having a disability. The patient's well-being and ability to live a more normal life has been greatly improved by the development of erythropoietin, which now enables us to achieve a haemoglobin of >100 grams/litre in almost everybody. Unfortunately, erythropoietin is extremely expensive and may not be available in all parts of the world, to people who would benefit from it. It is even questionable in Canada whether the government will continue to support erythropoietin at its current level of use.

Dr. Acharya asked me to say a few words about what I saw for the future of nephrology, and so I have taken my crystal ball and turned it in multiple directions. Over ten years ago, I sat on a panel discussing this same question and we talked about Dr. Kolff's vision of portable artificial kidneys. I think these are unlikely to have much success. The limiting problem for dialysis in the future will be the establishment of some form of satisfactory, permanent blood access, and I do not see an immediate solution to this problem. Undoubtedly, there will be developments in membrane technology and chemistry, out of these have already surpassed the knowledge of the clinicians. When a membrane chemist says to us today- "what kind of a

membrane do you want me to make for you?": as doctors, we are not able to provide her with the appropriate answer. Perhaps we will go to some form of sandwich kidney, composed of different membranes to remove different solutes and perhaps such a kidney might even include some absorbent material such as activated charcoal. But one of the limiting factors for such developments will be the cost of making it available to a large population. I think that there is a possibility that hemofiltration may ultimately supersede dialysis. It does, however, require access to expensive replacement fluid, but it might be possible to regenerate the ultrafiltrate by dialysis and absorption and return it to the patient. Whether this would be a significant advantage over current therapy, is highly debatable. I believe the physiological restrictions imposed by the human body's ability to adapt, have to a large extent, already set the limits as to how far we can go with haemodialysis techniques, and that what is needed is the provision of this treatment more widely and less expensively than is possible at present.

With respect to peritoneal dialysis, I think there is more room for improvement in technique and methodology. Better forms of indwelling catheters are, still possible, and Dr. Kolff suggested the implantation of a plastic reservoir below the skin having access to the peritoneal cavity. I am not aware that a practical version of this has yet been developed. Replacement solutions for peritoneal dialysis still have a long way to go. The current solutions are highly acidic and may lead to membrane failure. Nutritional balance is a problem in all forms of dialysis, which result in loss of amino acids and is an even greater problem in peritoneal dialysis, where protein is removed as well. Work is currently underway, in my own institution and elsewhere, on alternative dialysis solutions containing amino acids or other substances. I believe that machines for conducting overnight dialysis will continue to improve in reliability and price, but we will always be limited by the intrinsic, anatomical and physiologic character of the peritoneal membrane.

The future of transplantation, I think, is better than that of dialysis, because I believe the immunologists will find better ways of developing organ specific tolerance. It may even be possible to modify the gene structure of an animal, such as the pig, to allow effective xenografts. Should this become a reality, the major problem of transplantation will have been solved i.e. the lack of a sufficient supply of cadaver organs. Unless we can get a source other than human kidneys, transplantation will remain limited by the supply of donors, no matter how well we can induce graft tolerance.

Finally, we must not expect too much of dialysis and transplantation. We have lived through a dramatic period of development in this field over the last three decades. But, dialysis and transplantation, cannot reverse the aging process, they cannot treat sepsis, atherosclerotilc arteries, dementia and cardiogenic failure. They are treatments for a pathologic process that would be better prevented, just as respirators were a treatment for polio, which has been almost eliminated by the use of polio vaccine, and I think we should be looking more to the causes of renal disease, than to its treatment. Malaria is still one of the commonest causes of renal failure, although not in, my country. The mechanisms for glomerulonephritis are still poorly understood, and perhaps early intervention in patients with - glomerulopathies could reduce the instance of renal failure. One-third of our dialysis patients suffer from diabetes, and I believe there is room for major improvement in the management and possibly even the prevention of this disease.

Hypertensive arteriosclerotic vascular disease causes a significant amount of renal failure, requiring dialysis. Much of this is preventable by good management of hypertension and healthier lifestyles, at least In the western world, and particularly, the avoidance of cigarette smoking, which I believe has a very inimicable effect on renal vasculature; better forms of screening of surgically correctible disease, particularly in children, better treatment of acute and chronic urinary infections and stone disease. All of these are more achievable, in my opinion, than dramatic improvements in our current methods of handling the problem of end-stage renal disease. I believe we have moved from the exploratory and pioneering era in the field of nephrology, to an era requiring administrative and economic skills to make the benefits, which have been discovered, available to as many as possible.