

Technological advances in renal care

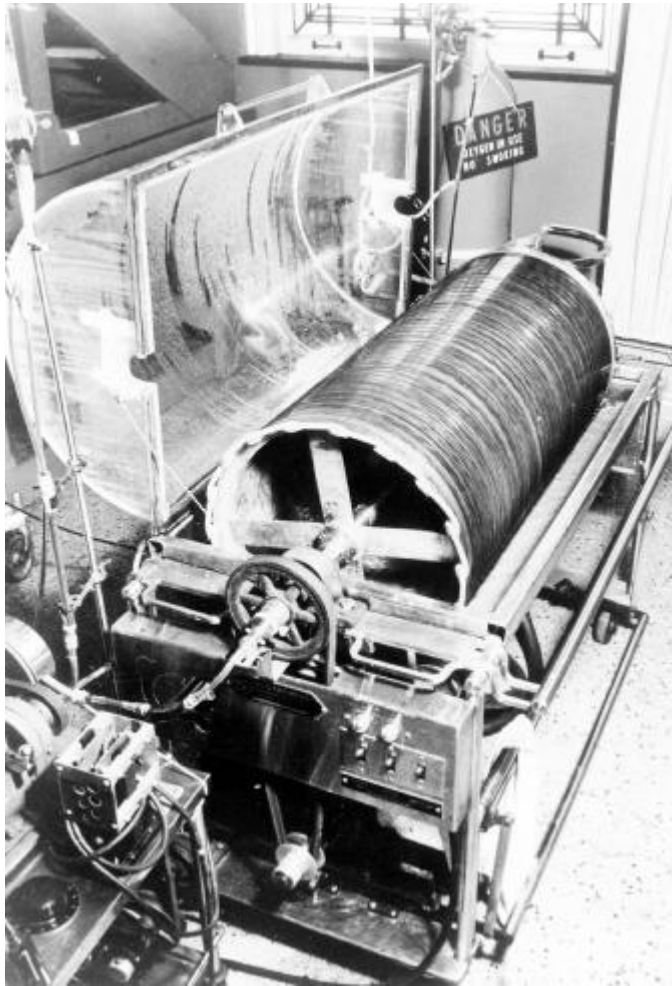
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Introduction: A brief history of renal replacement therapy

The human kidneys have several important functions. The best-known task of the kidney is regulation of the volume and composition of body fluids. Metabolic waste products and excess water and salts are filtered from the blood and excreted as urine by highly specialised functional units called nephrons. In addition to this regulatory process, the kidneys play an important role in the production of hormones involved in the control of blood pressure, production of red cells, and the uptake of calcium and phosphate needed for healthy bones.

Kidney failure, which may be acute (reversible) or chronic (irreversible), arises from a variety of disease states. Before the 1940's there was no effective treatment for kidney failure. In 1926, the German physician, Georg Haas (1886-1971) produced a clinical system for blood purification based on the physical principles of diffusion first described by Adolph Fick (1829-1901) and Thomas Graham (1805-1869). Dr Haas used hirudin derived from leeches to stop the blood clotting in his system, and collodion membranes. Unfortunately, none of his patients survived and almost two decades passed before Willem Kolff in the Netherlands developed the first successful haemodialysis machine, while working under the Nazi occupation. Blood was taken from an artery using a glass cannula and passed through a semi-permeable cellulose tube (actually artificial sausage skin) wound round a wooden drum. The drum was immersed in a bath containing a solution of electrolytes. Small molecules, such as urea, present in the blood as a consequence of protein breakdown passed easily through the cellulose membrane into the electrolyte solution but cells and protein were retained. The purified blood was returned to a vein.

In 1945, after 16 failures, Kolff succeeded in saving the life of 67-year-old Sofia Schafstadt. Toxins from a diseased gall bladder had caused Mrs Schafstadt's kidneys to fail, but after 12 hours of dialysis she started to produce urine again and made a full recovery. Kolff's dialysis machines were shipped to hospitals in Europe and North America. Devices based on his early designs saved the lives of many patients with acute, reversible renal failure over the next two decades. The UK's first acute dialysis centre was established in Leeds by Dr Frank Parsons in 1956.

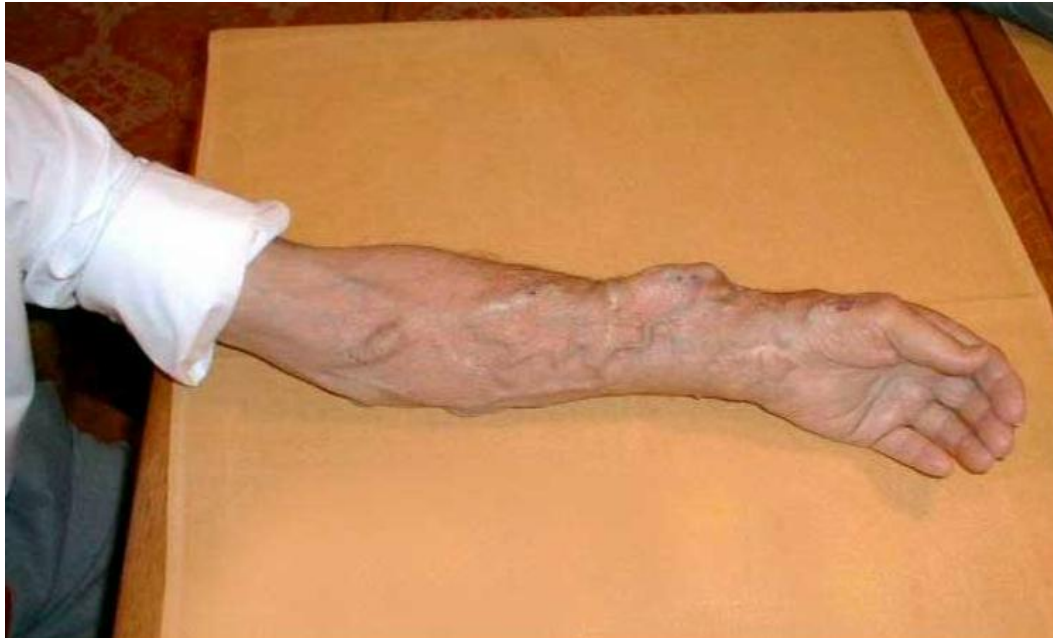


Willem Kolff's rotating drum dialysis machine

After these early procedures, the artery used had to be tied off to prevent haemorrhage. The loss of the arteries meant that haemodialysis could not be used to treat patients with chronic renal failure until 1960, when Belding Scribner and Wayne Quinton in Seattle, USA, devised a method for connecting an artery to a vein using a U-shaped Teflon tube or 'shunt'. The connections provided access to the blood for each dialysis session. The designers choose to make the shunt from Teflon because it would not react with human tissues. It was good fortune that Teflon's non-stick properties prevented the blood from clotting inside the shunt. Boeing machinist Clyde Shields, lived on haemodialysis for 11 years after becoming the first long-term dialysis patient to be fitted with Scribner's device.

Scribner's shunts were easily infected, but they made the treatment of chronic renal failure viable, albeit for a small and highly selected group of patients. A few years later, Michael Brescia and James Cimino were working in the Bronx treating Vietnam War veterans with kidney failure resulting from their war injuries. In 1966, they published a paper describing a

technique for forming an internal “arteriovenous fistula” by joining an artery in the arm directly to a vein. The vein swells under the abnormally high pressure and can be punctured repeatedly, while the overlying skin provides a natural barrier to infection. If used with care, a fistula can provide vascular access for 20 years or more (figure 2), and today it is still the first choice for vascular access.



This fistula between the radial artery and cephalic vein was created by Dr Stanley Shaldon in January 1970. The patient, who punctures the fistula himself, has been using it continuously for 32 years and is dialysing four times a week. The photo is reproduced from Dr Shaldon’s lecture “40 years of encounter with dialysis” for the 46th Annual Meeting of Japanese Society for Dialysis Therapy, which includes a fascinating history of the development of home haemodialysis in the UK. (www.mybesthealth.com/shaldon, August 2002).

The arteriovenous (AV) fistula, together with the introduction of smaller and more efficient dialysers and machines that could mix the dialysis fluid on demand and monitor the dialysis process, allowed home haemodialysis to become a well established therapy in the UK in the early 1970’s.

By 1980, the number of patients starting renal replacement therapy each year in the UK increased to around 30 per million population. An increasing number of these patients were treated with an alternative form of dialysis called ‘peritoneal dialysis’ (PD). In PD, the peritoneal cavity is filled with a solution of electrolytes and glucose. Small molecules in the blood vessels adjacent to the cavity can pass through the peritoneal membrane into the

solution. The glucose provides the osmotic pressure required to remove excess water from the blood. PD had been used to treat acute renal failure since 1946, but it was not until 1976 that Jack Moncrief and Bob Popovich from Austin, Texas described a technique for long-term treatment which involved manually draining and refilling the peritoneal cavity several times each day using a specially designed catheter inserted through the abdomen. This technique of “continuous ambulatory peritoneal dialysis” (CAPD) was originally devised to help a haemodialysis patient who had run out of blood vessels for vascular access to survive until a transplant was possible, but it is now the treatment of choice for many dialysis patients. Automated PD (APD), in which a machine carries out the fluid exchanges while the patient sleeps, was introduced some years later.

Dialysis does not replace all of the functions of the kidney. The early dialysis patients all suffered from anaemia, which was treated using blood transfusions until the development of genetically engineered human erythropoietin (EPO) in the 1980's. Recombinant DNA technology enabled human genetic material to be spliced into Chinese hamster ovary cells so that the cells secrete EPO that is virtually identical to the red cell growth stimulating hormone normally produced by the human kidneys. Renal bone disease, another common complication for patients on dialysis, is caused by the failure of the kidneys to produce the activated vitamin D that promotes absorption of calcium from the gut and the inability of the dialysis process to remove unwanted phosphate from the body. This can be partially resolved by the use of the activated vitamin D supplements (calcitriol and alfacalcidol) introduced in the 1970's, and phosphate-binding drugs to reduce the amount of phosphate absorbed from the gut. The newly developed vitamin D analogues and calcimimetic drugs may improve the treatment of bone disease.

The ideal method of replacing all the functions of the human kidney is by transplantation of a functioning kidney. The first successful kidney transplant operation between identical twins was performed in Boston In 1954. Eight years later, the same group carried out the first cadaveric transplant. The newly developed drug, azathiaprime, was used to prevent rejection. The other half of the first batch of this new drug was sent to Edinburgh and used to treat a young man who had received a kidney from his father. The kidney worked for over 20 years. Cyclosporin, licensed in 1983, significantly reduced early rejection rates but it is toxic to the kidney in the long term. The immunosuppressive drugs required to prevent the body rejecting the transplanted kidney have many side effects (including weight gain, excessive hair growth,

gum disease and mood swings) but transplantation has many benefits and is regarded as the best treatment for most patients with renal failure by patients and society.

In the UK today, approximately 30,000 people are kept alive by renal replacement therapy (RRT). About 47% have a functioning transplant, 36% are treated with haemodialysis and 17% with peritoneal dialysis. The UK Renal Registry reports on patient numbers on an annual basis¹. Their data indicates that the number of patients on RRT is increasing by approximately 5% each year.

This paper reviews some of the recent technological advances that aim to improve the quality of life and life expectancy for patients with end-stage renal failure.

Advances in haemodialysis

The development of the AV fistula was probably the most significant advance in haemodialysis. Almost 40 years later, it is still considered to be the gold standard for vascular access, despite the obvious disadvantage that it must be punctured using two large bore needles at every treatment session. However today many patients receiving treatment, especially are elderly, have poor vasculature and coexisting diseases that make their blood vessels unsuitable for creating a fistula.

The most frequently used alternative to the AV fistula is the Goretex graft, mainly due to the widespread use of these devices in the USA. Grafts made from other synthetic and biological materials have been tried but have not become popular. A graft is used to bridge the space between an artery and a vein and can be punctured with the same needles that are used for fistulas. Unfortunately grafts have a very high complication rate and usually require invention within a year. When there are no suitable peripheral vessels, and when surgical resources are limited, semi-permanent central venous catheters are introduced into the jugular or subclavian veins. Like graft, catheters have a high complication rate, mainly due to infection and thrombosis. Recent advances in vascular access technology have been focussed on finding innovative alternatives to grafts and catheters.

Two such alternatives are subcutaneously, implanted devices with valves just under the skin and tubes leading into the right atrium². Access to the patient's circulation is achieved by puncturing the skin using a needle designed to open the valve in the device below. The risk of

infection is minimised by using a germicidal solution to fill the valve and tube between treatments. Patients using these devices can bathe and swim as normal.

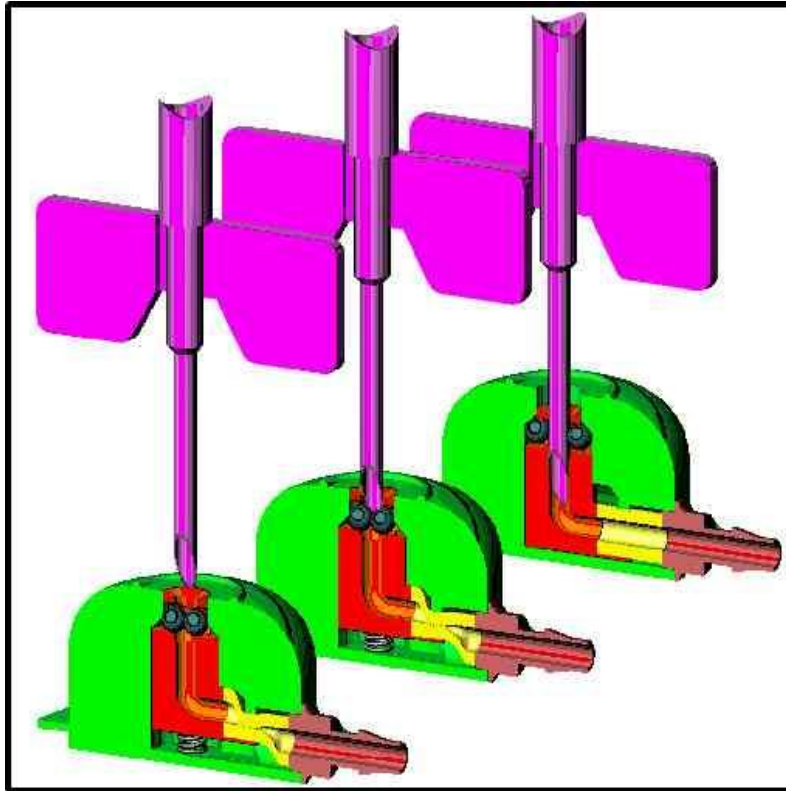


The dual-valve Dialock vascular access device showing the catheters that direct the blood from the right atrium to the dialysis machine and back to the right atrium

Although it is normally placed in the upper chest, at least 12 patients have had the dual-valve “Dialock” device implanted in the thigh so that the tubes could be passed through the femoral vein into the lower vena cava. In these patients, all of the normal vascular access locations in the upper body were exhausted but the subcutaneous access enabled them to continue dialysis³. The “LifeSite” device is implanted in pairs for haemodialysis, but a single valve is also undergoing trials for use as an alternative to the standard peritoneal dialysis catheter. It is more discreet than a catheter, and may be less prone to infection. Initial results from St Helier Hospital in Surrey have shown that patients find the “LifeSite” easy to use and that the ‘buttonhole’ tract that forms after repeated needling makes the procedure virtually painless. All the patients in the trial have shown a strong preference for the implanted device over the external catheters that are normally used.



The LifeSite vascular access device. Two devices are implanted for haemodialysis.



Internal structure of the LifeSite device showing the repositioning of the blood pathway when the needle is inserted.

As renal replacement therapy can be undertaken in the patient's home as well as in hospital, the safety of the process is paramount. All modern dialysis machines are fitted with protective systems that ensure that the patient is not harmed during the process from technical problems such as excessive loss of blood, the accidental ingress of air into the extracorporeal circuit, or treatment with a dialysis fluid that is at the wrong concentration or temperature.

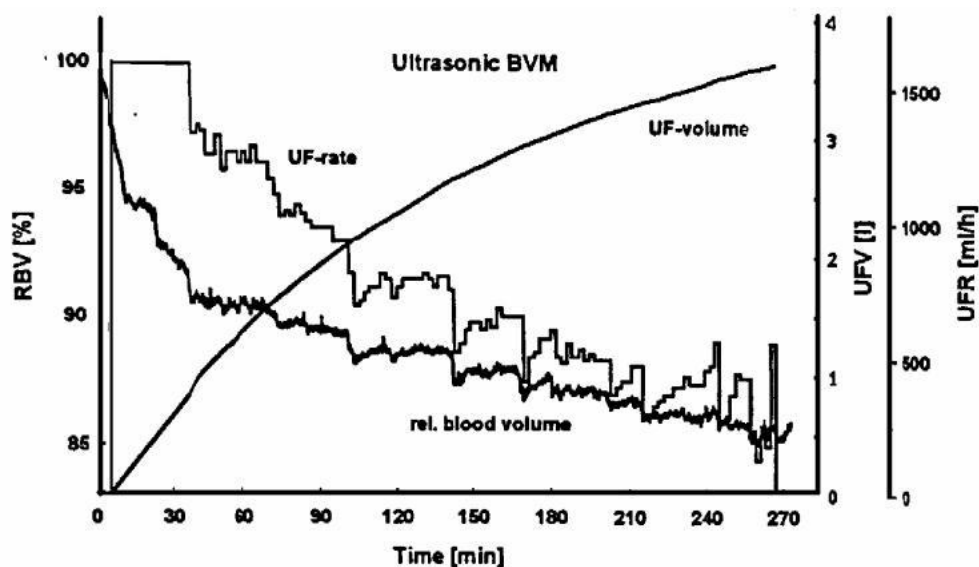
Unfortunately, these mandatory protective systems do not prevent the patient from the unpleasant side-effects of dialysis.

The most common intradialytic complications are dizziness, nausea, vomiting and cramps secondary to a fall in blood pressure during treatment. Factors involved in hypotension during dialysis include hypovolaemia (reduction of the blood volume) and heat retention due to vasoconstriction occurring as compensation to hypovolaemia⁴. Heat retention can be alleviated by manual or automated reduction of the dialysis fluid temperature. Hypovolaemia is caused by removing too much fluid or by removing the correct amount of fluid too quickly. The amount of fluid to be removed at each session is based on an estimation of the patient's ideal (or "dry") weight. If the dry weight is too low, the patient will be dehydrated during the

dialysis session. Advances in bioimpedance spectroscopy (BIS)⁵ may help staff to assess the dry weight more accurately.

Hypovolaemia usually occurs because fluid is removed from the patient too quickly. The excess fluid is distributed throughout the body, but the machine can only remove fluid from the blood. The movement of fluid into the blood (“refilling”) is controlled by many factors and the refilling rate is very variable. If a patient is refilling too slowly, their blood volume will decrease and eventually their blood pressure will drop too.

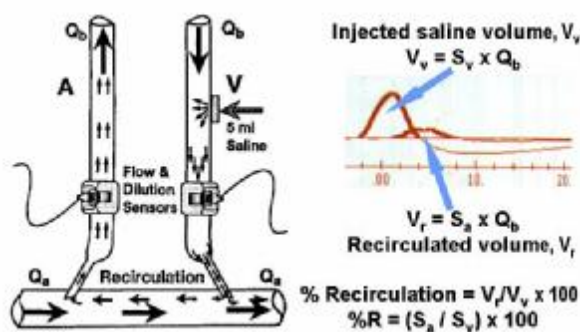
The latest generation of machines also feature sensors to monitor the patient’s refilling rate and software to adapt the fluid removal (“ultrafiltration”) rate accordingly^{6,7}. The sensors, which are positioned on the arterial bloodline between the patient and the dialyser, measure the concentration of red cells or protein in the blood using optical or ultrasound transmission respectively. As the blood volume decreases, the concentration of red cells and protein increases. If the sensor indicates that the volume is decreasing too quickly, the dialysis machine can temporarily reduce the ultrafiltration rate (UFR). Feedback systems that respond to changes in blood pressure have also been developed⁸. Currently, these biofeedback systems start with a high UFR because it is normally easier to remove fluid at the beginning of the session. A combination of rules is used to adjust the UFR based on the patient’s response (figure 6). In future, the machine may be able to remember the refilling characteristics of individual patients and customise the treatment.



Automated modification of a linearly decreasing ultrafiltration rate based on feedback from an ultrasonic blood volume monitor (Fresenius AG).

The technology used to monitor changes in blood volume in the lines to the dialysis machine can also be used to monitor the performance of the patient's vascular access. Recirculation is the mixing of blood that has already been dialysed with the fresh blood entering the dialyser, leading to a reduction of treatment efficiency. There are two types of recirculation, access recirculation and cardiopulmonary recirculation. Cardiopulmonary recirculation is inevitable when a fistula or graft is used for vascular access. It occurs because some of the newly dialysed blood, which returns directly to the heart without equilibrating in the capillary beds, is channelled straight back to the vascular access in the arm and dialysed again. Access recirculation occurs if the dialysis machine is pumping blood to the dialyser faster than the flow of fresh blood from the heart into the AV fistula or graft. When this situation arises, some of the blood returning from the machine through the venous needle is drawn back through the access and into the arterial needle.

Access recirculation can be measured by simply injecting a bolus of saline into the venous bloodline. In the presence of recirculation, a proportion of the bolus will appear moments later in the arterial line. This proportion can be measured using optical or ultrasonic sensors and used to quantify the recirculation^{9, 10}. Similar technology, with a slightly more complex procedure, can be used to measure the actual flow of blood through the access¹¹. A reduction in the blood flow, particularly in AV grafts, may indicate the presence of stenosis before it is too late to prevent the access from clotting.

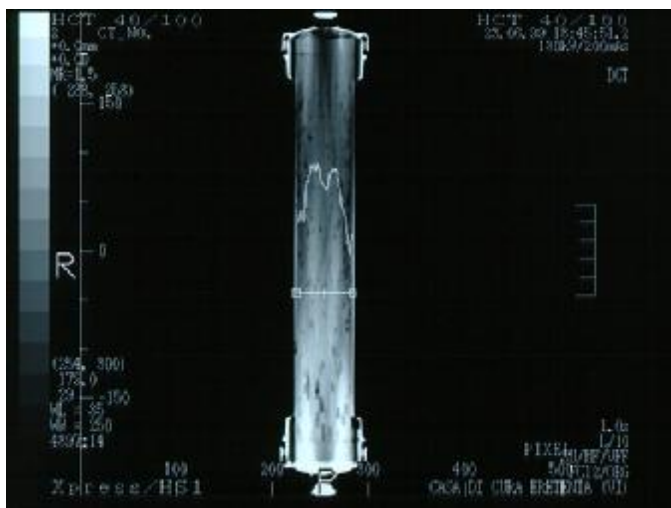
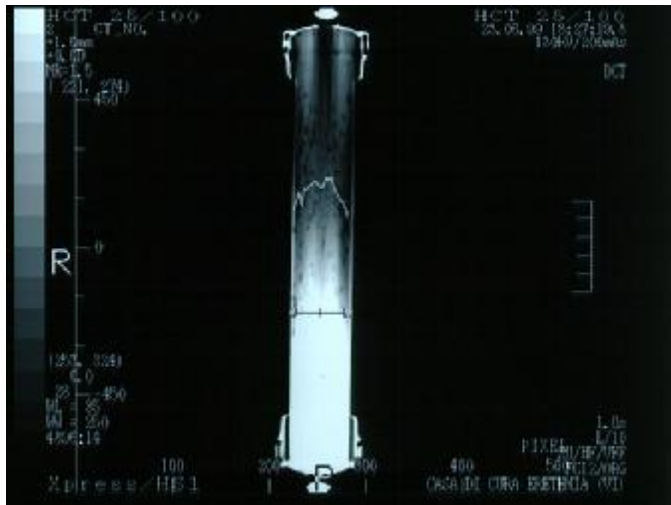


Access recirculation occurs when the blood flow to the machine (Q_b) exceeds the flow of blood into the access (Q_a). The blood pump then draws some of the dialysed blood back to the arterial bloodline. The proportion of blood that has been recirculated is measured by comparing the signals from the dilution sensors after injecting a bolus of saline into the venous line.

One aspect of dialysis technology has advanced continually ever since Dr Kolff's first successful treatment. The membrane material and the geometric configuration of the dialyser

(the artificial kidney) has improved dramatically and is still the subject of many research programmes. Conventional haemodialysers, just like Kolff's rotating drum, are simply mass exchangers in which the blood flows on one side of a semi-permeable membrane with a freshly produced electrolyte solution (the dialysis fluid) on the other side. Early developments, aimed at improving the consistency of performance, led to mass-produced devices in which the membrane is in the form of hollow fibres bundled into a cylindrical tube. Today the aim is to achieve the highest efficiency of solute removal for a given membrane surface area by optimising the geometry of the device and minimising the overall mass transfer resistance. Developers can exploit many of the concepts of heat and mass transfer but whereas heat exchangers have tubular, regularly spaced arrays, allowing interactions between adjacent tubes at high packing densities to be taken into consideration, the fibres bundled into a dialyser are more randomly distributed. Uneven flow and incomplete utilisation of the fibre bundle will reduce dialysis efficiency.

To ensure that the flow distribution is optimal, variations in blood and dialysis fluid flow in the dialyser must be quantified. This can be done by looking at the transit time distribution following the infusion of a non-dialyzable marker, or by the computerised helical scanning technique such as developed by Ronco et al¹². This technique has already shown that, at the high red cell concentrations associated with use of EPO to correct anaemia (and the reduction in blood volume that occurs during treatment), the blood flow rate through the fibres in the centre of the dialyser is much higher than in the peripheral regions¹³. The dialysis fluid tends to have the opposite distribution, with the highest flow in the peripheral space. As a result of this mismatched flow distribution, the concentration of solutes removed from the blood will build up rapidly in the dialysis fluid in the central part of the dialyser, reducing the rate of diffusion. The achievement of a more homogeneous flow distribution in the dialysate pathway has been achieved by using of spacer yarns to separate the fibres or by the use of wave patterned (Moiré structured) hollow fibres, which improve the fibre spacing within the device¹⁴.



Flow distribution and relative velocity in a cross sectional segment at haematocrits of 25% and 40% [Illustration courtesy of Claudio Ronco MD]

During the dialysis process, waste products arising from metabolism and fluid build up between treatments are removed and electrolyte and acid base abnormalities are corrected. Current technology allows small molecular weight solutes, such as urea, to be removed very efficiently, but our understanding of uraemia is developing and has identified a range of compounds with adverse effects that are not easily removed by conventional dialysis. These compounds, which include leptin (an appetite suppressant), β_2 -microglobulin (see below), inflammatory mediators (cytokines, C-reactive protein), advanced glycated end products and advanced lipid peroxidation compounds, contribute to the morbidity and long term complications associated with treatment by dialysis. Two approaches to improving the removal of these large molecules: convection and adsorption have been used.

Convective therapies, in which large quantities of water (often 20 litres or more) are pulled across the dialyser membrane under pressure, are not new. The advantage of these therapies is that larger toxins are transported across the membrane with the water. The disadvantage is that the patient must be rehydrated with a sterile, non-pyrogenic electrolyte solution at a rate that matches the fluid removal. In the past, this solution was purchased in sterile bags and was very expensive. Advances in fluid monitoring and the use of 'cold filtration' (in which the water and dialysis fluid are passed through two or three ultrafilters to produce sterile infusion fluid) have made 'on-line' convective therapies a viable treatment option for dialysis units¹⁵.

The second approach is to pass the blood through a sorbent cartridge. Sorbents have been used widely in the treatment of drug overdoses and poisoning (e.g. pesticides or toxic plants), and for the regeneration of dialysis fluid¹⁶. They have also been used for the elimination of circulating cytokines arising from sepsis in the blood of patients with acute renal failure^{17, 18}. The sorbents used were originally uncoated activated carbons, but this was associated with the release of micro particles (fines). Modern sorbents are coated carbons, ion exchange resins or non-ionic macroporous resins with a high surface porosity providing a large area available for absorbing toxins.

In chronic renal failure the development of sorbents has focused upon the removal of β_2 -microglobulin (β_2 M), a 12kD molecule produced during normal cellular turnover in the body. Production of β_2 M increases during inflammation since cells responsible for generation of β_2 M are involved in the body's immune defence against pathogens. β_2 M levels are normally controlled by the kidney and, as this molecule cannot be removed during conventional dialysis, the levels are elevated in dialysis patients. Non-enzymatic reactions with glucose in the body results in the formation of glycosylated β_2 M which is the main component of the amyloid fibrils associated with dialysis related amyloidosis. This complication of dialysis therapy leads to carpal tunnel syndrome and the generalised joint stiffness and pain. The use of biocompatible membranes and ultrapure dialysis fluid can decrease production of β_2 M by reducing the inflammatory response^{19, 20} but to date it has not been possible to normalise β_2 M levels in dialysis patients. Membranes with larger pores can remove β_2 M, but in practice the amount removed during dialysis is less than the amount produced between sessions. Augmentation of the removal by dialysis can be achieved using sorbents with a high affinity to β_2 M. Currently two types of material are undergoing clinical study; the first is manufactured from hydrated cross-linked polystyrene divinylbenzene resin²¹ the other is a

resin manufactured from cellulose to which ligands trapping β_2M are attached²². If these trials are successful, their incorporation into dialysis practice is likely as sorbent filters packed with resin beads can simply be inserted into the blood circuit after the dialyser, however their cost may limit use to patients at risk.

Sorbents are just one area where advances in materials science may have an impact on the process of dialysis. In haemodialysis and related therapies, the blood is exposed to foreign materials contained within the extracorporeal circuit and the dialyser. Contact with these materials activates a range of responses including the immune pathway and the coagulation pathways. This repeated activation has been extensively studied with a view to developing more biocompatible materials. Recently, concern has been raised over repeated exposure to polyvinylchloride (PVC) containing plasticisers²³. PVC is the material normally used to form the extracorporeal circuit. The replacement of PVC has begun, but alternatives remain more costly.

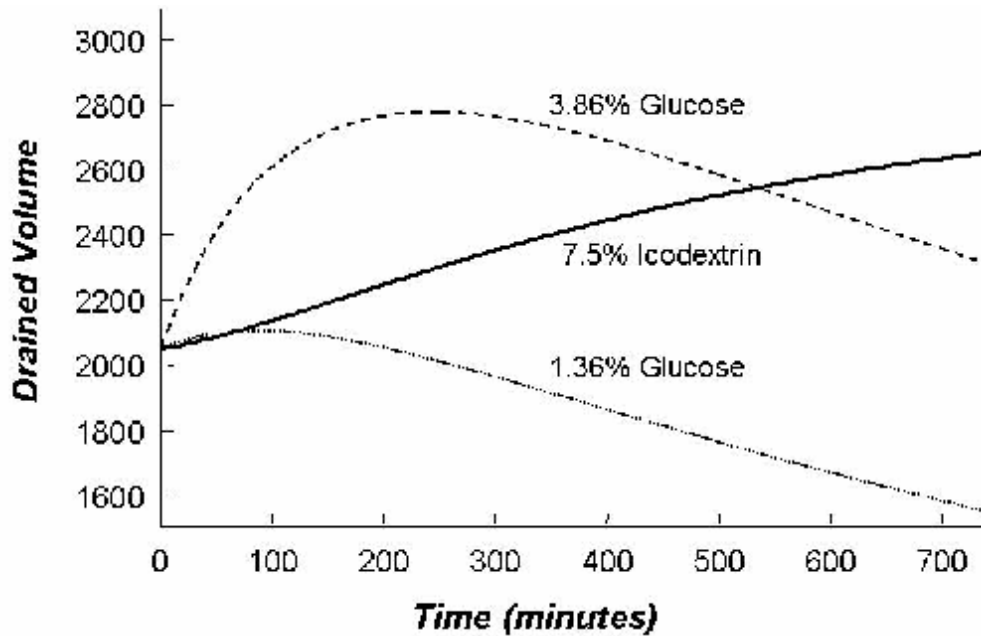
Dialysis makes extensive use of sterile, single-use products that are discarded following each treatment. The disposal of these products provides another reason for looking carefully at the materials used in the dialysis process. Since many of the items used contain blood residues they are classified as clinical waste for which disposal is via licensed contractors using incineration. It is known that the incineration of PVC contributes to the environmental load of highly toxic polychlorinated dibenzoparadioxins and dibenzofurans. A single dialysis procedure generates around 2.5 kg of clinical waste of which around 40% is plastic, mainly PVC. Thus, a renal unit treating one hundred haemodialysis patients produces 39 tonnes (39,000kg) of waste that has to be incinerated each year. Patients receiving standard CAPD treatment (four exchanges a day) generate 617 kg of clinical waste each year of which about 350 kg is plastic. To place these figures in context, the annual amount of domestic waste generated per family in Newcastle upon Tyne during 1997 was 975 kg of which plastic constituted 58 kg. The disposal of the huge quantities of clinical waste generated by dialysis has considerable cost implications, which have not been fully addressed to date. New technology for rendering clinical waste sterile, and safe for disposal via landfill sites, by granulation and sterilization is under investigation.

Advances in peritoneal dialysis

The efficiency of peritoneal dialysis depends on the volume of fluid infused into the peritoneum at each exchange, the timing of the fluid exchanges and the solute transport properties of the patient's peritoneum. Various techniques have been developed to monitor the function of the peritoneum, which can change with time, particularly if the patient suffers from bouts of inflammation of the peritoneal membrane (peritonitis). For each patient, an ideal regime can be devised and the latest equipment is designed to help the patients implement more complicated patterns of exchanges if necessary. The "Quantum" system allows patients to supplement their manual CAPD exchanges with an additional automated exchange during the night. Most APD systems now have programmes that accommodate an extra exchange in the afternoon or evening to supplement the overnight exchanges.

A more radical approach to increasing efficiency has recently been described. In "continuous flow" peritoneal dialysis, two catheters or a double lumen catheter are placed in the peritoneal cavity allowing simultaneous infusion and drainage of the fluid²⁴. The patient would require dialysis times comparable to overnight APD and the dialysis fluid would have to be produced 'on-line' to make the treatment cost-effective but has the potential to offer solute removal superior to three times weekly haemodialysis²⁵.

In contrast to haemodialysis, fluid removal from patients receiving peritoneal dialysis is achieved by osmosis. Traditionally, the osmotic agent used in PD fluid has been glucose. Glucose and lactate, the buffer normally used in PD fluid, are both known to be bioincompatible and to have a detrimental effect on peritoneal membrane function²⁶, limiting the long-term viability of peritoneal dialysis. Prolonged patient exposure to glucose not only influences peritoneal membrane function, but also leads to difficulty in the control of blood glucose in diabetic patients. Glucose absorption can lead to weight gain, which is often coupled with protein malnutrition, in both diabetic and non-diabetic patients. Alternatives to glucose as an osmotic agent have been developed and one (icodextrin) is now commercially available. Icodextrin a high molecular weight, glucose polymer derived from starch that is capable of providing the osmotic force required to sustained fluid removal over prolonged periods (12-16 hour) and has fewer side effects than glucose^{27, 28}.



Calculated fluid removed during a 12 hour dwell with standard glucose solutions and icodextrin (reproduced from Rippe and Levin²⁹)

The ideal buffer to restore the acid-base balance in the body is bicarbonate. In practice, lactate has been used because (unlike bicarbonate) it does not cause precipitation of calcium and magnesium salts in the fluid bags during storage. Modification to the packaging of the fluid, providing a bag with two chambers that can be mixed immediately before use, means that bicarbonate can now be used³⁰. Bags with two chambers also allow the glucose to be kept at a low pH when the bag is autoclaved. This dramatically reduces the harmful glucose degradation products present in the solution³¹. A third compartment can be added to provide the option of a low or high glucose solution in the same bag. So far, UK renal units have limited experience with these new solutions and the evidence to show that their use preserves peritoneal transport are not yet available.

Advances in transplantation

Until it becomes possible to grow organs that will not trigger the immune response of the recipient, the great majority of kidney transplant patients will have to take drugs to prevent rejection. Modern immunosuppressive regimens are already extremely effective in preventing acute rejection so the emphasis of research programmed has shifted to the induction of “transplant tolerance” and an improvement in long-term transplant survival.

Transplant tolerance, the non-reactivity of the immune system towards foreign antigens (obviating the need for chronic immunosuppressive therapy) has been achieved in animal

studies through massive depletion or blockade of the host defence systems. The toxicity of the treatment currently used is unacceptable for clinical studies, but a worldwide Immune Tolerance Network has been set up to co-ordinate research towards this ‘holy grail’³².

A transplanted kidney (or allograft) ‘lives’ until the recipient dies or rejects it, so that long-term allograft survival can be improved by reducing mortality rates in the recipients and by reducing chronic rejection. Transplanted patients have a higher than normal risk of cardiovascular disease, and there is some hope that preventative measures, such as the use of statins to decrease cholesterol levels and improved management of blood pressure, will be effective in reducing cardiovascular risk. These measures may also help reduce the risk of chronic rejection, and there is evidence that the newer immunosuppressive agents such as mycophenolate mofetil may be associated with superior long-term allograft survival³³.

The issue of xenotransplantation continues to attract media interest. Recent successes in cloning genetically modified pigs has led to the expectation that it may be possible to transplant their organs into primates without immediate uncontrollable rejection. However, the rejection would still be expected to be more severe than for a transplant between similar animals and it may be necessary to develop a new clan of drugs to deal with it. Another obstacle to be resolved before xenotransplantation is considered viable is the fear that ‘pig’ virus material may find a way into the human population.

Xenotransplantation, or even kidneys grown from embryonic stem cells, could reduce the waiting time for a transplant in future, but for the present the shortage of donor organs has led to a renewed interest in “non-heart beating donors” (NHBD). Heart-beating donors are brain-dead, but ventilated so that their organs are perfused with freshly oxygenated blood until the donation takes place. Kidneys from NHBD’s who have already suffered cardio respiratory arrest go through a phase when they are warm, but not perfused with oxygenated blood. This leads to ischaemic damage that makes the viability of the kidney difficult to predict. A transplant that fails to work is extremely traumatic for the recipient, both psychologically and physically, so renal units undertaking NHBD transplants are keen to minimise the ischaemic damage and to ‘bench-test’ the kidney before it is used. Two advances in viability testing have taken place recently. The first is the development of a biochemical test that can be used to quantify organ viability by measurement of glutathione S transferase enzyme³⁴. This test has already shown promising results. Viability can also be assessed by monitoring pressures in the kidney during hypothermic pulsatile perfusion³⁵. Although a good viability test result

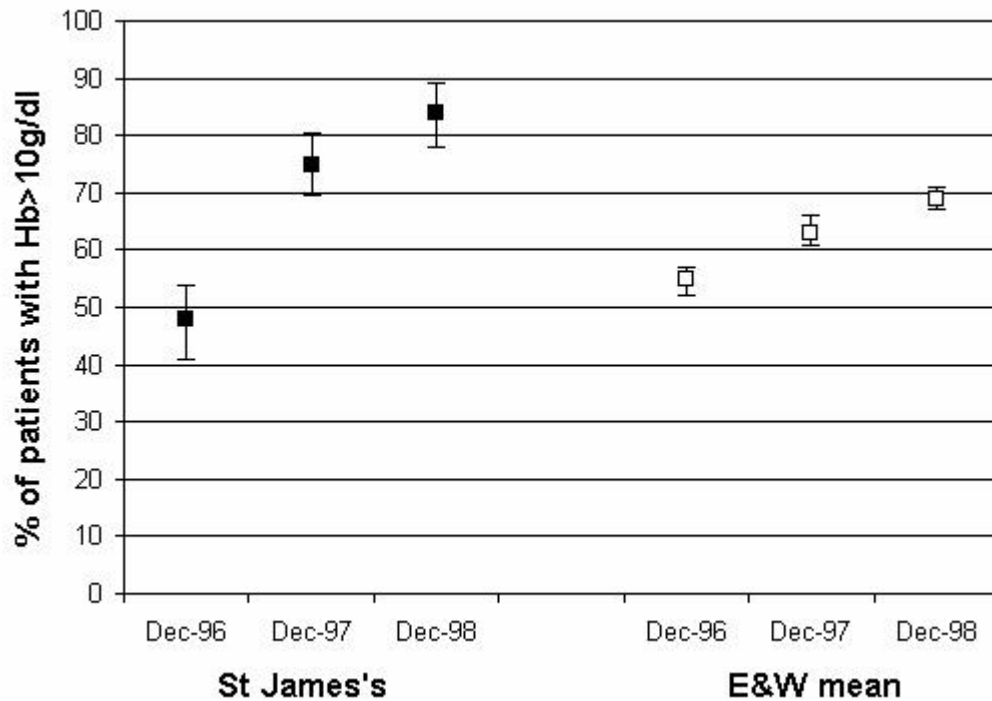
does not guarantee that the kidney will work, these approaches form the first stage of moving towards expanding the NHBD pool. More research is required to minimize the damage to the kidney when it is perfused again following retrieval from the donor. A number of different perfusion solutions are currently under investigation.

The role of IT

Information technology has an increasingly important role in all areas of medicine. In renal care, the national and international patient registries allow data from many centres to be pooled for analysis. This is particularly important where centres, or even countries, have very few patients. Strategies for managing rare childhood diseases or pregnancy in patients with end-stage renal failure, for example, can only be evaluated by sharing data.

The UK's Renal Registry is now collecting data from about half of the dialysis centres in England and Wales. Other centres are setting up the automated data transfer links required to participate. The annual audit reports produced by the Registry¹ allow participating centres can compare their performance with the rest of England and Wales and identify areas where improvement can be made.

Another important use of IT is in the development and implementation of clinical decision support systems. Following the publication of the 1997 Renal Registry report, staff at St James's University Hospital in Leeds could see that their anaemia management was below average. Half of the haemodialysis patients had haemoglobin levels that were less than the minimum recommended by the UK Renal Association. Over the next two years, medical and IT staff in Leeds developed a computer algorithm to automatically adjust the EPO and intravenous iron prescribed to each patient, based on their monthly blood chemistry³⁶. A nominated physician is required to review the computer report and approve the new prescriptions each month. A subsequent report from the Registry showed a dramatic improvement in the outcome of the patients. In theory, an identical result could have been achieved if staff had changed the prescriptions manually according to the algorithm rules but in practice this would have been extremely time consuming and prone to inconsistency. Use of the computer algorithm has also allowed staff at Leeds to reduce the cost of treating anaemia.



Percentage of haemodialysis patients with haemoglobin levels > 10 g/dl during the implementation of the anaemia management algorithm At St James's University Hospital in Leeds. The mean for all participating centres in England and Wales is shown for comparison.

Many of the usual clinical complications of renal failure, like renal anaemia, are amenable to management by protocols that can be computerised³⁷. Outcome data for the patient population in Leeds, and in many other units, is collected regularly and much of it is already stored in the renal unit computer where it can be analysed automatically. In future, the treatment for the control of blood pressure, cholesterol levels, renal bone disease and immunosuppression may be managed by a nurse practitioner or junior doctor working with a computerised decision support system, giving experienced nephrologists more time to manage the exceptional patients.

Conclusions

The technological advances in renal replacement therapy to date are very impressive. In less than 60 years, dialysis has grown from an experimental procedure to a life sustaining treatment for renal failure from which nearly one million patients around the world benefit. Renal transplantation has a high success rate and techniques for expanding the pool of donor organs and reducing the adverse effects of immunosuppression are developing. In the long-term, advances in molecular science, gene therapy and organ cloning may lead to a complete

revision in renal replacement therapy. An exciting area of innovative research is the development of a bioartificial kidney tubule utilizing porcine tubular epithelial cells grown in a hollow fibre. When incorporated into an artificial kidney, the epithelial cells lining the fibre can reabsorb solutes that would normally be lost in the ultrafiltrate, mimicking the normal kidney tubule³⁸.

Until the problems associated with replacing the kidney itself are resolved, a large proportion of patients with end-stage renal failure will be sustained on dialysis and researchers will continue to look for the dialysis strategy that gives the patients the best chance of survival and the highest quality of life. Registries, such as the UK Renal Registry, will continue to play an important role in improving standards. Studies comparing standard, thrice weekly, haemodialysis with more effective modalities (such as haemodiafiltration) will continue. Advances in dialyser technology and peritoneal dialysis fluids will also continue. The benefits of more frequent haemodialysis have been demonstrated in numerous studies³⁹ but it is costly, both in terms of consumables and time. New machines for use in patients' homes, with minimal set-up times and low consumable costs, are emerging⁴⁰. With these machines, more frequent dialysis may be a viable option for many patients.

Perhaps the most important developments in renal care will be in screening and prevention. Recent reviews of healthcare funding systems have indicated that the total dialysis costs in Europe range between 0.7 and 1.8% of healthcare costs⁴¹. These costs will rise as the population ages. An increasing number of patients are presenting with renal failure caused by hypertension and/or diabetes. In these patients, the need for dialysis or a kidney transplant can be delayed, or even avoided altogether, if adequate treatment is provided in time. Validated treatments already exist but can only be implemented with the right combination of technology and communication between the renal specialists and general practitioners in the community.

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